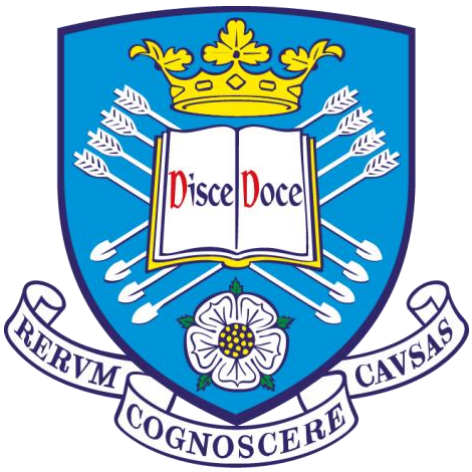
University of Sheffield

# The impact of MYT1L-syndrome on behaviour and cognition

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## Abstract

This thesis aimed to investigate the cognitive and behavioural phenotype of MYT1L-syndrome (2p25.3 deletion), a novel cause of intellectual disability. Initially, a systematic review was conducted exploring the cognitive and behavioural phenotype of children with genetic disorders affecting chromatin remodelling, a process which the MYT1L gene is also involved in. Generally, there are clear associations between genetic disorders implicated in chromatin remodelling and neurodevelopmental conditions.

Semi-structured qualitative interviews were then conducted with parents and caregivers of children with a diagnosis of MYT1L-syndrome to understand the lived experience of individuals with, and families of those, with the syndrome. Then, based on the findings of the systematic review and the insights provided by caregivers, a series of standardised measures were selected to quantitatively assess the cognitive and behavioural phenotype of individuals with the syndrome.

Collectively, the findings reported within this thesis advance our understanding of the cognitive and behavioural phenotype associated with MYT1L-syndrome. The impact is often complex, and there is notably a profound impact on multiple areas of life for individuals with the syndrome. Impacted areas include reaching developmental milestones, communication and social skills, anxiety, adaptive behaviour, and sensory processing. The research also found that there is frequently a significant and multi-faceted impact on caregivers, siblings, and the wider family. Collectively, this research provides a

detailed description of the cognitive and behavioural phenotype of individuals with MYT1L-syndrome. Additionally, the findings highlight some of the collective strengths and weaknesses of the cohort and recognises the intra-group heterogeneity. Clinical implications are discussed alongside recommendations for future research.

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# Chapter 1: Introduction

## 1.1. Rare diseases

### 1.1.1. What is a rare disease?

#### 1.1.1.1. Definitions and prevalence

A rare disease is a health condition affecting a small number of the population, defined by the European Union as less than 5 in 10,000 (Genetic Alliance UK, 2016). Over 80% of rare diseases are thought to have a genetic component which can be caused by alterations to a single gene, multiple genes, or changes at the level of the chromosome (Boat, 2015). Additionally, rare diseases can also be caused by rare cancers, infectious diseases, the disruption to development whilst in the womb, or the deterioration of body organs, but these are considered to exhibit specific characteristics and possess their own unique challenges (Haendel et al., 2020). Rare diseases are seldom curable or preventable, mostly chronic, and are noted to disproportionately impact children and adolescents, with most (75%) presenting during childhood, and almost a third of children affected by such conditions die before their fifth birthday (Azie & Vincent, 2012). These conditions are also referred to as 'orphan diseases' in the United States (US) following a law called the Orphan Drug Act. The law was intended to promote research and drug discovery, subsequently enhancing the ability to diagnose, prevent, and treat rare diseases (Dooms, 2015), although rare disease is considered the preferred terminology (Richter et al., 2015).

In the United Kingdom (UK), a rare disease is defined as a health condition which affects fewer than 1 in 2,000 people (DHSC, 2021). This number reflects over 3.5 million, or 1 in 17, people in the UK being affected by a rare disease during their lifetime. Whilst such diseases

are individually rare, collectively they are noted to affect a significant proportion of the global population. It is, therefore, surprising that, as confirmed by a recent systematic review, there are highly variable definitions of what a rare disease is depending on the country, and the governing jurisdiction responsible for defining them (Ferreira, 2019). The European Medicines Agency define a rare disease as occurring in less than 5 in 10,000 people, equating to 1 in 2,000, in line with the UK (Schuller et al., 2019). However, the National Institute of Health in the United States (US) define conditions occurring in fewer than 200,000 individuals as a rare disease, which equates to approximately 1 in 1,600 people or 9-12% of the US population (Franco, 2013; Griggs et al., 2009). In Japan, such diseases are defined as any condition occurring in less than 50,000 people in the country, equating to approximately 1 in 2,500 (Hayashi & Umeda, 2008). These varied definitions mean that a disease occurring in 1 in 2,000 people would be considered rare in the UK, Europe, and the US, but not in Japan. This lack of international consensus was validated by a systematic review which identified 296 different definitions of a rare disease from 1,109 organisations across 32 international bodies, signalling that there is no universal definition of what a rare disease is. The same review also highlighted that there is no consensus of the prevalence estimates but concluded that the average prevalence is between 40 and 50 cases per 100,000 people, or 1 in 2,500 people (Richter et al., 2015). Globally, rare diseases are thought to impact approximately 400 million people, but estimates differ given the highly variable definitions applied geographically (Wakap et al., 2020).

#### 1.1.1.2. Diagnosis and treatment options

There is also a lack of consensus when defining how many rare diseases exist globally, with most estimates in the literature ranging between 6,000 and 8,000 (Stephens & Blazynski, 2014). This number is thought to grow each year, with upwards of 250 novel diseases identified and added annually (Crooke, 2021). Historically, genetic anomalies were detected using G-Banded karyotype analysis, which is thought to identify clinically relevant anomalies in approximately 5% of children with such disorders (Miller et al., 2010). This has now largely been replaced by chromosomal microarray analysis (CMA), which is able to detect G-banded karyotyping alongside smaller chromosome abnormalities. CMA is thought to possess greater sensitivity, with an increased diagnostic yield to approximately 20% of children (Tammimies et al., 2015). The process utilises a microarray, which is a device used to detect the expression of thousands to millions of genes at the same time, identifying the genes present in a genome. The increased sensitivity of microarray testing means that CMA is now the recommended first-line genomic test for children with neurodevelopmental conditions (Martin & Ledbetter, 2017). The advent of microarray testing and other technologies such as gene panels and exome sequencing, and their ever-increasing adoption as part of routine clinical practice seeking to resolve unexplained developmental delay, intellectual disability, or autism spectrum disorders, means that this number is only likely to increase (Baker et al., 2014). Projects adopting these methods, such as the Deciphering Developmental Disorders (DDD) project based at the Wellcome Trust Sanger Institute which began in 2011 and sequenced 20,000 genes from 4,000 families with an affected child, have led to the discovery of many new developmental disorders and successfully diagnosed many children. In the case of DDD, 14 new developmental disorders

were identified following the exome sequencing of 4,293 families (Deciphering Developmental Disorders Study, 2017).

Whilst these technological advances will increase the speed and accuracy of diagnoses moving forwards, it is only in recent history (<10 years) that these methods of genetic testing have become cost-effective, more accurate, and therefore more widely and routinely utilised in clinical genetics (Marwaha, Knowles, & Ashley, 2022). Although these developments have rapidly advanced testing abilities, successful diagnostic rates remain below 50% (Lee et al., 2014). Many individuals, therefore, remain undiagnosed for a significant period of time and some die having not been accurately diagnosed. This often-long period of time that it can take for an individual to receive an accurate diagnosis for their condition, and the multiple hospital visits often required, is termed the diagnostic odyssey - the length of which varies widely, from months and years to decades, depending on the individual's age, phenotype and resources that are available in the local geography. The average time thought to receive a diagnosis is 6 years, and for many this initial diagnosis is incorrect (Basel & McCarrier, 2017; Molster et al., 2016). A survey of 886 patients and caregivers found that the average length to receive a correct diagnosis in the USA was 7.6 years and in the UK 5.6 years, and during this time families typically visited 8 clinicians and received four incorrect diagnoses (Global Genes, 2013). Another large study conducted in 17 European nations, spanning eight rare diseases, identified that a quarter of patients had spent between 5 and 30 years accessing the correct diagnosis and almost half received an initial diagnosis that was incorrect (EURORDIS, 2009).

Upon receiving a diagnosis treatment options are extremely limited, with more than 90% of rare diseases lacking an effective treatment (Groft, Posada, & Taruscio, 2021). The average cost of bringing a new drug to market is thought to exceed 2.5 billion dollars (DiMasi, Grabowski, & Hansen, 2016), and the small sample sizes that would potentially benefit from such a treatment mean that the incentive to invest in these therapeutics is low given the forecasted return on investment compared to other, more prevalent, therapy areas. These costs are often further exacerbated by the current lack of knowledge of many diseases due to a paucity of outputs from trial designs such as natural history studies, and recruitment costs are often much higher in trials due to the small initial sample size to recruit from and the global dispersion of potential participants (Gavin, 2015; Kaufmann, Pariser, & Austin, 2018).

### 1.1.2. The impact of rare diseases

It is well-documented that rare diseases are complex, and impact multiple aspects of life for the individual, caregivers, and members of the wider family. Additionally, there are numerous challenges presented to professionals involved in the care of individuals with rare diseases. The following sections will describe these areas of impact for individuals, caregivers, the wider family, and professionals.

#### 1.1.2.1. Individual impact

The impact of rare diseases on the affected individual are well-documented to impair quality of life, compromise the ability to undertake day-to-to activities, and severely hamper one's ability to be autonomous (Uhlenbusch et al., 2019). Lower health-related

quality of life is most attributed to challenges accessing a diagnosis and subsequent treatments or therapy, a lack of psychosocial support, and the stigma that is associated with a rare disease (Bogart & Irvin, 2017; Molster et al., 2016). The adverse impact on quality of life means that many individuals are reported to experience anxiety and depression (Uhlenbusch, Löwe, & Depping, 2019). Rare diseases are also widely reported to impact multiple domains of physical health, cognition, development, and behaviour in individuals (Heitz, Epelbaum, & Nadjar, 2017; Kehrer et al., 2014; de Winter et al., 2016). Affected children are reported to need adjustments in school, suffer impairments to social skills, and achieve lower attainment levels compared to typically developing children (Johansson et al., 2021; Verger et al., 2020).

#### 1.1.2.2. Caregiver impact

A recent systematic review identified that when compared to the parents of healthy children, parents of children with a rare disease have a lower quality of life (Boettcher et al., 2021). The well-documented delays in establishing a correct diagnosis are reported to lead to anxiety, loss of reproductive confidence, frustration, and stress in over half of caregivers of children with a rare disease, and when a diagnosis is received some parents (16%) reported feeling like the news was delivered with a lack of empathy and with insufficient accompanying information (Zurynski et al., 2017). Following a diagnosis, daily impact including stress and practical problems impeding a parent's ability to participate in day-to-day activities were most strongly associated with higher self-reported anxiety and depression levels (van Oers et al., 2014). Although caregivers do frequently feel overwhelmed by the needs of their child, most parents reported that they developed

considerable expertise in understanding, and managing, their child's conditions (Smith, Cheater, & Bekker, 2015). There are many other facets of life that are impacted for caregivers, including the inability to work, increased travel to appointments, and higher financial costs (Khair & Pelentsov, 2019; Verberne et al., 2022).

#### 1.1.2.3. Family impact

In addition to the impact on caregivers, there is also an impact on siblings and the wider family. There is often an adverse impact on family life, including an increased need to travel to hospital appointments, reduced ability to participate in recreational activities, and impairments to relationships of those in the wider family (Silibello et al., 2016). Siblings are reported to experience highly variable and contradictory feelings and emotional experiences, but some frequently reported concerns for the siblings of an individual with a rare disease include the practical implications, social impairments, and the impact on relationships with parents (Haukeland et al., 2015). Further, and similar to affected individuals themselves, siblings of a child with a rare disease, compared to typically developing individuals, were also found to have lower education attainment levels and increased behavioural disorders (Johansson et al., 2021; Limbers & Skipper, 2014). In contrast, one study identified that siblings show significantly fewer behavioural concerns and higher prosocial behaviour compared to the norm (Wiegand-Grefe et al., 2022). This demonstrates that whilst there is notable impact on the affected individual and their primary caregivers, there is also an often-considerable impact on other members of the wider family.

#### 1.1.2.4. Challenges for professionals

Individuals diagnosed with a rare disease, generally, are noted to utilise health services significantly more than those with other diseases or conditions (Navarrete-Opazo et al., 2021). These interactions are often challenging for both caregivers and physicians, which no doubt is somewhat attributable to the fact that less than a third of physicians reported receiving specific training in rare disease during their medical education (Ramalle-Gómara et al., 2020). Further, research identified that healthcare workers felt that they had insufficient knowledge about rare diseases, and therefore felt they were unable to appropriately support patients, and a recent survey found that only 5.3% of physicians reported feeling moderately aware of rare diseases (Kopeć & Podolec, 2015; Li et al., 2021). Additional challenges also arise due to the increased geographical distances between patients and clinicians who possess the required specialist knowledge (Ende et al., 1989). Educators are also posed with a unique set of challenges, such as a lack of awareness of how to best support the psychosocial, physical, and emotional needs of children with a rare disease, and how to best adapt the curriculum to enable equitable access to education (Foster et al., 2022; Runions et al., 2020). This lack of understanding means that children with rare diseases largely remain unsupported and arguably invisible in education (Paz-Lourido et al., 2020).

## 1.2. Neurodevelopmental conditions

### 1.2.1. Definitions and prevalence

The term neurodevelopment is broadly applied to many disabilities characterised by neurological and psychiatric problems including rare genetic syndromes, schizophrenia,

autism, and epilepsy (Thapar, Cooper, & Rutter, 2017). Neurodevelopmental condition (or NDC) is an umbrella term for a broad group of disorders that occur early developmentally, which are characterised by an impairment in one or more domains including cognition, emotion, behaviour, and motor (Rodriguez, Joya, & Hines, 2018). NDCs are recognised as contributing to a reduced quality of life for affected individuals, presenting a plethora of challenges for caregivers, and childhood morbidity is increasingly attributed to such disorders (Jeste, 2015; Eapen, Cavanna, & Robertson, 2016).

The DSM-III first included the term 'developmental disorders', comprising autistic disorder (American Psychiatric Association, 1980). However, it was the DSM-5 that included neurodevelopmental disorders (NDDs) as an overarching disorder category, defined as a group of conditions with onset in the developmental period, which produce impairments in functioning (American Psychiatric Association, 2013). The NDDs in this category are intellectual disability (ID); autism spectrum disorder (ASD); attention-deficit/hyperactivity disorder (ADHD); communication disorders; neurodevelopmental motor disorders; and specific learning disorders (including reading, writing, and mathematics). Other classifications of disease, such as the ICD-11 contain a similar definition of NDDs, comprising disorders of intellectual development; developmental speech or language disorders; ASDs; developmental learning disorders; developmental motor coordination disorder; ADHD; stereotyped movement disorder; and other neurodevelopmental disorders (World Health Organisation, 2019).

The prevalence of NDCs is of much debate, and it is thought that the identification and subsequent diagnosis of such disorders is much lower than the actual prevalence rates (Zwaigenbaum & Penner, 2018). A recent systematic review assessing papers reporting on the prevalence of NDCs worldwide concluded that the number is highly variable (ranging from 4.7% to 88.5%) and is likely caused by cultural context and the training levels of healthcare professionals (Francés et al., 2022). In the UK, NDCs are thought to affect up to 3-4% of children, and in the US, it is thought that as many as 17% of children aged 3-17 years are affected with up to 8.5% of children possessing a diagnosis of ADHD (Emerson, 2012; Zablotsky & Black, 2020; Yang et al., 2022). Estimates of the prevalence of NDCs in low and middle-income countries are thought to be approximately 7.6 per 1,000 people and are considered a significant burden (Bitta et al., 2018), but ranges to as many as 1 in 8 children aged 2-9 years in India (Arora et al., 2018). These differing prevalence rates may indicate that many individuals with NDCs are under-diagnosed.

#### 1.2.1.1. Intellectual disability

IDs are identified by cognitive, social, and adaptive skill deficits (Downs, Downs, & Rau, 2008; Zayac & Johnston, 2008), and individuals diagnosed with IDs have neurodevelopmental deficits including impairments to intellectual functioning, which is generally referred to as intelligence. Impairments to intellectual functioning, or intelligence, can result in deficits to logical reasoning, difficulties learning, and delays to speech (Lee, Cascella & Marwaha, 2019). The DSM-5 diagnostic criteria for ID comprises three domains: a) deficits in intellectual functioning, such as planning, problem solving, and academic learning, which is usually assessed via both clinical assessment and

standardised IQ testing, and scores <70 are indicative of ID, b) deficits in adaptive functioning which result in the impairment of one or more activities, including communication, social functioning, and independence, and is assessed by standardised assessments, and c) that the previous two criteria onset during the developmental period (APA, 2013). Many diagnoses are made in later childhood or even early adulthood based on the IQ score alone, but some people with ID are identified earlier than this based on overt developmental delays including speech, cognition, and irregular sleeping patterns (Reynolds et al., 2019). ID often has a genetic underpinning, including conditions such as Trisomy 21, or Down's syndrome, and Fragile-X syndrome (Silverman, 2007). However, there are other causes of ID, which include infections during pregnancy, traumatic brain injury, and problems during childbirth (American Academy of Paediatrics, 2012). Whilst differing according to country, one meta-analysis of 52 studies reported that the prevalence of IDs was 10 in 1000 (Maulik et al., 2011).

#### 1.2.1.2. Autism spectrum disorders

Individuals with IDs have been found to, at very high rates, also have traits, or a diagnosis, of ASDs (Matson & Shoemaker, 2009). Whilst there is no universally agreed term to describe autism, ASDs are recognised in 1 in 150 children and are characterised by impairment to social functioning and communication, and the presence of repetitive behaviours and restrictive interests (Rapin & Tuchman, 2008; APA, 2013). According to the DSM-5, a child must demonstrate impairments in all three areas of social communication and interaction, and two of the four types of restricted, repetitive behaviours (see Table 1.1; APA, 2013). These criteria must also present early in the developmental period, be causing clinically

significant impairment in important areas of current functioning (such as social), and not be better explained by ID.

| **Criteria** | **Domain** |
|---|---|
| A) Demonstrate deficits in each of the three domains of social communication and interaction | 1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.<br>2. Deficits in nonverbal communicative behaviours used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.<br>3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behaviour to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers. |
| B) Restricted, repetitive patterns of behaviour, interests, or activities, demonstrated through at least two of the following criteria | 1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypes, lining up toys or flipping objects, echolalia, idiosyncratic phrases).<br>2. Insistence on sameness, inflexible adherence to routines, or ritualised patterns of verbal or nonverbal behaviour (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).<br>3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).<br>4. Hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of the |

| | |
|---|---|
| | environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement). |

***Table 1.1.*** *DSM-5 diagnostic criteria for ASD*

However, many children with ASD also have ID, and up to 75% require significant levels of support in daily living, managing social relationships, and within education (Mefford, Batshaw, & Hoffman., 2012). ASD is thought to affect 1 in 100 children, although estimations are highly variable (Chakrabarti & Fombonne, 2005). A recent study utilising a longitudinal design identified that in the UK, the prevalence of ASD ranged from 1.9-3.2% and that rates were higher in secondary schools than in primary schools (McConkey, 2020). This is similar to the US, where the prevalence rate of ASD was recently estimated to be 3.14% among children and adolescents (Ames et al., 2022).

#### 1.2.1.3. Attention deficit hyperactivity disorder

ADHD describes a characteristic profile of persistent patterns of inattention, hyperactivity, and/or impulsivity that interferes with development or daily functioning (APA, 2013). To assess this characteristic profile, the DSM-5 stipulates that the following criteria must all be met in order to diagnose ADHD in children up to the age of 16: six or more symptoms of inattention (such as trouble holding attention on tasks; trouble organising tasks; and being forgetful in daily activities); six or more symptoms of hyperactivity and impulsivity (such as often fidgeting; often talking excessively; and often has trouble waiting their turn). Additionally, several of these symptoms must have been present before the age of 12 years, several symptoms are present in two or more environments, there is clear evidence that the

symptoms impact functioning, and symptoms are not better explained by another disorder, such as personality disorder (APA, 2013). Whilst estimates vary, globally it is thought that 4-12% of school-aged children are affected by ADHD (Polanczyk et al., 2007). The disorder has been found to significantly impact affected individuals both in childhood and adulthood, where people are likely to have fewer social relationships, poorer outcomes in relation to work, and caregivers of affected children are more likely to experience increased levels of depression and stress (Gardner & Gerdes, 2015; Fridman et al., 2022).

### 1.2.2. Co-occurrence of NDCs

Co-occurrence refers to the presence of two or more diseases in individuals, and in relation to NDCs refers to the co—occurrence of two or more different disorders (such as ASD and ADHD), which are defined in terms of their characteristic cognitive, motor, and/or behavioural deficits opposed to the underlying cause (Dewey, 2018). NDCs seldom occur singularly, and it is believed that there is significant overlap between different disorders and with other psychiatric disorders (homotypic co-occurrence and heterotypic co-occurrence, respectively; Hansen et al., 2018). Due to high rates of co-occurrence with other disorders that onset during the developmental period, ADHD has been identified as a highly heterogeneous disorder with estimations that 60-100% of affected children are also diagnosed with one or more co-occurring disorders (Gillberg et al., 2004; Gnanavel et al., 2019). Psychiatric disorders are also noted to co-occur with ADHD, including depressive, bipolar, and anxiety disorders (Blackman, Ostrander, & Herman., 2005; Galanter & Leibenluft, 2008; Busch et al., 2002). ASDs are also recognised to co-occur with other NDCs and psychiatric disorders, where 30% of individuals diagnosed have a co-occurring

diagnosis of epilepsy, 20-85% ADHD, and 50-80% ID (Tuchman & Rapin, 2002; Simonoff et al., 2008; Rommelse et al., 2011).

### 1.2.3. Defining typical functioning

When investigating disorders relating to neurodevelopment, it is important to consider how functioning is defined in a typically developing population. Between birth and approximately 5 years children acquire functional skills which can broadly be separated into four domains: gross motor; fine motor and vision; speech and language (in conjunction with hearing); and social, emotional, and behaviour. Developmental milestones are commonly referred to when discussing typical development, and broadly are age-related checkpoints that most typically developing children will meet at a similar time. Two key considerations are important to assessing typical functioning; 1) median age of acquisition, or when half of typically developing children meet the milestone, and 2) limit age, or the cut-off age which children should achieve milestones, which is usually two standard deviations from the mean age of acquisition. If children are not developing skills in line with the limit age, this is an important potential indicator of an NDC and is usually when clinical assessment will occur (Lissauer & Clayden, 2012). Typical developmental milestones, adapted from the Oxford Handbook of Paediatrics, Second Edition, are outlined in **Table 1.2** (Tasker, McClure, & Acerini, 2013).

| Domain | Milestone | Description and age |
|---|---|---|
| Gross motor development | Head control | Newborn-3 months |
| | Sitting | 6-8 months (limit age: 9 months) |
| | Locomotor skills | Cruising round the edge of furniture (10 months); 50% of infants walking independently (12 months; limit age: 18 months) |
| | Further motor skills development | Jump from a bottom step (3 years); Can balance on one leg for a few seconds (4 years); Can skip on both feet (5 years) |
| Fine motor and vision development | Early visual alertness | Fix or follow a near face (newborn); alert and will turn head through 90 degrees to follow an object (6 weeks); spend a lot of time watching their hands (3-4 months) |
| | Early fine motor skills | Grips with whole palm, holds objects with both hands, transfers objects between hands (6 months); developing pincer grip using thumb and finger (10 months); use index finger to point to objects (12 months) |
| | Preschool fine motor development | Scribbles (18 months); copies a circle (2.5 years); draws a circle (3 years); draws a cross (4 years); draws a square (4.5 years); draws a triangle (5 years) |
| Speech and language development | Early signs of normal hearing and vocalisation | Quieten to voices and startle to loud noises (newborn); responds to mother's voice (6 weeks); begins to coo and laugh (12 weeks) |
| | Early language development | Use consonant monosyllables 'ba' or 'da' (6 months); use non-specific two-syllable babble 'mama' or 'dada' (8 months); two-syllable words become appropriate and develops understanding of other single words 'drink' or 'no' (13 months); vocabulary of 10 words (18 months) |
| | Phrase and conversation development | Begins to combine 2 words together (24 months); knows age, name, and several colours (3 years) |

| | | |
|---|---|---|
| Social, emotional, and behavioural development | Early social | Starts smiling and becomes increasingly responsive socially (6 weeks); shows separation anxiety when separated from parents (10 months); begins to wave goodbye (10 months) |
| | Social and self-help skills development | Begins to start to feed self using fingers (8 months); will drink from a cup (12 months); uses spoon and feeds self (18 months); removes some clothes and will soon start to try and dress self (2 years) |
| | Symbolic play | Starts to copy actions and activities that they see around them (24 months); progress to play on their own or alongside peers in parallel play (24 months); start to have interactive play, taking turns and following simple rules (3 years) |
| | Cognitive function | Thought processes are called pre-operational, so children are at the centre of their world (pre-school); thoughts become operational and are more practical and orderly (junior school); formal operational thought has developed including abstract thought and complex reasoning (teenage years) |

***Table 1.2.*** *Summary of typical development milestones*

Whilst there are milestones, median ages of acquisition, and limit ages, it is important to acknowledge that there is huge variation in typical childhood development. Development is considered a dynamic process characterised by both continuous (change through a gradual process in a linear fashion as age increases) and discontinuous (rapid change in a stage-specific pattern). Therefore, children who are typically developing transition through milestones on a continuum and may lay behind peers or excel in relation to their expected development. Delays in reaching milestones, for that reason, may not always be indicative

of impaired functioning or developmental delay and children typically continue to develop in their own timeframe (Guerra, Williamson, & Lucas-Molina, 2012).

## 1.3. MYT1L-syndrome

### 1.3.1. The MYT1L gene

Neurogenesis is the process in the developing embryonic and foetal brain in which stem cells differentiate into mature neurons and migrate into the appropriate part of the central nervous system (Urban & Guillemot, 2014). The process is highly complex, and regulated by thousands of different genes. Disruption to neurogenesis by genetic variants or environmental factors (such as drug exposure or infections) is associated with NDCs. In NDCs, there can be inhibition of neurogenesis, leading to a reduction in neuronal numbers in the brain and reduced brain volume (Guarnieri et al., 2022). In NDCs associated with brain malformations, there is disruption to the normal process of neuronal migration. The MYT1L-gene, in mice, has been shown to suppress the activity of genes that would cause cells to differentiate into non-neuronal cells (Chen et al., 2022). There is no clinical or animal model evidence of brain malformations in MYT1L-syndrome. It is believed that in MYT1L-syndrome there is disruption to the process of neurogenesis and neuronal differentiation leading to NDCs (Stevens et al., 2011).

### 1.3.2. Global incidence

Given the rare nature of MYT1L-syndrome, there is very limited evidence indicating the incidence in the population, and as such there are no published epidemiological studies. The only current indication of the incidence of MYT1L-syndrome is provided by a family support group; which proposed in April 2022 that there were 142 identified cases globally,

with a division of 60% females and 40% males (see **Table 1.3**; Les Extra-Vaillants, 2022). Of these 142 individuals, 51% had a duplication on the MYT1L-gene, 34% a mutation, 4% a deletion, and for 11% this information was not reported.

| **Continent** | **Identified cases** |
|---|---|
| Europe | 79 |
| North America | 48 |
| Australia (Oceania) | 3 |
| South America | 3 |
| Asia | 3 |
| Africa | 3 |
| **Total** | **142** |

***Table 1.3.*** *Estimates of MYT1L incidence globally*

Whilst this is a useful indicator of how rare the syndrome is, it is very likely that there are cases not accounted for in this data for several reasons, including lack of engagement with the family support group, and misdiagnosis or lack of diagnosis.

### 1.3.3. How MYT1L-syndrome is diagnosed

People with MYT1L-syndrome may come to clinical attention via a variety of routes. They may present at birth with neonatal hypotonia and poor feeding (Mayo et al., 2015). Throughout childhood, they may present with delay to developmental milestones (such as speech acquisition) or learning difficulties at school. Behavioural issues or autistic symptomatology may also be present. In Western healthcare systems, such presentations would be investigated with diagnostic tests such as micro-array comparative genomic

hybridisation (aCGH) or exome/genome sequencing (Turro et al., 2020). Identification of a deletion at 2p25.3 (containing the MYT1L gene) via aCGH or of a single nucleotide change ("mutation") within the MYT1L gene on exome/genome sequencing would confirm the diagnosis of MYT1L-syndrome. In the UK, both aCGH and genome sequencing are funded for all people with NDCs.

### 1.3.4. What we know about MYT1L-syndrome

A thorough review of the published literature identified 18 papers reporting on the clinical phenotype associated with individuals diagnosed with MYT1L-syndrome, ranging from single case studies to case reports of up to 40 individuals. One of the first published accounts of the impact of a 2p25.3 deletion on the MYT1L gene is provided by Stevens et al., (2011), who described the physical malformations and developmental profile of 6 individuals, 3 adult siblings and 3 unrelated patients, affected by the deletion. The physical malformations, present in all individuals in the cohort, included a short, square-shaped, truncal build, hypotonia, and obesity. Developmental delay was also present in the cohort, with delays to psychomotor development, including delays to unsupported sitting, walking without support and first words. Additionally, individuals in the cohort were diagnosed with a variety of NDCs, including ID, ASD, psychotic behaviour, and hyperactivity.

Most of the published literature consists of single case studies or clinical reports. Many of the findings reported in these are consistent with Stevens et al., (2011) and acknowledge the presence of; physical malformations, including hypotonia, intellectual and psychomotor development delays, and speech delays (Carvalho et al., 2021; Loid et al.,

2018; Mayo et al., 2015; Sakaue et al., 2022; Al Tuwaijri & Alfadhel, 2019; Vlaskamp et al., 2017; Wang et al., 2016). Further, the behavioural profile reported in the single case studies published include anxiety, problem behaviours including aggression, hyperactivity, and repetitive behaviours (Wang et al., 2016; Carvalho et al., 2021; Mayo et al., 2015). Interestingly, one case study also describes the presence of aggressive behaviours specifically relating to the removal or denial of food (Carvalho et al., 2021). There is an indication of a heterogeneous behaviour profile in the syndrome population, as no behavioural concerns were reported by one of the case studies (Loid et al., 2018). Syndrome associated obesity was also reported by numerous case reports (D'Angelo et al., 2018; Al Tuwaijri & Alfadhel, 2019; Sakaue et al., 2022). One case report including the phenotype associated with affected monozygotic twins also confirms the presence of global developmental delay, hyperactivity, ASD, and obesity (Rio et al., 2013).

Three studies report the clinical phenotype of between 5-9 individuals, totalling 23 individuals, with MYT1L-syndrome (Doco-Fenzy et al., 2014; Blanchet et al., 2017; Windheuser et al., 2020). These studies also confirm the presence of hypotonia, developmental delay, ASD, behavioural outbursts or aggressive behaviour, and ID – although it is important to note that the presence of each is highly variable across the samples. This is also identified in a report of 22 individuals with a genetically confirmed 2p25.3 deletion, which proposed there is a positive correlation observed between affected individuals and ID, and 17 of the individuals presented with obesity/overweight, adding to the hypothesis that affected individuals may have a predisposition to weight problems with childhood onset (De Rocker et al., 2015).

One paper identified, in 43 individuals, that developmental and speech delays were present in 33% of the cohort, ASD (23%), intellectual disability (21%), and behavioural disorders (16%). The cohort study and literature review also reports that 21% of individuals exhibit symptoms consistent with schizophrenia, whereas 11 individuals did not demonstrate any obvious neuropsychiatric disorder (Bouassida et al., 2022). This is consistent with a systematic review that explored associations between the MYT1L gene and neuropsychiatric disorders. The review comprised 78 participants from 24 studies, and identified 33% of 2p25.3 duplications were associated with schizophrenic symptoms, with only one paper reporting no associations with neuropsychiatric disorders (Mansfield, Constantino, & Baldridge, 2020).

The largest primary data collection to date, to the author's knowledge, collated the genetic information and clinical case reports of 40 previously unreported individuals, ranging from 1.6-34 years of age (median 8.4 years), 18 of which were female (Coursimault et al., 2022). The study reports clinical observations and contributes to the characteristic dysmorphic features associated with MYT1L-syndrome, with features identified including almond-shaped eyes, a bulbous nose with slightly anteverted nostrils, and full and sagging cheeks. In relation to the neurodevelopmental profile of individuals, 71% of the cohort demonstrated motor delay, 81% fine motor delays, and 47% experienced hypotonia in childhood. Further, speech delay was present in most of the cohort (95%), with severe language delays meaning that the median age of the first spoken word was 2.3 years, and 5 years for first sentences. Of the 30 participants who were assessed for ID, 21 met the criteria,

5/21 (24%) were assessed as having mild ID, 9/21 (43%) moderate impairment, 4/21 (19%) severe impairment, and 3/21 (25%) had ID of unspecified severity. Regarding behaviour, all participants demonstrated behavioural disorders of varying severity; 43% had ASD, 45% exhibited self-harming behaviour including head banging, self-biting, and aggression to those around them, and 53% showed impulsivity behaviours. Additionally, ADHD was present in 37%, anxiety in 25%, and eating behaviour disorders in 45% of participants.

Only two published studies used standardised measures. Bonaglia, Giorda, & Zanini (2014) used the Leiter-R scale (Roid & Miller, 1997), identifying deficits in language comprehension and language production, and the Vineland Adaptive Behaviour Scales (Sparrow, Cicchetti, & Balla, 2005), which identified that at the age of 3 years old the individual demonstrated age equivalent scores of 1 years 7 months in receptive and expressive language, 1 year 11 months in socialisation, 2 years 2 months in daily living skills, and 2 years 9 months in motor skills. Further, the other case study found using the Wechsler Adult Intelligence Scale, 3rd Edition (Wechsler, 1997), that the participant aged 31-years-old had an IQ of 54, indicating mild intellectual disability (Sakaue et al., 2022).

Overall, the literature to date consistently presents the physical malformations associated with MYT1L-syndrome, which include hypotonia and obesity. Whilst not present in all of the studies identified, many suggest that individuals with MYT1L-syndrome may possess a predisposition to obesity. Delays reaching developmental milestones are also universally reported and include delays to unsupported sitting and walking, and speech delays in as many as 95% of individuals (Coursimault et al., 2022). Behavioural problems are also widely

reported and include varied characteristics, such as anxiety, repetitive behaviours, and problem behaviours including aggression and self-injury – which in some instances were associated with the removal or denial of food. The behavioural profile of individuals diagnosed with MYT1L-syndrome differs within and between the samples discussed in the papers identified. Similarly, there is also heterogeneity when considering associations between MYT1L-syndrome and NDCs including ID, ASD, hyperactivity, and ADHD. For instance, the incidence of ASD ranges from 23% to 43%, and the presence of ID ranges from 21% to 70% (Bouassida et al., 2022; Coursimault et al., 2022).

### 1.3.5. Limitations of previous research

Whilst the published literature does begin to define the cognitive and behavioural phenotype associated with MYT1L-syndrome, there are limitations. Firstly, most of the studies identified are single case studies, which does not allow for comparisons, or enable an understanding of the hetero- or homogeneity of symptoms. Further, only 2/18 studies, which reported on individuals, utilised standardised measures to assess the profile of individuals, allowing comparisons to normative data. Although this begins to ascertain, objectively, how individuals are affected, the findings of these studies are not necessarily generalisable to the wider population of individuals diagnosed with MYT1L-syndrome as they are both single case reports meaning it is difficult to ascertain the extent that the impact is related to the syndrome as opposed to individual differences. The remainder of the studies rely primarily on clinical records which often does not provide information on the level of impairment. Further, there is, at present, no published research that explores the cognitive and behavioural profile, or the caregiver or family impact, from the

perspective of a parent/caregiver. This is a key, and missing, element of the wider picture as caregivers provides a unique insight into the manifestation of syndromes given the proximity and consistent, longitudinal, exposure to affected individuals.

This thesis aims to overcome these limitations by conducting mixed-methods research, contributing to the evolving understanding of the phenotype associated with MYT1L-syndrome. The first empirical study, a qualitative interview study, will be conducted exploring a wide range of topics including the impact on cognition and behaviour, interactions with education and health providers, and on caregivers, siblings, and the wider family. The findings of this research will guide the standardised measures chosen as part of the quantitative study which will enable comparisons of the cognitive and behavioural profile to normative data and understand the variability of symptoms across the cohort.

### 1.4. Qualitative methodology

Multiple researchers have proposed that the topic of investigation should determine the methodology, rather than always utilising the methodology that is most widely accepted in research (Silverman, 2013). It is for this reason that qualitative methodology is commonly utilised to understand a person's lived experience. Qualitative research is an inductive approach that endeavours to achieve understanding and locate the meanings of events, processes, and assumptions (Pope, Van Royen & Baker, 2002). It is common for qualitative research to rely on semi-structured interviews with individuals/caregivers to understand their situation on a more in-depth level.

Qualitative research has previously been utilised in other rare genetic diseases to understand the lived experience of individuals and their caregivers, including Rett Syndrome, Duchenne Muscular Dystrophy and Huntington's Disease (Bendixen & Houtrow, 2017; Palacios-Ceña et al., 2019; Pelentsov et al., 2016). A search of the literature identified that multiple themes have previously been explored in other syndromes and resulted in meaningful interventions or educational opportunities in a plethora of sectors. The themes investigated included symptom onset (including diagnosis, managing care, and adjusting to having a child with a rare disease), individual impact (including behaviour, eating, and development), and the impact on family life (including the lived experience of parents/caregivers and siblings and factors such as financial implications). Given the paucity of research published about the impact of MYT1L-syndrome, conducting a qualitative interview study provides a critical opportunity to understand from caregivers how they and their child are most impacted, will allow cross-syndrome comparisons, and will enable the iterative design of the subsequent quantitative study based on key findings.

### 1.4.1. Analysing qualitative research

Whilst there are several approaches to analysing qualitative research, broadly there are two fundamental approaches: inductive and deductive. The research included in this thesis adopts an inductive approach which is the most common approach and enables methodological flexibility, and which does not rely on the application of any existing theory or framework, instead using the contents of the actual data to shape the analysis and the subsequent findings (Burnard et al., 2008; Liu, 2016). Conversely, the deductive approach involves the application of a pre-determined framework or theory, whereby the researcher

imposes their own theory on the data, and this informs the subsequent analysis (Williams, Bower, & Newton, 2004). There are multiple approaches to analysing qualitative data, which are outlined below.

#### 1.4.1.1. Thematic Analysis

Thematic analysis, or TA, is an approach to analysing qualitative data that enables the identification, analysis, and interpretation of patterns of meaning or themes, in relation to a research question, whereby a theme represents important patterns or meaning within the data (Braun & Clarke, 2006). TA provides systematic procedures for generating codes and themes from datasets, and has 6 key phases; 1) familiarising yourself with the data, which involves transcribing the data, reading and re-reading the data, 2) generating initial codes, through coding the interesting features and collating data that applies to each code, 3) searching for themes, or collating codes into broad groups, 4) reviewing themes, and checking that the themes represent the data, including the production of a thematic map, 5) defining and naming the themes, and 6) producing the report or presenting the analysis of the data. This approach enables researchers to identify and interpret important elements of qualitative data, guided by the initial research question.

#### 1.4.1.2. Other approaches to analysing qualitative data

In addition to TA, there are several other approaches to analysing qualitative datasets. Interpretative Phenomenological Analysis (IPA; Smith, Flowers, & Larkin, 2009) is an approach that focuses on how people make sense of, and perceive, their lived experience. The approach can be used to analyse small datasets or individual data. Whilst the ideal

sample size is of much debate, there is generally agreement that the approach is suitable when used with 6-8 participants. Further, it is recommended that the cohort has homogenous experiences, enabling the in-depth examination of certain phenomena (Pietkiewicz & Alan Smith, 2014; Alase, 2017). Another approach to analysing qualitative data is Grounded Theory (GT; Glaser & Strauss, 1967), which enables the study of a particular phenomenon and the subsequent discovery of new theories derived from the data. It is most appropriately used when there is no existing theory that provides a suitable explanation of the topic of study, or if there is an incomplete existing theory that can be contributed to. The application of GT to datasets is able to adapt to a diverse study phenomena but is noted to fail to recognise the influence of the researcher on the data analysis and requires a level of skilfulness to effectively apply the approach (Milliken, 2010; Bryant & Charmaz, 2007). A third approach to analysing qualitative data is Pattern-based Discourse Analysis (DA), which primarily investigates the functions of language and how meaning is constructed in different contexts and is most appropriately employed when investigating power or inequality, or how people communicate (Coyle, 2006; Coyle, 2007).

#### 1.4.1.3. Rationale for using thematic analysis

TA was deemed the most appropriate method to analyse the data resulting from the qualitative interview study for numerous reasons. The approach enables the analysis of a large dataset, and offers flexibility regarding dataset size, which is important as at the beginning of the research project there was uncertainty about how many participants may take part, given the rarity of the syndrome. As this is the first study, to the author's knowledge, exploring the parental/caregiver perspectives of MYT1L-syndrome, TA is

inductive in nature and can highlight similarities and differences across the dataset and allows the generation of unanticipated insights (Braun & Clarke, 2006). This was incredibly important when planning the qualitative research project as the findings were iterative and deployed a bottom-up approach based on the key findings from the data. Further, TA is considered appropriate for gaining insight into experiences, thoughts, and behaviours (Kiger & Varpio, 2020), all of which were key elements of the broad research question aiming to understand the impact of MYT1L-syndrome on multiple facets of life.

### 1.5. Quantitative methodology

Quantitative methods enable the exploration of phenomena through numeric patterns and are a way to understanding more about a population using data that are observed or measured to answer specific research questions (Ahmad et al., 2019). Quantitative research allows objective comparisons between and within groups using a variety of comparisons and statistical methods, and data is often collected using questionnaires, observations, and interviews (Goodman & Zhang, 2017). The standardised quantitative measures used in this research are outlined below and were chosen based on their routine use in research, including rare diseases (Salomon-Estebanez et al., 2017; Gergoudis et al., 2020; Selås & Helland, 2016), and to further explore the key themes identified in the qualitative research (including adaptive behaviour, ASD, anxiety, and communication).

### 1.5.1. Standardised quantitative measures

#### 1.5.1.1. Vineland Adaptive Behaviour Scale, Third Edition - Domain Level Parent/Caregiver Form (VABS-3)

Caregivers completed the domain level parent/caregiver form of the Vineland-III adaptive behaviour scale (VABS-3; Sparrow, Cicchetti, & Saulnier 2016). This is a standardised questionnaire used to measure adaptive behaviour and can be used from birth to 90 years old. Caregivers are asked to respond to items on a 3-point scale comprising 0 (never), 1 (sometimes), and 2 (usually or often). An overall level of adaptive functioning is calculated, called the ABC score, based on responses to the core 120-item scale. Domain-level scores for communication, daily living skills, and socialisation are also calculated and then compared to normative data, indicating levels of functioning compared to others in their age group. Lower scores within each domain indicate more impairment to adaptive behaviour, and scores <70 indicate potentially clinically significant impairment. The VABS-3 is a widely used measure of adaptive behaviour that has demonstrated reliability and validity (internal consistency reliability coefficient 0.94-0.99 and test-retest reliability 0.64-0.94; Pepperdine & McCrimmon, 2018). **Table 1.4** outlines the structure and content of the VABS-3 and provides examples of items within each domain.

| Adaptive behaviour composite (sum of domains) | Domain-level | Example items |
|---|---|---|
| | Communication | "Uses adjectives to describe things" |
| | | "Tells the basic parts of a well-known story" |
| | Daily living skills | "Puts on pullover clothing" |
| | | "Wipes up his/her spills" |
| | Socialisation | "Makes good eye contact" |
| | | "Is willing to compromise" |

***Table 1.4.*** *Content of the VABS-3, showing domains and example items*

#### 1.5.1.2. Social Responsiveness Scale, Second Edition (SRS-2)

The Social Responsiveness Scale, second edition (SRS-2; Constantino & Gruber, 2012) is a 65-item standardised questionnaire which is used to identify social impairments potentially associated with autism-spectrum disorders (ASD). Participants provide responses on a 4-point Likert-scale, where 1=not true, 2=sometimes true, 3=often true, and 4=almost always true. The measure generates scores for five subscales: social awareness (the ability to identify social cues), social cognition (the ability to interpret social cues), social communication (the ability to use expressive communication), social motivation (how motivated an individual is to engage in social behaviours), and restricted interests and repetitive behaviours (RRB; including highly restricted interests and stereotypical behaviours). A total score is computed (sum of all subscales), in addition to a composite score, called the social communication index (SCI), which is the sum of four of the treatment subscales (social awareness, social cognition, social communication, and social motivation). Two DSM-5 compatible subscales (SCI and RRB) enable the comparison of individual scores to DSM-5 diagnostic criteria for ASD and can be used to help determine whether individuals meet the current diagnostic criteria. Higher scores on the five subscales, SCI composite, and SRS-2 total score indicate an increased frequency of behaviours characteristic of ASD. Total scores can be converted into T-scores to provide an indication of how severe individual symptoms are, where scores categorised in the mild, moderate, or severe range suggest varying levels of impact on social interactions. Total scores on the SRS-2 have been found to successfully indicate individuals with ASD from non-ASD populations (Takei et al., 2014) and the measure shows good validity when used in populations with ASD, correlating with other measures of social behaviour (Chan et al.,

2017). The SRS-2 has strong internal consistency reliability in clinical (ASD) and non-clinical standardisation samples (*α*= 0.95 and 0.97, respectively), and has been validated against 'gold standard' ASD diagnostic measures including the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule (Charman et al., 2007; Constantino et al., 2003). Age-appropriate versions of the measure were used, where children aged 4 to 18 years old were assessed using the school-age form, and individuals aged over 18 years the adult form. Irrespective of the chosen version the questionnaire was completed by the parent/caregiver of each participant. **Table 1.5** presents the structure of the SRS-2 subscales and example items from each domain.

| | **Treatment subscale** | **Example items** |
|---|---|---|
| **SRS-2 total score (sum of treatment subscales)** | Social awareness | "Is aware of what others are thinking" |
| | | "…react to people as if they are objects" |
| | Social cognition | "Concentrates too much on parts of things" |
| | | "Has a sense of humour" |
| | Social communication | "Isolative; tends not to leave… home" |
| | | "Is emotionally distant" |
| | Social motivation | "Is too tense in social settings" |
| | | "Stares or gazes off into space" |
| | Restricted interests and repetitive behaviours | "Touches or greets others in an unusual way" |
| | | "Has repetitive, odd behaviours" |

***Table 1.5.*** *Structure of the SRS-2, showing subscales and example items*

#### 1.5.1.3. Short Sensory Profile 2 (SSP-2)

Caregivers completed the Short Sensory Profile 2 (SSP-2; Dunn, 2014), which is a 34-item questionnaire designed to measure sensory processing patterns in children aged 3.0-14.11 years. Respondents are asked to score, on a Likert scale ranging from 1 (when presented with the opportunity my child *almost never* responds in this manner" to 5 (when presented

with the opportunity my child *almost always* responds in this manner". Raw scores are computed for each of the four quadrants of sensory processing in line with Dunn's framework. The four quadrants are described in more detail in **Table 1.6**, alongside example items.

| **Sensory processing quadrant** | **Definition** | **Example item** |
|---|---|---|
| Seeking | The degree to which a child *obtains* a sensory input | "touches people and objects more than same-aged children" |
| Avoiding | The degree to which a child is *bothered by* sensory input | "is distressed by changes in plans, routines, or expectations" |
| Sensitivity | The degree to which a child *detects* sensory input | "looks away from tasks to notice all actions in the room" |
| Registration | The degree to which a child *misses* sensory input | "seems oblivious within an active environment (for example, unaware of activity)" |

***Table 1.6.*** *Structure of the SSP-2, showing quadrant definitions, and example items*

Using a Normal Curve and Sensory Profile 2 Classification System provided by Dunn and developed based on a large normative sample of typically developing children ($n = 697$), the raw scores for each quadrant can be categorised based on a bell curve normal distribution. Scores can be classified as being "Much less", "Less", "Just like", "More", and "Much more" than the majority of others. Those who are categorised as "Much less" or "Less" are between 1*SD* and 2*SD* below the mean, "Just like the majority of others" are $\pm$1*SD* away

from the mean and account for 68% of the normative sample, and "More than others" and "Much more than others" are 1*SD* to 2*SD* above the mean. Test-retest reliability (0.80-0.90) and internal consistency (*a*= 0.89-0.95) is good across quadrant scores, indicating that the measure has acceptable test-retest reliability and internal consistency (Ohl et al., 2012). The SSP-2 is a widely used measure to determine sensory processing impairments and has been deemed a valid measure with useful applications in children with ASD (Bak, Yoo, & Hong, 2020).

#### 1.5.1.4. Conners 3 ADHD Scale

The Conners 3 ADHD scale – Parent Short (Conners 3; Conners, 2008) is a 43-item measure for use in children aged 6-18 years that assesses attention deficit hyperactivity disorder and the most common co-occurring disorders. Caregivers rate items on a scale ranging from 0 (Not at all true [Never or Seldom]) to 3 (Very much true [Very often or Very frequently]). The scale provides scores for six domains: Inattention (e.g., has trouble concentrating), Hyperactivity/Impulsivity (e.g., is excitable and impulsive), Learning Problems (e.g., cannot grasp arithmetic), Executive Functioning (e.g., forgets to turn in completed work), Defiance/Aggression (e.g., starts fights with others on purpose), and Peer Relations (e.g., is one of the last to be picked for teams or games). Following the calculation of raw scores, standard scores are computed, where a higher score indicates a higher frequency of reported concerns. A score of $\geq$60 is interpreted as an elevated score from the average and may be indicative of ADHD, and a score of $\geq$70 is interpreted as a very elevated score and indicates that ADHD symptoms are more serious. The Conners 3 has been found to be a valid and reliable tool to assess ADHD (internal consistency reliability coefficient, 0.77-0.97

and test-retest reliability coefficient, 0.71-0.98) and is widely used in clinical practice (Izzo et al., 2019).

#### 1.5.1.5. Spence Children's Anxiety Scale - Parent Version (SCAS-P)

The Spence Anxiety Scale – Parent Version (SCAS-P; Spence, 1999) is a 38-item measure for use in 6–18-year-olds that measures anxiety. Caregivers are asked to rate each item on a 4-point scale from 0 (Never) to 3 (Always). The measure provides an overall anxiety score, alongside six domain-level scores of separation anxiety (e.g., would feel scared if s/he had to stay away from home overnight), social phobia (e.g., feels afraid when s/he has to talk in front of the class), generalised anxiety (e.g., worries that something bad will happen to him/her), panic/agoraphobia (e.g., complains of feeling suddenly as if s/he can't breathe when there is no reason), physical injury fears (e.g., scared of going to the doctor or dentist), and obsessive compulsive disorder (e.g., has to do some things over and over again, like washing hands or putting things in a certain order). All items are summed to create a total score with a maximum value of 114, where higher scores reflect increased symptom severity. The SCAS-P has been demonstrated to have good convergent and divergent validity and is considered a useful measure to assess anxiety symptoms (Li et al., 2016). Internal consistency ($a$= 0.86-0.93) and test-retest reliability (0.53-0.88) of the SCAS-P were also found to be good (Ramme, 2008).

#### 1.5.1.6. Children's Communication Checklist (CCC-2)

The Children's Communication Checklist (CCC-2) is a standardised questionnaire designed to assess the communication skills of children 4.0 to 16.11 years of age (Bishop, 2006).

Caregivers are asked to indicate, on each of the 70-items, the frequency in which their child shows certain behaviours relating to communication on a 4-point scale comprising 0 (less than once a week or never), 1 (at least once a week, but not every day), 2 (once or twice a day), and 3 (several times [more than twice] a day [or always]). The measure is divided into 10 scales, each containing 7-items, each with an average scaled score of 10 and a *SD* of 3 (see **Table 1.7** for further details on the subscales, and example items from each).

| **Domain measured** | **Subscale** | **Example items** |
|---|---|---|
| Speech and structural language | A. Speech | "Pronounces words in a babyish way" |
| | B. Syntax | "Gets mixed up between he and she" |
| | C. Semantics | "Forgets words s/he knows" |
| | D. Coherence | "Gets the sequence of events muddled up" |
| Pragmatic language | E. Inappropriate initiation | "Talks to people too readily" |
| | F. Stereotyped language | "Repeats back what others have said" |
| | G. Use of context | "Misses the point of jokes and puns" |
| Autistic features | H. Non-verbal communication | "Stands too close to other people" |
| | I. Social relations | "Is left out of joint activities" |
| | J. Interests | "Talks about lists of things memorised" |

***Table 1.7.*** *Subscales of the CCC-2, and example items*

In addition to subscale scores, a General Communication Composite (GCC) score indicates an overall ability to communicate, where scores <55 indicate significant communication difficulties. Composite scores for Language Structure and Pragmatic Language can also be calculated, where scores >24 indicate typical functioning, 17-24 indicate borderline functioning, and <17 indicate impaired functioning. The measure has been found to possess a good internal consistency reliability coefficient ($\alpha$= 0.65 or more for all scales) and test-retest reliability coefficient ($\alpha$= 0.85). The CCC-2 has demonstrated a specificity value of .97

and a sensitivity value of .89 for identifying children with pragmatic social impairment (Bishop, 2006).

### 1.6. Thesis overview

This thesis presents a novel investigation of the cognitive and behavioural profile of MYT1L-syndrome. The second chapter presents a systematic review exploring the cognitive and behavioural profile of other rare genetic syndromes implicated in the same pathway as MYT1L-syndrome. Alongside presenting the key findings of these studies, the review also draws conclusions about the utilisation of standardised outcome measures. Next, chapters three and four outline two analyses carried out on the qualitative interview data collected from the parents/caregivers of affected children. This focuses initially on the cognitive and behaviour profile of individuals, from the perspective of a caregiver, and then focuses on the impact on family life, including caregivers, siblings, and the wider family. Based on the utilisation of standardised measures examined through the systematic review and problem areas highlighted by caregivers during the primary qualitative research, the fifth chapter is a quantitative study utilising standardised assessments of anxiety, social responsiveness, adaptive behaviour, communication, sensory processing, and ADHD to understand objectively how levels of impairment in the cohort differ from typically developing individuals. The results of these studies will inform future research, influence support packages for affected individuals and their families, and inform healthcare professionals and educators involved in the care of individuals about the syndrome and empower them to provide better support and appropriate interventions. This thesis is the first

comprehensive investigation in MYT1L-syndrome undertaking a mixed-methods approach to understand more about the cognitive and behavioural profile of affected individuals.

# Chapter 2: The cognitive and behavioural phenotype of children with genetic disorders affecting chromatin remodelling: a systematic review

## 2.1. Introduction

Given the paucity of research investigating the cognitive and behavioural phenotype associated with MYT1L-syndrome, it is appropriate to look to the literature published on other genetic disorders along the same pathway as MYT1L-syndrome to ascertain the phenotype associated with those syndromes. Additionally, the findings will enable the examination of the utilisation of standardised empirical measures in the published research, informing the design and execution of the primary research discussed in this thesis. It is also important to understand the cognitive and behavioural profile of neurodevelopmental conditions to effectively implement appropriate, domain specific, interventions, for example within education, according to relative strengths and weaknesses to hopefully improve outcomes.

This systematic review will identify the most relevant literature published which investigates the cognitive and behavioural profile of disorders implicated in chromatin remodelling using standardised, empirical, outcome measures. The review will then discuss and critically appraise the findings. It is appropriate to examine the literature assessing the cognitive and behavioural phenotype of other genetic disorders involved in chromatin remodelling, as there is evidence that alterations to chromatin remodelers contribute to the presence of NDCs (Iwase et al., 2017). There are associations between alterations to genes involved in chromatin remodelling and NDCs, with observations of ID,

speech impairments, ASD symptomatology, and developmental delay reported as part of the clinical phenotypes associated with affected genes, including CHD7, CHD8, EHMT1 and KMT2D (Mossink et al., 2020; Gabriele et al., 2018). As the MYT1L gene also plays a role in chromatin remodelling, it may be expected that individuals with alterations to the gene will also present with NDCs, as observed in other genetic disorders affecting the same pathway. There are, to the author's knowledge, currently no published systematic reviews that explore the cognitive and/or behaviour profile of genetic disorders implicated in chromatin remodelling. In addition, the review will report the most widely used standardised measures of assessment in relation to cognitive and/or behavioural profiles.

### 2.2. Methods

The protocol of this systematic review was pre-registered and is available on the PROSPERO website at the link **https://www.crd.york.ac.uk/prospero/** (last accessed in February 2023), and whose registration number is CRD42020216463. This systematic literature review was conducted in line with the PRISMA guidelines for systematic reviews (Moher et al., 2009).

#### 2.2.1. Selection of genetic disorders

To select appropriate genetic disorders to focus the literature search, those implicated in the same pathway as MYT1L-syndrome, chromatin remodelling, were identified through a literature review exploring associations between chromatin remodelers and neurodevelopmental conditions conducted by Mossink et al. (2021). Following the identification of disorders implicated in the pathway, scoping searches were conducted to

confirm which appeared common enough to have published literature pertaining to the cognitive and behavioural profile of affected individuals. Following these searches five disorders were selected, CHARGE syndrome; CHD8 syndrome; Kabuki syndrome; Kleefstra syndrome; and KBG syndrome, each of which are described below.

#### 2.2.1.1. CHARGE Syndrome

Most individuals diagnosed with CHARGE syndrome possess mutations within the CHD7 gene, and the term 'CHARGE' is an acronym describing the cardinal features of the syndrome: Coloboma, Heart defects, choanal Atresia, Retardation (of growth and/or development), Genitourinary malformation, and Ear abnormalities (Vissers et al., 2004; Pagon et al., 1981). The incidence of CHARGE in the population is estimated to be between 0.1-1.2/10,000 live births (Blake & Prasad, 2006). In addition to the physical malformations which are characteristic of CHARGE syndrome, there are also numerous cognitive and behavioural symptoms associated including intellectual disability, aggressive behaviour, sleep difficulties, and self-injurious behaviour (Thomas et al., 2022).

#### 2.2.1.2. CHD8 Syndrome

CHD8 syndrome is a NDC associated with generalised overgrowth, ASD, neuropsychiatric issues, neurologic problems, gastrointestinal issues, and developmental delay/intellectual disability (Yasin et al., 2019). Microscopic deletions on the CHD8 gene at chromosome 14q11.2 were first associated with ID and ASD in 2007, following the description of three affected individuals (Zahir et al., 2007). The syndrome is thought to have an incidence of somewhere in the region of 7.53 per 100,000 births (Lemke, 2020).

#### 2.2.1.3. Kabuki Syndrome

Initially recognised as describing a cohort of individuals with characteristic facial features, short stature, skeletal anomalies, and mental retardation, Kabuki syndrome is a rare genetic syndrome thought to affect 1 in 32,000 individuals (Niikawa et al., 1981; Kuroki et al., 1981; Cheon & Ko, 2015). The most notable features of Kabuki syndrome are the associated facial features, which is usually the symptom prompting further clinical investigation, including arched eyebrows, depressed nasal tip, and prominent ears (Adam & Hudgins, 2004).

#### 2.2.1.4. Kleefstra Syndrome

Kleefstra syndrome is diagnosed by a deletion at chromosome 9q34.3 that includes at least part of EHMT1 or a heterozygous intragenic EHMT1 pathogenic variant (Harada et al., 2004; Kleefstra & de Leeuw, 1993). The core features of the syndrome include developmental delay, language delay, hypotonia, obesity, and behavioural and sleep problems (Kleefstra et al., 2009; Stewart and Kleefstra, 2007). Although thought to be an underestimate of the actual number of affected individuals, 1 in 120,000 is the suggested incidence rate of the syndrome (Huang et al., 2021).

#### 2.2.1.5. KBG Syndrome

Characterised by developmental delay and intellectual disability, skeletal abnormalities, postnatal short stature, and craniofacial anomalies, KBG syndrome is an autosomal dominant disorder resulting from heterozygous loss of function mutations or deletions of

the ANKRD11 gene at chromosome 16q24.3 (Gnazzo et al., 2020; Sirmaci et al., 2011). Named after the last initials of the first three families described, KBG syndrome was first described in 1975 and diagnosis was dependent on numerous features including mental retardation, however subsequent research has identified that KBG syndrome has a characteristic cognitive and behavioural profile including ID, impairments to communication skills, and anxious traits (Herrmann et al., 1975; Lo-Castro et al., 2013).

### 2.2.2. Search strategy

Initially, to develop the search strategy for this review, domains of cognition and behaviour that could potentially be impacted by the selected genetic conditions were formulated, and subsequently relevant key words were identified. The initial search strategy was checked, amended, and validated against those used within numerous systematic reviews investigating the published literature on the cognitive and behavioural phenotypes in other health conditions (Ferrero & Rossi, 2022; Hronis, Roberts, & Kneebone, 2017; Ben-Pazi, Jaworowski, & Shalev, 2011; Lehtonen et al., 2013).

Search terms (**Table 2.1**) were input into the following electronic databases: Ovid MEDLINE, PubMed, PsycInfo, Science Direct, and Web of Science. In addition to conducting a search of computerised databases, the content pages of high-impact factor journals that notably publish articles relating to neurodevelopment, genetic disorders, or intellectual disability were searched including: Journal of Intellectual Disability Research, Child Neuropsychology, American Journal of Medical Genetics, Frontiers in Behavioral Neuroscience, and Journal of Psychopathology and Clinical Science. To identify

unpublished materials or grey literature, a search of OpenGrey was also conducted. Individual searches were conducted for each genetic syndrome, meaning multiple searches were conducted. Different variants and identifiers of each genetic syndrome were included in the hope that this would enable a robust and thorough search of the literature. Initially, the term 'CHARGE' was used to identify publications relating to CHARGE syndrome, however the broadness of this term resulted in >40,000 results, therefore the decision was made to use the term "CHARGE syndrome" to limit the number of results.

| **Search terms used** |
| --- |
| *Behaviour/cognition terms:* autis* OR adhd OR psychosis OR dcd OR conduct OR motor OR action OR dyslexia OR dyspraxia OR dyscalculia OR anx* OR mood OR emotion OR behavio* OR intelligence OR iq OR mental OR "Pervasive Developmental Disorder" OR "intellectual disability" OR cogniti* OR verbal OR language OR performance OR attention OR memory OR "executive function" OR "problem solving" OR logic OR mathematic OR apraxia OR development* OR milestones OR speech OR communication OR *motor<br>AND<br>*Genetic disorder terms:* "CHARGE syndrome" OR CHD7 OR CHD8 OR 14q11.2 OR kabuki OR kdm6a OR kmt2d OR kleefstra OR ehmt1 OR 9q* OR "KBG syndrome" OR ankrd11 |

***Table 2.1.*** *Search terms used in the systematic review literature search*

*, are wildcard searches

### 2.2.3. Inclusion criteria

#### 2.2.3.1. Participants

Only papers that reported on people with a genetically confirmed diagnosis of the genetic disorder of interest, or where a clinician had officially diagnosed the individual, were included. There was no minimum or maximum age of participants. If a paper reported on a mixed sample, reporting on additional genetic disorders to just the one of interest, it was excluded unless it was possible to extract only the findings pertaining to the population of interest. Any study that explicitly reported on participants with multiple diagnoses or life-altering illness was excluded, as it could not be determined what impairments were potentially associated with the syndrome of interest.

#### 2.2.3.2. Study design

Due to time constraints only papers that were published, or had translated versions available, in English were included. Only studies that were cohort or population studies were included, and studies such as descriptive single clinical case reports were excluded. Single case reports were excluded for the systematic review as the findings provided by such studies may not be generalisable to the wider population(s) of interest, are based on a subjective clinical perspective as opposed to a standardised method of assessment, and therefore may possess a consequent risk of over-interpretation. The paper also had to demonstrate that primary research had been undertaken exploring cognition and/or behaviour in the genetic disorder of interest. Where studies had recruited from an already established population of participants (such as the Deciphering Developmental Disorders project) they were included as they are robust, and recognised, databases, and given the

difficulties researchers may face accessing sufficiently sized samples given the rarity of the genetic disorders of interest. The outcome of the study had to be focussed on extending understanding of the cognitive and/or behavioural profile of the genetic disorder of interest, although it did not matter which domain(s) the study focussed on in these areas. Only papers that utilised standardised, quantitative, measures to assess these domains were included, and clinical observations or retrospective analyses of health records were not included. Papers outlining both researcher/clinician reports and parent/caregiver proxy reports were deemed appropriate to include in the review. Empirical quantitative evidence was also sought as an additional aim of the systematic review was to assess the utility of quantitative standardised measures in rare disease populations, informing the design of the primary quantitative research discussed in Chapter 5 of this thesis.

### 2.2.4. Data extraction

Following the literature search, and the application of the inclusion criteria, any duplicated papers across the online electronic databases were removed. The studies remaining were scanned and any titles seemingly relevant to the research question were identified and included in the next stage of screening. The abstracts of selected papers were then read, and the full-text was obtained for those deemed relevant, after this the full-text was read to assess eligibility for inclusion in the systematic review based on the set inclusion criteria.

### 2.2.5. Quality Checklist

The 'Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields' (Kmet, Cook, & Lee, 2004) was used to assess the quality of the included

studies in relation to the research question, study design, sampling strategy, data analysis, and reporting of the findings. The checklist was chosen for use in this systematic review as it is designed for use with quantitative studies, and provides a reproducible and systematic means of assessing the quality of study designs. Further, it has been shown to be effective in assessing the quality of papers chosen for inclusion in numerous other systematic reviews across varying health conditions (Radez et al., 2021; Reardon et al., 2017), including a review of the cognitive and behavioural profile associated with Sotos syndrome (Lane, Milne, & Freeth, 2016). This review only sought to include quantitative studies containing empirical data from standardised methods of assessment, and therefore research adopting qualitative methodology were not included. Therefore, only the quantitative elements of the quality checklist were applied. The assessment tool contains 14 questions; however, items 5-7 of the tool were removed as this systematic review did not seek to include intervention studies, so they were not applicable. Intervention studies were not included in the systematic review as the research question did not seek to understand the efficacy of a certain intervention, and instead hoped to ascertain an understanding of the cognitive and behavioural profile associated with the genetic syndromes of interest. Each item of the checklist was scored against the criteria of 2 - indicating that the item is fully met, 1 – partially met, or 0 – not met or not applicable, where the highest possible score was 22. Where papers reported on other domains of impairment, the quality assessment criteria were only applied to information pertinent to the cognitive and behavioural phenotype, the topic of interest for this review. There were no quality criteria for inclusion within the systematic review, and therefore papers were included irrespective of the quality score. All papers meeting the inclusion criteria were included as there is a paucity of research

investigating the cognitive and behavioural impact of the rare genetic syndromes of interest, and including all relevant published literature was deemed appropriate to understand the current evidence-base. Despite the inclusion of papers, assessing the quality was considered important as other systematic reviews investigating rare genetic syndromes have previously highlighted the varying levels of quality across the published literature (Lane et al., 2016).

## 2.3. Results

### 2.3.1. Outline of Selection Process

A summary of the process to screen the published literature is outlined in **Figure 2.1**. A total of 7484 papers identified through the selected electronic databases and other searches were reduced to 7297 once any duplicates were removed. Based on relevance to the research question, 140 titles were selected, which led to the inclusion of 48 of those based on deeming the content included in the abstract suitable. 22 of those papers were removed following a review of the full-text article; 15 did not use a standardised measure to assess cognitive/behavioural characteristics, 3 did not report that the participants included had a genetically confirmed diagnosis and 3 did not report the results in a manner that enabled the identification of data focused only on the genetic disorders of interest, and the final paper was not available in English. One additional paper was identified through a search of the bibliographies of the selected texts. Therefore, 26 of the papers identified were included in this review. **Table 2.2** outlines the process to screen and narrow down the published literature on each of the selected genetic disorders to the reviewed papers, split into individual summaries per the genetic disorders of interest.

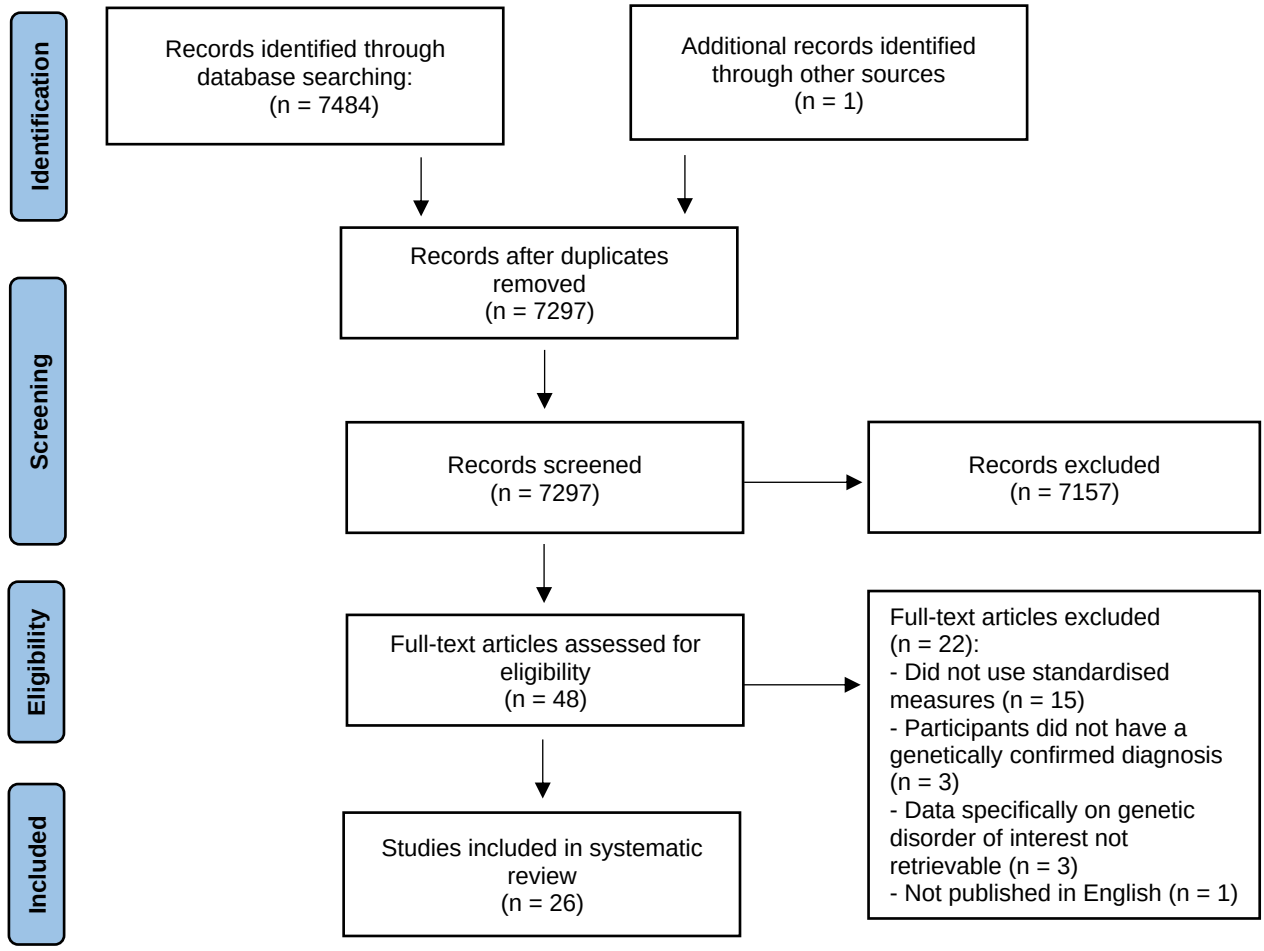


***Figure 2.1.*** *PRISMA diagram outlining search strategy and study inclusion*

| Syndrome/Search Strategy | Records identified through initial database search with filters applied | Records after duplicates removed | Titles selected | Abstracts selected | Papers selected |
|---|---|---|---|---|---|
| *Behaviour/cognition terms* AND **"CHARGE syndrome"** OR **CHD7** | 2821 | 2772 | 33 | 17 | 11 |
| *Behaviour/cognition terms* AND **CHD8** OR **14q11.2** | 258 | 244 | 11 | 3 | 2 |
| *Behaviour/cognition terms* AND **kabuki** OR **kmt2d** OR **kdm6a** | 2202 | 2150 | 39 | 13 | 7 |
| *Behaviour/cognition terms* AND **"KBG syndrome"** OR **ankrd11** | 225 | 181 | 36 | 8 | 4 |
| *Behaviour/cognition terms* AND **kleefstra** OR **ehmt1** OR **9q*** | 1978 | 1950 | 21 | 7 | 2 |
| ***Total*** | **7484** | **7297** | **140** | **48** | **26** |

**Table 2.2.** Outline of the systematic review search strategy and study inclusion per genetic syndrome

### 2.3.2. Summary tables of findings

**Table 2.3** presents a summary of the 26 papers included in this review. This includes information about the year and country of study, participant demographics such as sample size, gender split, and mean age and range. It also outlines the assessment(s) used to assess the cognitive and/or behavioural profile of affected individuals, key findings, and the quality score. A summary of the domain(s) of interest, per study, is outlined in **Table 2.4**.

| Author, country of study, year of publication | Sample size (n) | Gender | Mean age, in years, months (range) | Assessment(s) used | Findings | Quality score (0-22) |
|---|---|---|---|---|---|---|
| **CHARGE syndrome** | | | | | | |
| Abadie et al., France, (2020) | 64 | 29 (M), 35 (F) | 10y 7m (9m-30y) | • ADI-R (Rutter, Lord, & Le Couteur, 2003): semi-structured parent interview investigating autistic behaviours<br>• Developmental behaviour checklist-parents (DBC-P; Einfeld et al., 2002): 96-item parental questionnaire assessing behaviour problems<br>• Vineland adaptive behaviour scale (VABS-II; Sparrow, Cicchetti, & Balla, 2005): adaptive functioning<br>• Dunn's sensory profile (Dunn, 1997): 125-item measure investigating sensory profiles | • Sensory profile: 72% of individuals had more particularities related to emotions and endurance than normal, 65% had sensory hyporeactivity, 51.3% more active and restless than normal<br>• Adaptive behaviour: 70% had mild or moderate impaired adaptive functioning, and 16% had severely impaired adaptive functioning<br>• ASD: 54% had a strict diagnosis of ASD in line with the DSM-5, 89% had positive results for at least one criterion in the DSM-5 domains. At age 5, 28% had exceeded the cut-offs in all three domains and might have a diagnosis of autism<br>• Behaviour problems: 20% had mild behavioural disorder and 35% had major behavioural disorders | 19/22 |
| Graham et al., USA, (2005) | 14 | 14 (M) | 12y 4m (6y-21y) | • Child Behaviour Checklist (CBCL; Achenbach, 1991): affective problems, attention-deficit/hyperactivity, anxiety, oppositional defiance, somatic problems, and conduct problems | • Behaviour: CS showed fewer internalising behaviours and were less anxious and withdrawn compared to PWS. Individuals with CS and PWS were more withdrawn. Scores for externalising behaviours (aggressiveness) were similar for CS, DS | 12/22 |

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| | | | | • Aberrant Behaviour Checklist (ABC; Aman & Singh, 1986): psychiatric symptoms and behavioural disturbance<br>• Reiss Personality Profiles (Reiss & Havercamp, 1998): test of motivation and influence | and WS - and significantly lower than those for PWS. CS did not show an increased risk of aggression and appeared at low risk for maladaptive behaviours<br>• Aberrant behaviour: CS individuals scored highest on irritability and hyperactivity, with moderately high scores on social withdrawal and stereotypic behaviours<br>• Personality: CS scored lower than DS, PWS and WS on social contact and the same as PWS on frustration, more than WS and DS. PWS and WS are more likely to seek attention than CS. PWS demonstrated the most interest in food, followed by CS, WS and DS. CS most interested in maintaining order, followed by PWS, DS and WS | |
| Lasserre, Vaivre-Douret, & Abadie, France, (2013) | 8 | 7 (M), 1 (F) | 9y 8m (7y-13y) | • K-ABC (Kaufman & Kaufman, 1993): hand movement subtest - testing short-term memory<br>• Wechsler Intelligence Scale for Children (WISC; Wechsler, 1992): number repetition subtest - testing short-term memory<br>• NEPSY (Korkman, Kirk, & Kemp, 1997): phrase repetition subtest, tower test, visual attention subtest, | • WISC: Broad range of IQs from 54 to 92, 48 to 96 for verbal IQ and 59 to 94 for performance IQ. Lowest median score was from nonverbal tests<br>• Most children had difficulties on the hand-moving subtest of K-ABC, the same 6 children had severe difficulties on the WISC number-memory subtest<br>• NEPSY 'phrase repetition': all children had difficulty with long-phrases - failure due to inaccuracies in vocabulary and forgetfulness | 14/22 |

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| | | | | narrative memory sub-test - testing short-term memory and logical reasoning, planning skills and selective attention | • NEPSY 'tower test': 7 children scored above average. Most found new procedures that break established habits difficult because of impulsivity<br>• NEPSY 'visual attention': tests were good for all children, although complex items (with several criteria), 6 children had poor results<br>• NEPSY 'narrative memory': 2 children had severe difficulty in repeating by memory, in order, the sequences of the story | |
| Hartshorne & Jacob, USA, (2005) | 85 | 41 (M), 44 (F) | 12y 5m (8y-20y) | • Adaptive behaviour quotient (ABES; McCarney, 1995): measure of adaptive behaviour | • Adaptive behaviour: mean score 71.9 (n=80) (scores below 85 are considered to be in the impaired range for adaptive behaviour skills)<br>• Most common score was 55, falling within the "below normal" range (70 or below). Highest score was 107<br>• 50% of n scored above 70, 13% of n above 90 | 20/22 |
| Hartshorne et al., USA, (2005) | 160 | 85 (M), 75 (F) | 10y 9m (3y-33y) | • Autism Behaviour Checklist (ABC; Krug, Arick, & Almond, 1993): 57-item, score of 68 and above are considered indicative of autism | • Autism behaviours: Total score obtained for children with CHARGE was 48.5, lower than the autistic norms but higher than the norm for deafblind individuals<br>• Average score for CHARGE fell between that expected from those with autism and norm scores for people who were deafblind, as predicted<br>• Standard deviation for CHARGE was considerably greater than for other | 19/22 |

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| | | | | | groups, indicated children with CHARGE are extremely variable in their behaviour (scores ranged from 0-81)<br>• Using the ABC cut-off score for classification as autistic, 27.5% of the cohort could be classified as autistic<br>• Highest average score was 59, from children in the youngest age group (also smallest group - finding may be due to a sampling error) | |
| Hartshorne et al., USA, (2007) | 98 | 58 (M), 40 (F) | 10y 6m (5y-18y) | • Behaviour rating inventory of executive function (BRIEF; Gioia et al., 2000) - parent version: assessment of executive functioning (scores of 65 or higher considered potentially clinically significant)<br>• Autism Behaviour Checklist (ABC; Krug, Arick, & Almond, 1993): component of the Autism Screening Instrument | • Executive function: of the 10 scales of the BRIEF assessment, the mean score of Shift was the only scale that reached clinical significance, followed by the mean scores of Inhibit and Monitor which were both over 64, but under the clinical significance threshold of 65<br>• Except for the Organisation of Materials scale, when scores in the CHARGE cohort were compared to the standardised mean of 50 all scales were significantly different<br>• More than half of the sample achieved a score of over 65 on Shift, Monitor, and the Behavioural Regulation Index<br>• For most scales, the majority of the sample did not achieve clinically significant scores<br>• As age of walking increases, scores on the BRIEF were found to be more clinically significant | 15/22 |

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| | | | | | • Whilst not a strong predictor, high ABC scores were found to be a predictor of a clinically significant score on the BRIEF assessment | |
| Johansson et al., Sweden, (2005) | 31 | 15 (M), 16(F) | 8y 11m (1m-31y) | • Wechsler Intelligence Scale for Children (WISC; Wechsler, 1992): intelligence<br>• Vineland Adaptive Behaviour Scales (VABS; Sparrow, Cicchetti, & Balla, 1984): adaptive behaviour<br>• Autistic Behaviour Checklist (ABC; Krug, Alrick, & Almond, 1980), and the Childhood Autism Rating Scale (Schopler et al., 1980): autism behaviours | • Intelligence (assessed in 28 individuals): 22/28 had impaired intellectual disability seemingly associated with a learning disability – 3 of these had severe learning disabilities, and 10 had mild. 6/28 had intelligence in the normal range<br>• Adaptive behaviour: 3 individuals demonstrated impairments in social interaction, communication, or behaviour. 2/3 also demonstrated vocal and/or motor tics<br>• ASD (assess in 25 individuals): 5/25 met the diagnostic criteria for ASD, 5/25 for an autistic-like condition, and 7/25 demonstrated autistic traits<br>• Problem behaviour: self-injury corelated to severity of ASD ($p$<0.05). Hyperactivity was significantly correlated with severity of intellectual disability, but not severity of ASD ($p$<0.05). Impulse control, aggressive behaviour, and attention deficit traits were common but not correlated with either severity of ASD or ID | 16/22 |
| Santoro et al., Italy, (2014) | 35 | 17 (M), 18 (F) | Not reported (5m-33y) | • “Progress guide”, consisting of 10 domains: gross-motor skills, fine-motor skills, | • Developmental delay (DD): 100% of participants scored within the | 13/22 |

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| | | | | cognitive skills, socialisation and play, self-care (feeding, washing, dressing, sphincter toileting), communication, and expressive skills | boundary indicative of developmental delay<br>• In all domains, the median age-equivalent score was lower than the chronological age<br>• Participants aged ≥3 exhibited the greatest levels of DD, compared to those aged ≤3, and median age-equivalent scores in all domains was significantly lower than the median chronological age<br>• Feeding, dressing, toileting, and communication had median quotients of 30% of the normal development; with others at about 50%, and washing was the most developed with a median score of over 75%.<br>• Washing abilities were significantly higher than eating, dressing, sphincter control, and communication abilities<br>• Expressive skills appear to be preserved in the cohort | |
| Smith et al., Canada, (2005) | 13 | 8 (M), 5 (F) | 9y (2y-24y) | • Child Development Inventory (CDI; Kovacs, 1992): 300-item parent completed questionnaire assessing developmental functioning<br>• Behaviour Assessment System for Children (BASC; Reynolds & Kamphaus, 1998): parent-rated tool collecting information on behaviours | • Developmental functioning: participants exhibited relative strengths were exhibited in fine motor skills (mean = 65), but gross motor skills scores were weaker (mean = 35). 3/13 demonstrated relative strengths, but most exhibited global development impairment<br>• Scores on the General Development, Expressive Language, Language | 17/22 |

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| | | | | displayed in the previous 6 months<br>• Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2003): 40-item assessment derived from the ADI-R; purpose is to identify those likely to meet the criteria for autism<br>• Vineland Adaptive Behaviour Scales (VABS; Sparrow, Cicchetti, & Balla, 1984) – interview edition, survey form: measure of adaptive functioning | Comprehension, and Gross Motor scales were all 3SD or more below the standardised mean. Similarly for 12/13 on the Self-help scale<br>• 4/13 individuals received average scores, and 6/13 scored 1.5SD below the mean on the Social Development or Fine Motor scales, indicating relative strengths in these areas<br>• Behaviour: Scores on the Social Skills domain were overall below average, but there was variability in scores, whereas mean scores on other domains (Internalising and Externalising, Behavioural Symptoms Index, and Adaptability) were average<br>• Social communication: 6/13 demonstrated moderate to strong evidence of ASD, and 5/13 exhibited some evidence of ASD<br>• Adaptive behaviour: Adaptive Behaviour Composite (ABC) scores ranged from ≤20-68 (mean = 50), with most scores indicating adaptive behaviour impairment | |
| Souriau et al., Canada, (2005) | 71 | Not reported | 8y 1m (6m-30y) | • Pilot of newly developed questionnaire: assessing perception, motor skills, eating/feeding, independence, behaviour, social relationships, | • 38 (54%) of the sample exhibited behaviours considered hyperactive, including being permanently on the move<br>• 3/71 (4%) were reported capable of waiting for their turn to speak – | 16/22 |

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| | | | | communication, and cognitive skills | potentially indicative of a dual sensory impairment<br>• Understanding and using social rules was reported challenging for 27 (38% of the sample<br>• Anxiety was reported to affect 22 children, where a significant relationship was found between anxiety and depression<br>• Some children (11/71) found some noises painful, but most did not (45/71)<br>• 59% of the cohort were reported unable to cope with complex information and needed time and repetition | |
| Vesseur et al., Netherlands, (2016) | 50 | 32 (M), 18 (F) | 10y 5m (1y-56y) | • Bayley Scale of Infant Development – Dutch version (BSID-NL-II; Bayley, 1993)<br>• Wechsler Intelligence Scale for Children – Revised and Third Edition (WISC-RN and WISC-III-NL; Kort et al., 2005)<br>• Reynell Developmental Language Scales (Reynell & Gruber, 1990)– Dutch version | • Intelligence (data available for n= 41): 24/41 scored low IQ (<70), 8 subnormal (IQ = 70-85), and 9 normal (IQ = 86-115)<br>• Language (data available for n=22): the majority of the cohort scored below the age equivalent scores on the receptive language and expressive language domains. Mean receptive language scores were 2SD or more below the standardised mean, and expressive language was 1SD or more below the standardised norm<br>• Cognitive abilities and language development were found to vary, but were mostly below average in the cohort | 18/22 |
| **CHD8 syndrome** | | | | | | |

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| Arnett et al., USA, (2020) | 14 | 9 (M), 5 (F) | 12y 1m (5y-21y) | • Autism Diagnostic Interview Revised (ADI-R; Rutter, Le Couteur, & Lord, 2003): semi-structured parent interview investigating autistic behaviours<br>• Vineland Adaptive Behaviour Scales (VABS-2; Sparrow, Cicchetti, & Balla, 2005): adaptive behaviour<br>• Differential Abilities Scale, second edition (Beran & Elliott, 2007) for participants aged 5-17, and Wechsler Abbreviated Scales of Intelligence, second edition (Weschler, 2011) for participants aged 18+: used to generate verbal and non-verbal scores | • Adaptive behaviour: scores ranged from 24-83, where 54% of the sample had a diagnosis of ID and 100% of ASD<br>• Age of first phrase was found to explain the variance in nonverbal IQ over other variables, indicating impairment in nonverbal cognition. The age of first phrase in the sample ranged from 12 months to never obtained (n=2)<br>• Children who had attained motor and verbal milestones by the age of 5 were found to have highly variable nonverbal and verbal ratio IQ scores<br>• Phrase speech and adaptive behaviour scores were found to be correlated, meaning phrase speech development may be indicative of neurodevelopmental impact more broadly | 19/22 |
| Beighley et al., USA, (2020) | 15 | 9 (M), 6 (F) | 11y 5m (4y-21y) | • Autism Diagnostic Observation Schedule, second edition (ADOS-2; Lord, Rutter, & Goode, 1989) and Autism Diagnostic Interview-Revised (ADI-R; Rutter, Le Couteur, & Lord, 2003): used to clinically assess ASD symptoms<br>• Differential Abilities Scale, second edition (Beran & Elliott, 2007) for participants aged 4-17, and Wechsler | • ASD: All individuals with a CHD8 mutation were diagnosed with ASD, and scores were indicative of increased symptom severity compared to other gene groups assessed<br>• Adaptive behaviour: Scores were <70 on all domains, indicating impairments in adaptive functioning. The lowest score was reported on the socialisation domain (mean =63) | 17/22 |

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| | | | | Abbreviated Scales of Intelligence, second edition (Weschler, 2011) for participants aged 18+: used to generate IQ scores<br>• Social Responsiveness Scale, second edition (SRS-2; Constantino & Gruber, 2012): used to assess social awareness, social cognition, social communication, social motivation, and autistic mannerisms)<br>• Vineland Adaptive Behaviour, second edition (VABS-2; Sparrow, Cicchetti, & Balla, 2005): used to assess adaptive behaviour<br>• Achenbach Behaviour Checklist (Achenbach & Rescorla, 2001): used to measure internalising and externalising behaviour challenges | • Increased social motivation problems were identified in individuals with an ASD diagnosis<br>• Repetitive and restrictive behaviours were reported to be the most problematic domain, followed by social awareness and social motivation<br>• 53% of the cohort were found to display behaviours indicative of an intellectual disability diagnosis | |
| **Kabuki syndrome** | | | | | | |
| Caciolo et al., Italy, (2018) | 17 | 8 (M), 9 (F) | 8y 7m (2y-21y) | • Leiter International Performance Scale – Revised (Leiter-R; Roid & Miller, 1997) - Visualisation and Reasoning Battery: assessment of cognitive profile | • Cognitive profile: 41% (7/17) individuals scored 2SD or more below the mean, 24% (4/17) scored 1SD or more below the mean, and 35% (6/17) fell within the thresholds of an average score<br>• Language (data was obtained for 15/17 participants): regarding lexical | 17/22 |

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| | | | | • Peabody Picture Vocabulary Test (PPVT; Dunn & Dunn, 1997): lexical comprehension<br>• Boston Naming Test (BNT; Kaplan, Goodglass, & Weintrab, 2001): lexical production<br>• Test for Reception of Grammar-2 (TroG-2; Bishop, 2003): morphosyntax comprehension<br>• Beery-Buktenica Developmental Test of Visual Motor Integration (VMI; Beery & Buktenica, 1997): tests integration of visual and motor abilities<br>• Vineland Adaptive Behaviour Scale (VABS; Sparrow, Cicchetti, & Balla, 1984): adaptive behaviour<br>• Achenbach Behaviour Checklist (Achenbach & Rescorla, 2001) – Parent-report: measure of problem behaviour<br>• Conners Parent Rating Scale-Revised (CPRS-L; Conners, 1997): attention/hyperactivity behaviour measure | comprehension, 53% of individuals scored 2SD or more below the mean, 13% scored 1SD or more below the mean, and 14% obtained an average score. 43% of participants scored 2SD or more below the mean in sentence comprehension, 14% scored 1SD or more below the mean, and 43% obtained an average score<br>• Oromotor function: 69% of individuals had difficulty imitating non-verbal movements, and 71% had a phonological disorder. 2/17 (13%) obtained an average Global Moto Index score, and 59% scored in the $5^{th}$ percentile or lower in visual-motor integration<br>• Adaptive behaviour: scores were converted into percentiles, and in the communication domain 50% of participants scored $\leq 5^{th}$ percentile, 75% in daily living, and 56% in the socialisation domain. Data was collected for 8/17 in the motor domain, and 86% scored $\leq 5^{th}$ percentile<br>• Behaviour: 26% (4) participants obtained clinically significant scores in the internalising problem scale, 13% (2) in externalising problems, and 26% (4) in total scores. A total of 73% of participants obtained scores indicative of impairment in cognitive/attention | |

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| | | | | | problem subscale, 67% in the DMS-5 attention problem subscale, and 60% in the ADHD subscale | |
| Harris et al., USA, (2019) | 22 | 3 (M), 19 (F) | 15y 6m (Not reported) | • Rey Complex Figure Test (Meyers & Meyers, 1996): assessing visuo-constructional ability and visual memory<br>• Wide Range Achievement Test-3 (Wilkinson & Robertson, 2006), Word Reading, and Sentence Comprehension<br>• Beery Developmental Tests of Visual Motor Integration and Visual Perception (Beery & Buktenica, 2004)<br>• Wechsler Intelligence Scale for Children-IV (Wechsler, 2003), coding, cancellation, and block design | • Intelligence: mean Full scale IQ score in the cohort was 67.82<br>• Cognition and executive functioning: there were no significant differences observed between affected individuals and the control group in general cognition or executive functioning (mean scores of 18.14 and 20.36, and 3.00 and 2.95, respectively)<br>• Language: compared to the control group affected individuals had a higher mean score on the sentence comprehension task, and lower mean scores than the general population on every other subtest<br>• Visual motor/perception: significant differences were observed in all measures of visual motor and visual motor memory performance, and on some measures of the visuospatial perception test when compared to the control group | 18/22 |
| Lehman et al., France, (2017) | 31 | 16 (M), 15 (F) | 11y 6m (6y-15y) | • Wechsler Intelligence Scale for Children – Fourth Edition (Wechsler, 2003) - Verbal Comprehension Index (FCI); Perceptive Reasoning Index (PRI); Working Memory Index (WMI); Processing Speed Index | • Intelligence: mean full-scale IQ score was 57.4 (SD = 14.6; range 40-103), indicating most of the cohort possess moderately impaired IQ, and reduced IQ was correlated with visual deficiency<br>• Approximately half of the cohort demonstrates strengths in the working | 17/22 |

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| | | | | (PSI); Full Scale Intelligence Quotient (FSIQ) | memory index and weaknesses in the perceptive reasoning index | |
| Mervis et al., USA, (2005) | 11 | 7 (M), 4 (F) | 12y 6m (2y-19y) | • Differential Ability scale (Elliott, Murray, & Pearson, 1990): measuring verbal reasoning, inductive and sequential reasoning, visuospatial constructive abilities, spatial memory, and reasoning<br>• Mullen Scales of Early Learning (Mullen, 1995): visual reception, fine motor, receptive and expressive language<br>• Peabody Picture Vocabulary Test, 3rd edition (Dunn & Dunn, 1997): receptive vocabulary, and Expressive Vocabulary test: measures expressive vocabulary<br>• Scales of Independent Behaviour-Revised (Bruininks et al., 1996): adaptive behaviour<br>• Achenbach Behaviour Checklists (Achenbach & Rescorla, 2001): problem behaviour<br>• Conners' Parent Rating Scales-Revised (Conners, 1997): ADHD behaviours | • Intellectual ability (n=6; one participant was excluded from the analysis due to a score at the floor of the normed data): the mean General Conceptual Ability (GCA) score was indicative of mild mental retardation, with 4/6 children scored within this range, 1/6 within the borderline range, and 1/6 within the average range. Performance was similar on the Nonverbal Reasoning and Spatial Cluster domains. Spatial Cluster scored were significantly lower than GCA scores<br>• Language (n=7): 6/7 children scored within the borderline to low average range in receptive language, and weaker scored in the expressive language domain with 5/7 scoring within the range of mild mental retardation<br>• Adaptive and maladaptive behaviour (n=10; one child received the lowest possible score of 0 and was removed from the analysis): the mean Broad independence score fell within the range of mild adaptive impairment, where 5 participants scored moderate impairment, 3 mild impairment, and 2 borderline to low impairment. Group | 17/22 |

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| | | | | | performance was highest in the Social Interaction and Communication Skills cluster – where 5/10 participants obtained standard scored in the low to average ability range<br>• Problem behaviour (n=11): at a group level, problem behaviour scores were within the normal ranges for participant chronological age<br>• ADHD behaviour (n=11): all but two of the subscale means were within 1SD of the normative data mean scores | |
| Morgan et al., Australia, (2015) | 16 | 4 (M), 12 (F) | 11y (4y-21y) | • Clinical Evaluation of Language Fundamentals (Semel, Wiig, & Secord, 2003): measures social functioning such as conversation skills, responding to information and non-verbal skills, receptive and expressive language<br>• Goldman-Fristoe Test of Articulation (Goldman & Fristoe, 2000): articulation skills<br>• Diagnostic Evaluation of Articulation and Phonology (Dodd et al., 2002): consistency of speech production<br>• Verbal Motor Production Assessment for Children | • Language: individuals were most impacted in the domains of dysarthria and delays were present in articulation and phonology<br>• Receptive and expressive language abilities were impaired in the majority of individuals and deficits were observed in all sub-domains of language (including semantics, syntax, morphology, and pragmatics)<br>• Oromotor functioning impairments were evident in all participants, and Global Motor and Focal Oromotor Control subscale scores were classified as severe in nearly all participants | 16/22 |

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| | | | | (Hayden & Square, 1999): oromotor function | | |
| van Dongen et al., Netherlands, (2019a) | 28 | 15 (M), 13 (F) | 17y 2m (5y-48y) | • Vineland Adaptive Behaviour Scales, Survey Form (Dutch version; Sparrow, Cicchetti, & Balla, 1984): adaptive behaviour<br>• Beery-Buktenica Developmental Scale of Visual-Motor Integration (Beery & Buktenica, 2004): measure of visual and motor abilities<br>• Wechsler Adult Intelligence Scale-IV (Wechsler, 2003): intelligence<br>• Cambridge Neuropsychological Test Automated Battery (CANTAB; Luciana & Nelson, 2002): cognitive flexibility and planning<br>• Dutch Theory of Mind test-revised (Steerneman & Meesters, 2009): social cognition | • Adaptive behaviour: the mean chronological age, in months, of the cohort was 206.4 (range 63-577) whereas the mean developmental age was 61.9 (range 13-145), based on the normative means of the Vineland-Z<br>• Cognition (social cognition/cognitive flexibility): affected individuals scored lower than the control group on all cognitive tests, however verbal memory appears to be a relative strength | 20/22 |
| Vaux et al., USA, (2005) | 15 | 7 (M), 8 (F) | Not reported (8m-14y) | • Instruments varied depending on data collection site (range of instruments unspecified) | • Language (available for 7 participants): the average receptive language score was 56 (range 38-84), and the expressive language mean score was 68 (range 18-80) | 10/22 |

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| | | | | | • Cognition (available for 7 participants): average cognitive score was 62 (range 32-89) | |
| **KBG syndrome** | | | | | | |
| Alfieri et al., Italy, (2019) | 17 | 9 (M), 8 (F) | 12y 5m (7y-23y) | • Wechsler Intelligence Scale for Children, 4th edition (WISC; Wechsler, 2003): intelligence<br>• The Leiter International Performance Scale, 3rd edition (Cornoldi et al., 2016): language impairment and ID<br>• Schedule for Affective Disorders and Schizophrenia (Kaufman & Schweder, 2004): psychopathological signs<br>• The Children's Global Assessment Scale (Shaffer et al., 1983): functioning levels<br>• Child Behaviour Checklist (Achenbach & Rescorla, 2001), Multidimensional Anxiety Scale for Children (March et al., 1997), Children's Depression Inventory (Ireton, 1992): psychopathological aspects<br>• Children's Yale-Brown Obsessive-Compulsive Scale (Scahill et al., 1997): test of obsessions and compulsions | • Intelligence: participants were characterised by a low mean score of 66 (SD = 16.2)<br>• Psychopathological aspects: of all CBC domains, participants mostly scored within the clinical range in anxiety (37.5%), depression (37.5%), and attention problems (31.2%). Internalising and externalising problems were clinically significant for 56.3% and 25% of the cohort, respectively<br>• Psychiatric disorders: ADHD traits were identified in 5 (29%) of the cohort, anxiety in 9 (53%), OCD traits or disorder in 14 (82%), and depressive traits in 4 (24%)<br>• Obsessions and compulsions: compulsions, including hoarding, ordering, and checking were found be higher in participants, 65%, 35%, and 35% respectively, compared to obsessions including hoarding, contamination, and superstitions, 41%, 6%, and 6% respectively | 15/22 |

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| Alfieri et al., Italy, (2021) | 24 | 14 (M), 10 (F) | 11y 9m (6y-23y) | • Wechsler Intelligence Scale for Children, 4th edition (WISC; Wechsler, 2003): intelligence<br>• Vineland Adaptive Behaviour Scale, 2nd edition and Adaptive Behaviour Assessment (VABS-2; Sparrow, Cicchetti, & Balla, 2005): adaptive behaviour | • Intelligence: scores were highly variable, 25% of the cohort presented a full-IQ score 3SD or more below the control population, 33% between 3SD and 2SD below, and 9% scored above 1SD below<br>• Adaptive behaviour: mean scores across all domains fell 2SD or more below the average within the cohort, demonstrating global impairment to adaptive behaviours. 74% of participants scored within the threshold indicative of significant impairment, or 2SD or more below the mean in adaptive functioning | 18/22 |
| van Dongen et al., Netherlands, (2017) | 18 | 7 (M), 11 (F) | Not reported in this format | • Wechsler Intelligence Scale for Children, 3rd edition and Wechsler Adult Intelligence Scale, 4th edition (Wechsler, 2003): intelligence, speed of information processing, working memory, verbal comprehension, and perceptual reasoning | • Intelligence: no significant differences were found, when compared to a control group, in global level of intelligence scores<br>• Subtest results: similarly, no significant differences were found in comparison to the patient control group | 18/22 |
| van Dongen et al., Netherlands, (2019b) | 18 | 7 (M), 11 (F) | 18y 7m (6y-66y) | • Child Behaviour Checklist (Achenbach & Rescorla, 2001), Strengths and Difficulties questionnaire, and Children's Social Behaviour Questionnaire: frequency and nature of problem behaviour | • Behaviour: compared to a control group, participants demonstrated a higher number of problem behaviours for all social, emotional, and behavioural functioning. The highest deviations were present in subscales relating to attention/ADHD (>1.5SD) and social problems (>1SD). Fewer | 20/22 |

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| | | | | • Cambridge Neuropsychological Test Automated Battery and Behavioural Assessment of the Dysexecutive Syndrome battery (Luciana & Nelson, 2002): cognitive flexibility<br>• Dysexecutive Questionnaire and Behaviour Inventory of Executive Functioning (Wilson et al., 2004): executive functioning<br>• Rey Auditory Learning Test, Rey Auditory Verbal Learning Test for Children, Paired Associates Learning Test and Pattern Recognition Memory Test (Schmidt, 1996): memory<br>• Dutch Theory of Mind test-revised (Steerneman & Meesters, 2009): social cognition | problems were reported in participants with KBG were reported on social, affective, and somatic functioning, and somewhat higher problems were reported in the domain of attention on the CBCL<br>• Cognitive functioning: participants with KBG showed substantially lower scores on all tests of cognitive functioning, alongside a higher number of perceived cognitive problems – as reported by caregivers on the BRIEF questionnaire, compared to controls. In comparison, KBG participants also showed slightly lower scores in sustained attentional functioning and shifting and flexibility. In contrast, results between the two groups did not differ in executive functioning problems and KBG participants demonstrated better functioning in visual memory and delayed recall of the semantic memory tasks. Regarding social functioning, a higher performance was observed in participants with KBG compared to the control group on both social cognitive tasks | |
| **Kleefstra syndrome** | | | | | | |
| Schmidt et al., Norway, (2016) | 8 | 4 (M), 4 (F) | 10y 9m (2y-27y) | • Vineland Adaptive Behaviour Scale, 2nd edition (VABS-2; Sparrow, Cicchetti, & Balla, 2005): adaptive behaviour | • Adaptive behaviour: ABC scores, for all participants, were at or below age-matched normative data, and 7/8 scored 2SD or more below. Correlation | 18/22 |

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| | | | | • Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2003)<br>• Child Behaviour Checklist (CBCL) and Adult Behaviour Checklist (ABCL; Achenbach & Rescorla, 2001) | analysis indicates that higher age may be associated with lower ABC scores. Scores for all subscales were significantly below the means of normative data, and communication was significantly lower than daily living skills and socialisation<br>• Behaviour: 6/8 participants scored at the borderline, or within, the clinical range on the problem behaviour domain. Internalising and externalising domain scores were at the borderline of or within the clinical range for 3/8 participants<br>• Social communication: data was collected for 6/8 participants, all of which scored within a range indicative of possible ASD – where the mean score was 22.8 (range 17-28), clearly above the cut-off of 15 in all cases | |
| Vermeulen et al., Netherlands, (2017) | 24 | 9 (M), 15 (F) | 15y 4m (3y-37y) | • Vineland Adaptive Behaviour Scale (VABS; Sparrow, Cicchetti, & Balla, 1984): adaptive behaviour<br>• Autism diagnostic observation schedule (ADOS; Lord et al., 1989)<br>• The mini psychiatric assessment schedules for adults with developmental disabilities (mini-PAS-ADD; Prosser et al., 1997) | • Adaptive behaviour: the control group of typically developing individuals scored better than participants with the syndrome in all domains, where mean scores were slightly lower than the control group. No correlation was present between scores in the Kleefstra group and age<br>• Maladaptive functioning: compared to the control group, individuals with the syndrome demonstrated significantly higher prevalence of ASD, major | 17/22 |

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| | | | | | depressive disorder, and OCD, and all participants aged 15+ have, or had, psychosis. All participants in the syndrome group fit the diagnostic criteria for ASD | |

***Table 2.3.*** *Description of studies investigating the cognitive and behavioural profile of syndromes associated with chromatin remodelling (n = 26)*

| Study | Domain of investigation | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Adaptive functioning | Anxiety | Attention/ADHD traits | Autistic behaviours | Developmental delay/ID | Executive function | Intelligence | Memory | Obsessions and compulsions | Problem behaviour | Psychiatric symptoms | Sensory profile | Speech, language, and communication |
| **CHARGE syndrome** | | | | | | | | | | | | | |
| Abadie et al., France, (2020) | ✓ | | | ✓ | | | | | | ✓ | | ✓ | |
| Graham et al., USA, (2005) | | | ✓ | | | | | | | ✓ | ✓ | | |
| Lasserre et al., France, (2013) | | | | | | ✓ | | ✓ | | | | | |
| Hartshorne & Jacob, USA, (2005) | ✓ | | | | | | | | | | | | |
| Hartshorne et al., USA, (2005) | | | | ✓ | | | | | | | | | |
| Hartshorne et al., USA, (2007) | | | | ✓ | | ✓ | | | | | | | |
| Johansson et al., Sweden, (2005) | ✓ | | | ✓ | ✓ | | | | | ✓ | | | |
| Santoro et al., Italy, (2014) | | | | | ✓ | | | | | | | | ✓ |
| Smith et al., Canada, (2005) | ✓ | | | ✓ | ✓ | | | | | ✓ | | | ✓ |
| Souriau et al., Canada, (2005) | | ✓ | ✓ | | | | | | | | | | ✓ |
| Vesseur et al., Netherlands, (2016) | | | | | ✓ | | ✓ | | | | | | ✓ |
| **CHD8 syndrome** | | | | | | | | | | | | | |
| Arnett et al., USA, (2020) | ✓ | | | ✓ | | | | | | | | | ✓ |
| Beighley et al., USA, (2020) | ✓ | | | ✓ | ✓ | | | | | | | | |
| **Kabuki syndrome** | | | | | | | | | | | | | |
| Caciolo et al., Italy, (2018) | ✓ | | | | ✓ | | | | | ✓ | | | ✓ |
| Harris et al., USA, (2019) | | | | | ✓ | ✓ | ✓ | | | | | | ✓ |
| Lehman et al., France, (2017) | | | | | ✓ | | ✓ | | | | | | |
| Mervis et al., USA, (2005) | ✓ | | ✓ | | ✓ | | ✓ | | | ✓ | | | ✓ |
| Morgan et al., Australia, (2015) | | | | | | | | | | | | | ✓ |
| van Dongen et al., Netherlands, (2019a) | ✓ | | | | ✓ | ✓ | | ✓ | | | | | |
| Vaux et al., USA, (2005) | | | | | ✓ | | | | | | | | ✓ |
| **KBG syndrome** | | | | | | | | | | | | | |
| Alfieri et al., Italy, (2019) | | ✓ | | | | | ✓ | | ✓ | | ✓ | | |
| Alfieri et al., Italy, (2021) | ✓ | | | | | | ✓ | | | | | | |
| van Dongen et al., Netherlands, (2017) | | | | | | | ✓ | ✓ | | | | | |

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| van Dongen et al., Netherlands, (2019b) | | | | | ✓ | ✓ | | | | ✓ | | | |
| **Kleefstra syndrome** | | | | | | | | | | | | | |
| Schmidt et al., Norway, (2016) | ✓ | | | ✓ | | | | | | ✓ | | | |
| Vermeulen et al., Netherlands, (2017) | ✓ | | | ✓ | | | | | | | ✓ | | |

***Table 2.4.*** *Summary of domain(s) of cognition and behaviour investigated, per study*

### 2.3.3. Description of studies (per genetic disorder)

#### 2.3.3.1. CHARGE syndrome

The literature search identified 11 studies which investigated the cognitive and/or behaviour impact of CHARGE syndrome, and the total number of individuals reported on across the studies was 629 (where sample size ranged from 8-160 across the studies). The most common method of recruitment was via patient support groups, predominantly the International CHARGE Syndrome Support Group, from which half of the studies sought to recruit participants (Graham et al., 2005; Hartshorne & Jacob, 2005; Hartshorne et al., 2005; Hartshorne et al., 2007; Souriau et al., 2005). Three of the studies recruited via specialist clinics (Lasserre et al., 2013; Santoro et al., 2014; Smith et al., 2005), one study conducted a new primary analysis of existing data collected from the University Medical Centre in The Netherlands (Vesseur et al., 2016), and one study recruited participants through an advertisement in the Journal of The Swedish Medical Association (Johansson et al., 2005). It was unclear for one of the studies how participants were recruited, although confirmation of CHARGE syndrome was evidenced via genetic testing (Abadie et al., 2020).

The presence of traits characteristic of ASD in individuals with CHARGE syndrome were assessed by five studies using the Autism Diagnostic Interview - Revised (Abadie et al., 2020); Autism Behaviour Checklist (Hartshorne et al., 2005; Hartshorne et al., 2007; Johansson et al., 2005); and the Social Communication Questionnaire (Smith et al., 2005). Adaptive behaviour was assessed by four studies, three of which used the Vineland Adaptive Behaviour Scales (Abadie et al., 2020; Smith et al., 2005; Johansson et al., 2005), and one using the Adaptive Behaviour Quotient (Hartshorne & Jacob, 2005). The domains

of development and executive functioning were assessed using the Behaviour Rating Inventory of Executive Function (BRIEF; Hartshorne et al., 2007), the Child Development Inventory (CDI; Smith et al, 2005), and the Wechsler Intelligence Scale for Children-Revised and Bayley Scale of Infant Development – Dutch version (Vesseur et al., 2016; Johansson et al., 2005). Additionally, three studies assessed the presence of problem behaviours in participants with CHARGE syndrome utilising the Developmental Behaviour Checklist-Parents (Abadie et al., 2020); Child Behaviour Checklist (Graham et al., 2005); and the Behaviour Assessment System for Children (Smith et al., 2005). Language, sensory profiles, and memory were assessed using Reynell Developmental Language Scales – Dutch version, Dunn's sensory profile, and various subtests of the K-ABC, WISC, and the NEPSY including the hand movement, number repetition, and narrative memory subtests (Vesseur et al., 2016; Abadie et al., 2020; Lasserre et al., 2013, respectively). Additionally, the domains of personality and psychiatric traits were assessed by Graham et al. (2005) using Reiss Personality Profiles and the Aberrant Behaviour Checklist. Two studies used a single measure that assessed multiple domains including cognitive skills, self-care, motor skills, and social relationships, which were the Progress Guide (Santoro et al., 2014) and a newly developed questionnaire (Souriau et al., 2005).

#### 2.3.3.2. CHD8 syndrome

Two studies were identified through the literature search that investigated the cognitive and/or behaviour phenotypes associated with CHD8 syndrome. One study recruited 14 individuals from the TIGER study at the University of Washington, consisting of 170 individuals and representing one of the largest registries of individuals diagnosed with ASD

with differing genetic aetiologies (Arnett et al., 2020). The second study recruited 15 participants by recontacting individuals who had participated in a recent study, had a genetically confirmed diagnosis, and had consented to recontact (Beighley et al., 2020).

The Vineland Adaptive Behaviour Scale, 2nd edition, was used in both studies to investigate adaptive behaviour, and intelligence was explored in both studies using the Wechsler Abbreviated Scales of Intelligence and the Differential Abilities Scale. Whilst both studies reported on the domain of ASD behaviours and used the Autism Diagnostic Interview-Revised, one study additionally used the Autism Diagnostic Observation Schedule (Beighley et al., 2020). The same study also utilised the Social Responsiveness Scale and Achenbach Behaviour Checklist to understand social responsiveness and problem behaviours.

#### 2.3.3.3. Kabuki syndrome

Of the 27 papers identified, 7 of these focused on Kabuki syndrome. The most common method of recruitment within these studies was via specialist hospital clinics, which is the method that 5/7 studies recruited participants. The recruitment sites varied, including the Epigenetics of Chromatin Clinic, Rome; Kennedy Krieger Institute, which primarily specialises in investigating development and cognition, not genetics; and the Royal Children's Hospital, Melbourne (Caciolo et al., 2018; Harris et al., 2019; Morgan et al., 2015; van Dongen et al., 2019a; Vaux et al., 2005). One of the remaining two studies recruited via a French Research Group (Lehman et al., 2017), and the other did not specify the exact recruitment method but located participants in three metropolitan areas of the US (Mervis et al., 2005).

In the studies investigating the cognitive and behavioural profile of Kabuki syndrome, language and communication were the most explored domains. Facets including expressive and receptive language, conversation skills, articulation skills, and consistency of speech production were assessed by numerous standardised assessments including the Peabody Picture Vocabulary Test - 3rd edition, the Mullen Scales of Early Learning, and the Goldman-Fristoe Test of Articulation in 4 of the 7 studies (Mervis et al., 2005; Morgan et al., 2015; Caciolo et al., 2018; Harris et al., 2019). Cognitive profile was assessed primarily using the Wechsler Intelligence Scale (child and adult versions; Harris et al., 2019; Lehman et al., 2017; van Dongen et al., 2019a), but other measures were used including the Leitner International Performance Scale-Revised (Caciolo et al., 2018) and the Differential Ability Scale (Mervis et al., 2005). The adaptive behaviour profile in Kabuki syndrome was assessed in three of the studies identified which used one of two studies, either the Vineland Adaptive Behaviour Scale (Caciolo et al., 2018; van Dongen et al., 2019a) or the Scales of Independent Behaviour-Revised (Mervis et al., 2005). The same three studies assessed visual abilities using the Beery-Buktenica Developmental Scale of Visual-Motor Integration. Two of the studies included assessed problem behaviour, using the Achenbach Behaviour Checklist, and ADHD traits, using the Conners 3 (Caciolo et al., 2018; Mervis et al., 2005). Finally, one study included assessed both cognition and language abilities, but used a variety of unspecified standardised instruments.

#### 2.3.3.4. KBG syndrome

Standardised measures were used in four papers to investigate the cognitive and/or behavioural profile associated with KBG syndrome. All studies recruited participants via specialist clinics, including the Radboud University Nijmegen Medical Centre, (van Dongen et al., 2017; van Dongen et al., 2019b) and the Bambino Gesú Children's Hospital and Centre for Rare Diseases and Congenital Defects at Gemelli Hospital (Alfieri et al., 2019; Alfieri et al., 2021).

Three of the four papers reported on intelligence using the Wechsler Intelligence Scale (Alfieri et al., 2019; Alfieri et al., 2020; van Dongen et al., 2017). Other domains of interest, each investigated by only one of the four papers, include problem behaviours, cognitive flexibility, psychopathological signs, and memory. One study investigated adaptive behaviour and utilised the Vineland Adaptive Behaviour Scales, consistent with many of the other studies in the systematic review (Alfieri et al., 2020).

#### 2.3.3.5. Kleefstra syndrome

Two of the papers identified investigated Kleefstra syndrome. One study recruited a sample of participants with genetic disorders of differing aetiologies from the department of Human Genetics, Radboud University Medical Centre, The Netherlands. 24 of the 58 participants recruited had a genetically confirmed diagnosis of Kleefstra Syndrome. The second study recruited 15 participants via a variety of routes including the registry of the Norwegian National Advisory Unit on Rare Disorders, and through four Departments of Medical Genetics in Norway (Schmidt et al., 2020).

Both papers assessed adaptive behaviour using the Vineland Adaptive Behaviour Scale (VABS), and both studies investigated behaviours consistent with ASD but used different measures, the Social Communication Questionnaire (Schmidt et al., 2016) and the Autism Diagnostic Observation Schedule (Vermeulen et al., 2017). Psychiatric symptoms and problem behaviours were also explored (Vermeulen et al., 2017 and Schmidt et al., 2016, respectively).

### 2.3.4. Quality of Included Studies

In accordance with the detailed scoring guidance included within the quality assessment manual, each of the papers were assessed to ascertain the quality of the study. The quality score for each of the studies included in this systematic review are including in the final column of **Table 2.3**. A second reviewer also scored 20% of the papers, independently, to ensure that the assessment was reliable, and both reviewers ranked the papers in the same order of lowest to highest quality. The mean quality assessment score was 16.7 (*SD* = 2.47), and the quality of the published literature identified assessing the cognitive and/or behavioural profile of five genetic disorders affecting chromatin remodelling is highly variable, highlighted through the range of quality scores (10 – 20).

## 2.4. Discussion

### 2.4.1. Summary of review

The objective of this systematic review was to both assess the application of standardised measures in rare genetic syndromes and understand the cognitive and behavioural profile of syndromes associated with chromatin remodelling, the same pathway implicated in MYT1L-syndrome. 7484 papers, utilising systematic review methodology in line with the PRISMA guidelines, were narrowed to 26 studies, applying a strict inclusion and exclusion criteria, which used standardised measures of assessment to investigate the cognitive and behavioural profile of one of the five selected rare genetic disorders. The inclusion criteria means that the papers included in this review represent, to the authors knowledge, the extent of the research applying standardised measures to understand cognition and behaviour currently published in this area.

### 2.4.2. Cognitive and behavioural phenotype of children with genetic disorders affecting chromatin remodelling

The selected papers provided insight into multiple facets of cognition and behaviour in individuals diagnosed with a genetic disorder affecting chromatin remodelling, including ASD traits, developmental delay, cognitive impairment, and problem behaviours. Each of these domains will now be discussed in turn, collating evidence across different genetic disorders affecting chromatin remodelling. This was deemed appropriate to ascertain any similarities and differences in the cognitive and behavioural profile of individuals diagnosed with disorders affecting chromatin remodelling.

Of the papers identified in this review, 12 investigated adaptive behaviour, or adaptive functioning, across the five genetic disorders of interest. Impairments to adaptive behaviour were present in all 12 of the studies, however there was heterogeneity in levels of impairment within, and between, the groups of investigation. 9/12 studies assessed adaptive behaviour using the VABS which, whilst studies used varying editions, enables a more consistent and reliable approach to comparing the findings. In CHARGE syndrome, most studies identified borderline to moderate adaptive behaviour impairment – although it is important to note that, except for one study, some participants scored within the 'within normal limits' range (Abadie et al., 2020; Hartshorne et al., 2005a; Johannson et al., 2005; Smith et al., 2005). In addition to the presence of adaptive behaviour impairments, where the most severe impairment was identified in the socialisation domain, in CHD8 syndrome both papers identified co-occurring ID and ASD, with one of the two studies identifying that 54% and 100%, respectively, had these additional diagnoses (Arnett et al., 2020). This finding is consistent with the published clinical observations of individuals with CHD8 syndrome, and with the broader literature that has found high incidence rates of severe impairment to the adaptive behaviour socialisation domain and ASD (Ostrowski et al., 2019; Golya & McIntyre, 2018). In Kabuki syndrome, all the papers identified also reported the presence of impairments to adaptive behaviour however, unlike in CHD8 syndrome, one of the papers found that the mean score of the socialisation domain was the highest compared to other adaptive behaviour domains (Caciolo et al., 2018; Mervis et al., 2005; van Dongen et al., 2019a). Similarly, in Kleefstra syndrome and KBG syndrome adaptive behaviour scores demonstrated significant impairment (Alfieri et al., 2021). Interestingly, Schmidt et al. (2016) proposed that as age increases ABC scores decrease,

whereas Vermeulen et al. (2017) reported a null finding in relation to this hypothesis. This is an important area for future exploration to begin to understand how the cognitive and behavioural phenotype may change over an individual's lifespan. Establishing changes within cognitive phenotypes across the lifespan enables the implementation of timely interventions, and in Down Syndrome (DS), for instance, impairments to adaptive behaviour has been found to be most problematic in children, with symptoms improving as individuals progress into adulthood (Bunster et al., 2022). Hyperactivity, characteristic of ADHD, was also present in CHARGE syndrome, Kabuki syndrome, and Kleefstra syndrome and was noted as particularly problematic in CHARGE syndrome, where hyperactivity scores were amongst the highest on the Child Behaviour Checklist (Graham et al., 2005). Johansson et al. (2005), also investigating CHARGE syndrome, found that hyperactivity was significantly correlated with the severity of ID, but not ASD, which is reflective of the wider literature where children with ADHD are typically found to have co-occurring ID, marking an important consideration for treating clinicians acknowledging the presence of these co-occurring disorders in children affected by either ADHD or ID (Ahuja et al., 2013).

Nine of the papers identified investigated the presence of behaviours associated with ASDs. The studies, to varying extents, all identified ASD traits in the cohorts tested. The 5 studies that explored ASD traits in CHARGE syndrome each found that most individuals either met the full diagnostic criteria for ASD, or at least one of the diagnostic criteria (Abadie et al., 2020; Hartshorne et al., 2005; Hartshorne et al., 2007; Smith et al., 2005; Johansson et al., 2005). However, one study identified that the standard deviations reported for individuals with CHARGE syndrome were considerably higher than that found in other syndromes,

indicative of a high variability in ASD traits reported within the sample (Hartshorne et al., 2007). In CHD8 syndrome, both identified studies found that 100% of individuals met the criteria for ASD (total n = 29), and in one of the studies scores indicated that compared to other genetic groups assessed, where 78% of the other gene group were found to have traits characteristic of an ASD diagnosis (Arnett et al., 2020; Beighley et al., 2020). It is important to note that the small sample sizes which each of these studies reported on, 14 and 15 respectively, may not be representative of the wider CHD8 population and larger samples may identify a more varied profile. Although using small sample sizes, this finding is consistent with the wider literature where there are well-documented associations between overgrowth disorders, of which CHD8 is, and ASD (Campbell, Chang, & Chawarska, 2014). Two studies also reported findings pertaining to ASD in Kleefstra syndrome, and similarly both found that most of the cohort displayed traits indicative of an ASD diagnosis, where six out of eight participants were found to have a diagnosis of ASD in one study (Schmidt et al., 2016) and all participants met the diagnostic criteria for ASD (Vermeulen et al., 2017). As with CHD8 syndrome, the small sample sizes may mean that the profile of ASD in affected individuals is more nuanced than reported, nevertheless the findings do indicate that ASD is prevalent within at least some of these individuals. These findings suggest that individuals diagnosed with disorders affecting chromatin remodelling are more likely to present with symptoms associated with ASDs than typically developing children, and future research should ascertain whether there is a genetic predisposition to ASD in these genetic disorders. An increased incidence of ASD is also present in other studies of genetic disorders such as Rett's syndrome and Cohen's syndrome where, utilising standardised measures of assessment, 61% and 54% of individuals diagnosed are estimated to have either meet the

full diagnostic criteria, or meet numerous criteria, of ASDs (Richards et al., 2015). Individuals with Down's syndrome (DS) are also considered to be at an elevated risk of ASD, where a recent study of 18 infants identified using the Autism Observation Scale for Infants that 39% were considered at risk for ASD, and 100% of participants demonstrates at least one of the diagnostic features of ASD, the same study evaluated a typically developing control group and found that 11% were considered at risk for ASD (Hanh et al., 2020). The study concluded that early signs of ASD-associated behaviours appear to be detectable in infancy in those diagnosed with DS, which marks an important avenue for further research in other conditions where earlier diagnosis may lead to the advent of more effective and appropriate interventions.

Findings relevant to other problem behaviours were reported in 8 of the 27 papers identified in this systematic review. In CHARGE syndrome, some participants were found to display profiles consistent with mild and major behavioural disorders. However, within the cohort problem behaviours were also in the typical range, and in one study over 50% of participants presented with no problems in this domain (Smith et al., 2005). When compared to individuals with Prader-Willi Syndrome (PWS), individuals diagnosed with CHARGE syndrome demonstrated fewer internalising behaviours, but scored within the same range for those recorded in PWS for externalising behaviours (Graham et al., 2005). These findings were also present in the other syndromes of interest, although there is potentially variability in the presence of problem behaviour in Kabuki syndrome as one study more than a quarter of the sample (n = 17) scores within the threshold of clinically significant behaviour problems, whereas another found that none of the 11 participants

scored outside of the normal range for behaviours based on their chronological age (Caciolo et al., 2018; Mervis et al., 2005). Both measures used the same standardised assessment of problem behaviour, the Achenbach Behaviour Checklist, and therefore, although based on small sample sizes, may indicate variable problem behaviours in diagnosed individuals. For both Kabuki syndrome and Kleefstra syndrome, the severity of problem behaviours does seem to be diminished in comparison to CHARGE syndrome, as fewer participants in these syndromes were reported as possessing clinically significant problem behaviour scores – however there is also apparent variability in CHARGE syndrome, too. There is a general lack of specificity in relation to the incidence and prevalence of problem behaviours depending on variables such as gender and age in the studies included in this review, which will hopefully be further understood in future studies that possess greater power from larger sample sizes. This is important to understand and has been researched in Fragile-X Syndrome (FXS), where a systematic review of 28 studies found that significant gender differences were present in relation to problem behaviour incidence and different types of problem behaviours were more prevalent depending on the individual (Hardiman & McGill, 2018). This warrants further research in the genetic disorders in this review as more effective interventions will be able to be implemented depending on the individual variables potentially influencing the behavioural profile. Two of the studies identified explored the presence of symptoms associated with anxiety in individuals diagnosed with CHARGE syndrome (Souriau et al., 2005) and KBG syndrome (Alfieri et al., 2019), and found that between 31% (22/71) and 53% (9/17) of the sample was affected by elevated anxiety levels. More broadly, rare disease populations are noted to have high co-occurring anxiety prevalence rates which is largely thought to be caused by

challenges present because of their diagnosis (Uhlenbusch et al., 2021). This is, therefore, an important consideration for healthcare professionals supporting individuals with rare diseases, and should be further explored within the genetic disorders discussed in this review as there is currently a paucity of evidence in CHD8 syndrome, Kleefstra syndrome, and Kabuki syndrome relating to this domain of impact. There is also, largely, a lack of published research exploring other important co-occurring symptoms such as those related to psychiatric diagnoses. Three studies did explore this domain, one of which report that OCD and depressive traits were present in in 82% and 24%, respectively, of the 17 individuals included in the study (Alfieri et al., 2019). Again, this finding is consistent with the broader rare disease literature, where depression has been found to be the most common psychiatric problem in DS, and also significantly impact individuals with PWS (Walton & Kerr, 2015; Dykens & Shah, 2003).

More papers (12/27) investigated developmental delay/ID than any other domain explored within this systematic review, and 6 of these used standardised measures to assess the IQ levels of diagnosed individuals. All of the studies included that reported empirical data relating to the full-scale IQ (FSIQ) used a variation of the Wechsler Intelligence Scale. In CHARGE syndrome a total of 49 participants were included in the two studies investigating IQ, and the range of FSIQ scores were between 54-115 (Lassere et al., 2013; Vesseur et al., 2016). Whilst most participants did fall in the threshold of impaired FSIQ, the findings do illustrate that there is some variability in IQ as Vesseur et al. (2016) reported 8/41 scored within the subnormal range (scores between 70-85) and 9/41 participants scored within the normal range (scores 85 and above). Verbal and performance IQ were only reported by one

of the studies, but verbal IQ scores appear to be the most impaired (Lassere et al., 2013). In Kabuki syndrome mean FSIQ scores ranged from 57.4 (n =31) and 67.82 (n = 22) in the two studies identified (Harris et al., 2019; Lehman et al., 2017), and in KBG syndrome, 66 (n =17) and 65 (n = 24) (Alfieri et al., 2019; Alfieri et al., 2021). In the latter study, 35% of participants fell 3SD or more below the control group of typically developing age-matched participants. Collectively, these findings indicate that ID is a key feature of genetic disorders impacting chromatin remodelling and is a valuable area for other disorders affecting the same pathway. Additionally, whilst IQ is a useful indicator of general impairment further testing using a battery of tests assessing specific domains of intelligence would be valuable to indicate where specific relative strengths and weaknesses lie within the group, which will guide the implementation of more specific interventions addressing more specific problems relating to ID. In addition to ID, 10 of the studies in the review investigated levels of impairment to the domains of speech, language, and communication in three of the disorders of interest. Studies investigating communication abilities in CHARGE syndrome reported significant expressive and receptive language challenges, where in one study scores on both domains were 3SD or more below the mean of typically developing children of the same ages (Smith et al., 2013). Although communication was still deemed a concern, another study found that receptive language was more severely impacted, with mean scores 2SD or more below the mean typically developing score, compared to expressive language which was generally 1SD or more below (Vesseur, 2016). This demonstrates the presence of relative strengths and weaknesses relating to communication in CHARGE syndrome and Santoro et al. (2014) found that 30% of participants (n = 35) scores within the normal communication quotient, suggesting there is also heterogeneity in individual

abilities. This was also reported in the studies of individuals with Kabuki syndrome as in three of the five studies assessing language, receptive language was found to be more significantly impaired than expressive language (Mervis et al., 2005; Morgan et al., 2015; Vaux et al., 2005). Further, conflicting evidence was present in two of the studies identified as one reported that sentence comprehension for 14% of individuals (n =17) was 2SD or more below the normative data (Caciolo et al., 2018), whereas another found that sentence comprehension scores were higher than the typically developing control group (Harris et al., 2019) – again, this is another suggestion of heterogeneity between individuals affected by the same disorder. Language challenges were also reported in the one study exploring CHD8 syndrome, and a positive correlation was identified between phrase speech onset and adaptive behaviour, suggesting that the delayed onset of phrase speech may be indicative of more severe neurodevelopmental impairment more broadly (Beighley et al., 2020). These findings suggest that it is highly likely that communication difficulties are a cardinal feature of disorders affecting chromatin remodelling, and that there may be links between speech onset and wider neurodevelopmental delays. However, it is important that further examination is conducted at an individual level to guide any interventions, given the variability reported between individuals relating to different speech and language domains.

This systematic review included the findings of 26 studies investigating the cognitive and behavioural phenotype associated with syndromes affecting chromatin remodelling using standardised measures. The findings of this systematic review demonstrate that there are commonalities in the cognitive and behavioural profiles of genetic disorders affecting

chromatin remodelling. Across the genetic disorders of interest, many studies report impairments to adaptive functioning, the presence of ASD traits, developmental delay, problem behaviour, and speech delays. Many of the impairments discussed are also present in the literature describing the phenotype of MYT1L-syndrome (discussed in section 1.3.4.), therefore it can be postulated that there are commonalities between the cognitive and behavioural profile of genetic syndromes implicated in chromatin remodelling. It is important, however, to note that based on the literature there are potentially syndrome-specific traits associated with MYT1L-syndrome including syndromic obesity which were not identified in the other genetic disorders along the same pathway discussed in this review. Although it is useful to understand broadly how cognition and behavioural challenges manifest in disorders affecting chromatin remodelling, there is an inherent risk of researcher bias in the study selection of systematic reviews – efforts were made to overcome this by AM (PhD supervisor) screening 20% of the initial papers and also screening the selected abstracts to validate the application of the inclusion and exclusion criteria. Further, due to restrictions within the research team only papers published in English language were included.

### 2.4.3. Limitations of the included studies

All of the studies included in the review collected data at only one time point and whilst this is a useful indicator of impairment across the syndrome population, does not contribute to understanding how the cognitive and behavioural phenotype may change at different stages across the lifespan. This is critical to guiding appropriate and timely interventions, and research adopting a longitudinal design should be a priority for future research. Such

research has established changes to the phenotype in DS, where individuals are noted to experience different cognitive and behavioural challenges at various stages of development across the lifespan (Pulsifer, 2021). A notable issue of the studies included in this review is the low sample sizes used and, although this is potentially inevitable given the low incidence of the genetic disorders of interest in the wider population, researchers should make use of all available recruitment strategies in the hope of collecting data from a larger, and therefore more representative, group of individuals. Additionally, and whilst to the author's knowledge there is no known overlap in the samples across the included studies, it would be beneficial for future research to share participant data as part of the open science framework to enable the identification of overlapping samples across research studies. Whilst practical, and appropriate in many conditions given the high levels of co-occurring ID, caution should also be taken when using parent-reported standardised measures of assessment, as parent reports have been found to be discrepant compared to objective reports of impairment in domains of cognitive impairment (Williams et al., 2022). The appropriateness of using some standardised measures in rare disease populations should also be considered, as whilst only reported in one study in this review, participants were excluded from analyses due to achieving the lowest possible score on a measure, thus avoiding any impact on statistical analyses due to the floor effect but excluding participants from an already notably small population. Another limitation relating to the use of standardised measures in the studies identified in this review is the highly variable levels of detail provided in relation to the standardised measures used, their validity and reliability, and the key findings – as evidenced by the variable quality scores reported.

### 2.4.4. Conclusion

The studies reported on in this systematic review begin to describe some of the features relating to cognition and behaviour which may be observed across numerous genetic disorders affecting chromatin remodelling, including impairments to adaptive behaviour and speech and language, and higher prevalence rates of co-occurring NDCs such as ADHD, ASD, and ID. Whilst it does appear that there are similarities in the phenotype associated with genetic disorders affecting chromatin remodelling, and therefore impairment to the cognitive and behavioural profile of diagnosed individuals should be expected to some extent, given the variation reported between the disorders it is important that further research is conducted to understand individual disorder phenotypes, which will enable more concrete cross-syndrome comparisons. A limitation of the general approach used is that the included studies only report findings pertinent to a single data collection point and therefore no assumptions can be made regarding how the cognitive and behavioural phenotype of affected individuals may change across the lifespan, an area that would benefit from future longitudinal research. There is also a need for future studies to use standardised measures more consistently that are reported to be valid and reliable for use in rare disease populations, and report the descriptive statistics of findings, such as the mean, median, and range of scores, enabling more robust within and cross-syndrome comparisons. This review also highlights that despite associations with impairments to cognition and behaviour there is variance between individuals, and therefore although individuals should be routinely screened and tested for impairments pertinent to these domains, it is important that particular effort is taken to understand relative strengths and weaknesses in order to guide meaningful interventions at an individual level. Individuals

diagnosed with other syndromes affecting chromatin remodelling should also be routinely tested for impairments in these domains, leading to a greater understanding of underlying phenotypes associated with the genetic basis of the syndromes.

# Chapter 3: The impact of MYT1L-syndrome on behaviour and cognition: a parent/caregiver perspective

## 3.1. Introduction

Given the lack of research investigating the impact of MYT1L-syndrome on cognition and behaviour, there is no defined cognitive or behavioural phenotype. Understanding the phenotypes associated with rare genetic syndromes enables others to acknowledge the challenges faced by affected individuals and understand how an individual interacts with the environment around them (Waite et al., 2014). Understanding these interactions has the potential to lead to the development of valuable interventions that can be utilised by caregivers and educational professionals to reduce stress, increase quality of life, and empower individuals with rare genetic syndromes to engage in formal education through the adaptation of the curriculum and implementation of interventions to reduce barriers currently in place. Identifying the key challenges faced by the families of individuals with MYT1L-syndrome will also highlight important avenues for future research.

Qualitative research provides a unique opportunity to investigate the cognitive and behavioural phenotype of individuals with MYT1L-syndrome as caregivers have varied, hands-on experience supporting their child and therefore are able to recognise and describe the cognitive and behavioural profile their child possesses. When qualitative research techniques were adopted when exploring the cognitive and behavioural profile of foetal alcohol spectrum disorder, researchers reported that caregivers were able to recognise scarcely reported situation-specific triggers and observe behaviours not appearing on standardised measures or clinical checklists (McDougall et al., 2020). Another

qualitative study, investigating parent experiences in Sanfilippo syndrome applied, although through focus groups and a questionnaire, the same principles of thematic analysis (Porter et al., 2021). The research sought insight from 25 parents and found high caregiver burden across all stages of the disease. The qualitative data also highlighted multiple areas of unmet need including the quality of life of the affected individual and wider family, impairments in children's ability to communicate, sleep, and manage mobility. Additionally, important areas warranting further research were identified including elevated levels of problem behaviour and anxiety in affected individuals. The research was also able to seek parental perspectives on which key symptoms would enhance quality of life most if they were targeted through specific interventions and understand from the community priorities for the focus of future research into the syndrome.

Based on the unique perspectives and insight qualitative research can provide, in addition to the application of the method in other syndromes, it is appropriate to conduct a qualitative interview study with the parents and caregivers of individuals diagnosed with MYT1L-syndrome to begin to form an understanding of which elements of the cognitive and behavioural phenotype associated with the syndrome are most problematic or prevalent. This will inform the design of the quantitative research, conducted as part of this thesis, ensuring that appropriate standardised measures are chosen to objectively assess levels of impact.

To understand the cognitive and behavioural profile of MYT1L-syndrome, interview questions and prompts were devised by drawing insights from the published literature

examining MYT1L-syndrome, and more broadly from qualitative research conducted in other rare genetic syndromes. Although the interview schedule was intentionally broad by design, topics discussed in the MYT1L-syndrome literature (outlined in section 1.3.4) were included as this provided an opportunity to gain qualitative insights from caregivers regarding the published clinical observations and case reports. These areas of interest included challenging or problem behaviour, speech and language development, and cognitive abilities including the presence of ID or developmental delays. Areas of social impairment characteristic of ASD were also explored. These are all topics also explored in other qualitative studies investigating the cognitive and behavioural phenotype from the perspective of a parent or caregiver, including FXS, Rett Syndrome, and DS (Brady et al., 2006; McGraw et al., 2023; Sheldon, Oliver, & Yashar, 2019). Developmental delay and early indications of missed milestones were assessed using questions adapted from the interview schedule used by Raspa et al., (2016) in their investigation of developmental delay in young children. Key objectives included understanding the first concerns of caregiver to examining required support services. Following reports that individuals with MYT1L-syndrome exhibit challenging behaviours relating to food and diet (Carvalho et al., 2021), this was also included as a topic of interest. Specific behaviours relating to food were investigated, as described by Goldstein et al., (2008) in their qualitative examination of managing food related behaviours in children diagnosed with PWS.

Based on the previous literature describing MYT1L-syndrome, it can be hypothesised that caregivers in this study will describe delays reaching milestones, the presence of challenging behaviours – potentially linked with food and diet, and communication

difficulties. It is also expected that caregivers will describe social impairments associated with autism symptomatology, including challenges communicating, establishing and maintaining peer relationships, and impaired social awareness.

## 3.2. Methods

### 3.2.1. Ethics

All participants received written and oral information about the study and had to provide written consent to participate. Participants were also made aware of the right to withdraw from the research at any time. Ethical approval was obtained by the University of Sheffield Ethics Committee (reference number 034734).

### 3.2.2. Participants

The parents and caregivers of individuals with a genetically confirmed diagnosis of MYT1L-syndrome, classified through a 2p25.3 deletion or mutation, were eligible to participate irrespective of their location. The inclusion criteria for participation were that participants were over 18 years of age, were primarily responsible for providing care to the affected individual, and were able, and happy, to provide informed consent. To reduce potential bias or social desirability, caregivers were invited to participate on an individual basis without, for instance, the presence of another family member, and no financial incentive was offered. Participants were recruited via parent support groups listed on Facebook, and with support from the charity UNIQUE using their database of MYT1L-syndrome families and social media channels. After participating in the research, participants were invited to

pass on study information and researcher contact details to other MYT1L-syndrome families that may have been missed through other recruitment methods.

The sample consisted of 18 parents of individuals with a genetically confirmed diagnosis of MYT1L-syndrome. Eligibility to participate was confirmed by genetic test report. See **Table 3.1** for participant characteristics.

| | |
|---|---|
| **N** | 18 |
| **Age in years** (of individual reporting on) | |
| Mean (SD) | 11.87 (8.91) |
| Range* | 0-5 (7), 6-11 (3), 12-17 (4), and 18+ (4) |
| **Sex** (of individual reporting on) | |
| Male (%) | 8 (44%) |
| Female (%) | 10 (56%) |
| **Relation** (to individual reporting on) | |
| Mother (%) | 14 (78%) |
| Father (%) | 4 (22%) |
| **Location of residence** | |
| United Kingdom (%) | 7 (39%) |
| United States (%) | 4 (22%) |
| Europe (%) | 3 (17%) |
| Other (Australia, Canada, and South America) (%) | 4 (22%) |

**Table 3.1.** Participant characteristics – Cognitive and behavioural impact qualitative analysis

**Individual ages are reported in range brackets to protect participant anonymity*

### 3.2.3. Interviews

To guide the interviews and ensure all topics of interest including problem behaviours, delays reaching milestones, and speech and language (further outlined in section 3.1.) were discussed LS designed, and used, an interview schedule (**Appendix 1**) with questions and prompts based on topics discussed in relevant literature conducted in other rare genetic syndromes. Due to the COVID-19 pandemic, all interviews took place via the secure online video platform Google Meet, which is approved for use by the University of Sheffield, and consent was sought to record both the video and audio of the online call to facilitate transcribing the interviews later in the analysis. All interviews were conducted by LS, who had no relationship with the participants prior to the interview. After the interview was conducted, participants were invited to submit any additional comments to the researchers which, for those who did send further information, was added to the end of each transcript, and included in the analysis. In line with the reflexive practice encouraged as part of TA, a reflexive journal was kept throughout the research process (**Appendix 2**).

Each participant was allocated a participant code (beginning at #1, then #2 etc.). Following the interview, all interviews were transcribed verbatim and any personally identifiable information was redacted to ensure anonymity. All interviews were transcribed by LS using the premium version of the transcription software F5 for Mac (https://apps.apple.com/gb/app/f5-transcription-pro/id935669212?mt=12), and verified by AM and MF. Transcriptions were reread to ensure familiarity prior to coding.

### 3.2.4. Data Analysis

Interview transcripts were input to analysis software NVivo (QSR International, 2020) and analysed according to the 6-step Thematic Analysis framework (outlined in further detail in Section 1.4.). Initially, a coding framework was developed through the analysis of four interviews by LS and MF, who coded the transcripts independently, discussed, and then resolved any disagreements so consensus was reached. An initial coding framework developed from this initial stage of analysis and was then developed into a codebook (**Appendix 3**) as further interviews were analysed, and 20% of the subsequent transcripts were analysed by MF to ensure reliability. The codes and subsequent themes were independently scrutinised by the research team, then discussed, and verified to ensure rigour and validity. Results of the study are reported according to the Consolidated Criteria for Reporting Qualitative Research Guidelines (COREQ; Tong, Sainsbury, & Craig, 2007).

### 3.3. Analysis

The analysis resulted in the identification of three core themes: 1) behaviour, 2) speech, language, and communication, and 3) cognitive ability and profile. Each of the main themes has several subthemes (see **Table 3.2**). Theme 1 focuses on the behavioural profile of MYT1L-syndrome, as reported by caregivers. This includes impaired sensory responses including hyper- and hypo-sensitivities, challenging behaviour including hitting, biting, and self-injury, elevated levels of anxiety, an inability to appropriately regulate emotions, the presence of stereotypically autistic traits, and an overview of the social profile. Theme 2 focuses on the, widely reported, speech, language, and communication delays present in the cohort. Theme 3, cognitive ability, and profile, presents an overview of the presence of intellectual disability in the sample, relative strengths and weaknesses relating to memory, and a descriptive summary of numeracy and literacy skills. Where appropriate, to provide additional context and protect individual anonymity, age brackets of baby (during pregnancy, at birth and up to 1 year), toddler (1-3 years), child (4-12 years), adolescent (13-17 years) and adult (18+ years) are provided alongside participant quotes.

| Themes | Subthemes |
|---|---|
| Theme 1: Behaviour | 1.1. Sensory responses |
| | 1.2. Challenging and unusual behaviour |
| | 1.3. Anxiety |
| | 1.4. Executive functioning and emotion regulation |
| | 1.5. Perceived autistic traits |
| | 1.6. Social relationships |
| | 1.7. Motor |

| | |
|---|---|
| Theme 2: Speech, language, and communication | |
| Theme 3: Cognitive ability and profile | 3.1. Intellectual disability |
| | 3.2. Memory and encoding |
| | 3.3. Numeracy |
| | 3.4. Literacy (reading and writing) |

***Table 3.2.*** *Themes and subthemes relating to behaviour and cognition in MYT1L-syndrome*

### 3.3.1. Theme 1: Behaviour

**3.3.1.1. Subtheme 1.1: Sensory Responses**. Interviewees provided insight into how the sensory profile of those with MYT1L-syndrome differs from a typically developing person and the challenges that this presents on an often daily basis. Sounds in public places, such as a retail store, were a particular area of sensitivity: "*I couldn't even take him to the store … the sound of the cart bothered him*" and "*the overhead lights will hum, and she doesn't like that – the noise*". Loud noises evoked a fearful response in some individuals as mentioned by one caregiver: "*sirens from ambulances coming from miles off … that always used to terrify her*". Too much noise was a clear trigger, for some, in the onset of negative behaviours where one interviewee said their child would "*lose it in public … if it is too noisy*", and another that "*the fire alarms were going off and that sends her crazy*". This sensitivity is not exclusive to noise, but also present with light and certain visual stimuli as described by one caregiver of an adult with MYT1L-syndrome: "*some days it is too bright, like driving at night she wears sunglasses because of the oncoming cars – they are really bright to her*". This was shared by other participants, and environments that were "*very brown and tan and natural colours*" were reported to be less overwhelming and less visually stimulating.

Opposed to a hypersensitivity some interviewees reported that their child had a hyposensitivity, specifically in relation to pain: "*they broke their leg without us really noticing and… without complaining too much*". Multiple participants reported that often one of the main indicators of pain or distress was a spike in the onset of negative behaviours, for example "*they had a cavity that would turn into an abscess and then their behaviour spiked*". Parents also reported that the high pain tolerance of their children was particularly problematic during periods of ill health and sickness, where parental intuition was often the only identifier of illness. In some cases, this led to difficulties when interacting with healthcare professionals:

> *"I had to guess all the time. I just thought that she's just not right, and I had so many battles with the doctors over the years … She could deal with that amount of pressure and pain and she was fine in herself. It was just instinct really – I just knew."*

This hyposensitivity to pain was also noted to be problematic in relation to self-injurious behaviour and behavioural outbursts. Where a typically developing child may respond to being hurt or in pain, parents reported that this was not always the case in children with MYT1L-syndrome: "she *has bitten herself with blood and doesn't seem to react*". This may be linked to a broader lack of tactile processing ability, or lack of sensitivity to touch, as "*to touch her you really have to hold her for her to feel anything*". Self-injurious behaviours, in some cases, appeared to be linked to the presence of anxiety, where self-injury was exacerbated during periods of high anxiety:

*"Her pain tolerance is over the top, she has no sense of pain I don't think, some days she rips off toenails, full toenails. She tends to bend; you can tell she is getting really anxious if she starts bending her fingers backwards."*

**3.3.1.2. Subtheme 1.2: Challenging and Unusual Behaviours**. Many of the parents and caregivers interviewed acknowledged the presence of unexpected behaviour very early on in the development of their children, which for some was an early indication that their child was not typically developing. For some parents/caregivers this was as early as birth where:

"*She didn't open her eyes when she first came out, she cried with her eyes closed and over the next three months… barely opened her eyes. Maybe two or three times a day she would just kind of peek at you a little bit and keep them closed and she would clearly be awake but just keep her eyes closed."*

Another overarching feature of unusual behaviour that presented at a young age was a lack of movement, with typical examples being: "*she was a very floppy baby when she was born*" and "*he didn't move much… he was kind of just there*". Parents that were interviewed recalled their initial perceptions that their child was "*a really easy baby… a dream baby… [that] slept through the night and during the day and was very placid*". These misconceptions were more common in parents where the MYT1L-syndrome individual was their first child and therefore did not have a typically developing comparator:

> *"I guess I didn't notice that she wasn't doing the things that she should have been doing because she was my oldest. If I would lay her on a baby mat to play, she wouldn't necessarily interact with it, she'd just lie there so I just thought that she was a very content baby but actually it probably was that she was suffering developmental delays which meant she just didn't interact with the things that she should."*

For other parents or caregivers, whilst they acknowledged that their child was not performing expected behaviours as a baby, it was a friend or relative that suggested that their child did not appear to be typically developing, due to a lack of expected behaviour and placidity and ought to seek additional support from a healthcare professional:

> *"She was such a good, good, baby… she didn't cry, I don't think I heard her cry for several months. She didn't really do anything, and everyone was like 'wow, she's such a good baby!'. It wasn't until she was about four months old that I went to visit my family and my mum was like 'it's kind of odd that she hasn't, she doesn't move'… you could put her on almost anything and she wouldn't move. She wouldn't even wiggle."*

In addition to a lack of crying, children had "*limited babbling*" and were reported to be calm babies with limited movement. This led parents to seek support from healthcare professionals who conducted exploratory hearing tests; in some cases, hearing problems were a related factor but speech/babbling was still delayed or absent post-intervention. One parent reported that whilst their child had multiple developmental concerns the most impactful, to them as a parent, was the lack of smiling: "*it was very difficult because you see*

*that your child has all these complications… what made me the saddest was that he didn't smile*".

Many caregivers highlighted that their children had delays toileting: "*Um, incontinence too, and I don't know – like he's going to be eight in March, so sometimes he gets really excited and he'll urinate, you know*"; "*So, um, yeah, as she's got older the gap has widened so the expectations of potty training for us have been very significant. We've tried so many times and everybody is convinced that she's been ready quite a few times, but we only actually managed it over the springtime. Um, so it's taken until she's nearly 8 to go to the toilet, but she really has got it now. She does have accidents; she does soil sometimes*". This was a challenge, for some, when considering education as described by the caregiver of a child: "*He still has nappies, and I don't know, he is not clean. School is totally out of the question*", but for others school aided the achievement of this milestone: "*Oh, school is her life, and… they've got her clean, they've got her dry. They've taught her so much*".

At home, and with siblings, negative behaviours were also present that impacted family dynamics: "*she might lash out at particularly her siblings, um, very rarely, if ever, people outside of her direct and close circle. So that hasn't really happened but within her siblings she has expressed a lot of anger and frustration and that has sometimes been physical*". This impacted levels of independence and trustworthiness: "*With that behaviour it's hard because it's not happening every day, it's happening infrequently so I'm just kind of like, if I ever let my guard down then she could burn the house down. So, yeah, as far as behaviours I think it's the absolute worst that I've ever seen with a child, I hate to say that about my own*

*kid because she does have her amazing moments where she is so great but, yeah, she has definitely had really severe ones*.", and impacted family relationships and social circles:

> *"Your circle of friends diminishes rapidly because he pulls their hair, and he pushes hot tea on top of them and they don't want to bring their children. Even family start to move away, yeah, they do. So, you end up with a very small circle of people and you can't bring him out to play centres or, because he would just pull hair, especially girls with long hair, he loved that. He would rob people's food and bite them and pinch them and all that sort of thing so you would just bring him to forests here it is nice and quiet and he runs around. Even his Grannies, he would pull their hair."*

The triggers leading to the onset of negative behaviours were notably unpredictable and diverse: "*And it's always something slightly different and you never quite know what it is that's going to set her off. Um, it doesn't matter if we have guests over – if they touch her food, if they look at her wrong, somebody else eats the last whatever, that's disaster. She always has to have as much as she wants – she'll just keep going, if there is food on the table then she'll keep going and stuff it in*."

At school, whilst some respondents did note that behaviours were improved in comparison to at home, negative behaviours remained apparent and impacted the school's ability to manage the child: "*Um, and he went to a huge school and there were like 30 kids in his class and he's used to having like a one to one or a very small classroom. Um, and he just couldn't handle it. He like locked the school down, he was having accidents, he was throwing up, taking*

*his clothes off, running, you know, um, so then they moved him to this other school*". All aspects of life, in some way, were challenged by behavioural outbursts for a significant portion of the respondents.

Whilst causation cannot be confirmed, it was reported that injurious behaviour was a problem in children with MYT1L-syndrome. This was present in interactions with siblings: *"Um, she's quite aggressive with her brother and she's constantly hitting him, pinching him*"; *"Sometimes he'll hit his brother*" and caregivers alike:

> *"At 6 years-old, maybe, she started hitting us, basically me. I've been her main target. It's almost like she will give you a hug and in the same breath she will punch you in the head whilst she is hugging you and then she will look at me and be like 'you happy? You smile? Show me teeth'."*

Respondents also said that biting was a common occurrence: "*She'd be segregated from the other children in class because she would bite people at school and family as well, her brother, [brother's name], she used to target him, a lot, when he was younger*"; "*She was aggressive with me for a while and she bit me, the last time that she really hurt me was last year and she bit me really bad, and it left a bruise*". Biting was not solely inflicted on people, but also objects, indicating that there may be a sensory element:

> *"She's always liked Play-Doh and, um, I guess the biggest thing over time is that she's stopped biting things. We've had to be really careful and limit in our house what toys*

*do come in because everything goes in her mouth, she chews everything, bites everything, tastes everything. Um, so especially if she goes to a birthday party and they get a little goodie bag we always have to rifle through it and take everything out before she gets it… The other day for some reason she found one of my silver chains and it was in her mouth, chewing on it, and I was like what are you doing? So, I mean, I keep thinking that she's over the chewing of toys but she's obviously not."*

Negative and harmful behaviour was not always directed at others and was reported, in a limited number of a cases, to also be directed at affected individuals themselves, as described by the parents of adults diagnosed with MYT1L-syndrome: "*She punches, she hits, she pulls her own hair. Everything that she does, she does to herself, but she also does it to other people. Um, she talks very loudly, and… she swears quite a bit, as well*"; "*There is a lot of self-injury*". This was noted to be a challenge to manage by caregivers and was often without a clear rationale: "*Before all of that he would have a hard time sitting in his car seat and want to get out of his car seat, you know, he would be self-injurious and he would injure himself, but… there was no rhyme or reason. He would just be mad, and that was difficult to handle*".

Although not widely reported, in addition to directing anger at others and themselves, individuals with MYT1L-syndrome were also reported to damage property: "*holes in the walls, she broke her brother's laptop, she punched a hole through our TV*", further highlighted through the following example of an affected child:

> *"The next one is property destruction… since about two to three years old every time she would get mad, she would break chairs and it was this big thing where she would just run up and just start flipping chairs and flipping tables and flipping anything that she could imagine and breaking them. She would throw things, um, she broke our TV stand because she threw an object at it, and it shattered… I think she just wanted to get our attention, so she went and broke all of the glasses in our kitchen and threw them on the ground, there was glass everywhere. That was a big one."*

Many parents and caregivers reported during the interviews that their screaming was commonplace. There are several potential reasons for this, which are explored in more detail below. It is plausible that, as individuals with MYT1L-syndrome are noted to have impacted speech, an inability to communicate was also a driver of behaviours including screaming: "*Well it all began with screaming, obviously when she was a baby, but when she got to about three or four, she just used to scream constantly. Um, and not just crying, just screaming and being really noisy. She didn't speak properly until she was four so, I think the screaming was probably maybe where she wanted to, I don't know what that was – but she used to scream a lot*."; "*She'd either scream or talk to you, but she would just hold her mouth open and couldn't use her mouth properly and she only had a cry that was one level – with most babies you can tell if it's a hunger cry or an angry cry or a pain cry, with her you really couldn't tell it was just a cry, always the same cry*".

An inability to communicate may not be wholly responsible for screaming and other factors should also be considered including feeling overwhelmed by a situation, as highlighted in the following example from a parent of a child:

> *"Dinner is a complete disaster every night. It's slowly easing up now but for years it's been, we're going to start dinner and then she starts like, escalating, because it's exciting or she's hungry or she's tired and then she screams throughout dinner until she's had a few bites into her and she's maybe calmed down and can start eating. But, there's a lot of, I don't know if it's anxiety or if it's excitement – we've never been 100% able to figure it out, but dinner time is a screaming fit every single night."*

It may also be that children with MYT1L-syndrome find it more challenging to manage being stopped from doing something or being told no by a parent, which leads to negative behaviours including screaming:

> *"Sometimes he has his little cries, you know, tantrums because he wants to do one thing and I say no because we're going to do something else and then it's hard for him to understand that I've said no so he screams and screams and screams. Then… you can change his idea by just 'oh, look over there' and then he'll stop crying and he will laugh - that happens quite a lot where he doesn't like my decision and then screams his eyes out, so that happens - a lot of screaming."*

**3.3.1.3. Subtheme 1.3: Anxiety**. The presence of anxiety in children with MYT1L-syndrome was reported by parents/carers in almost all interviews conducted in this study, with numerous respondents highlighting anxious traits came to the forefront as their child reached adolescence: "*as she gets older that's changing a bit because her anxiety is starting to take over*". The interviews revealed that education was a particular stressor that caused anxiety in MYT1L-syndrome individuals, with a typical example being travelling to an educational environment: "*There are some days that he is really anxious, and he doesn't want to go*". The separation from a parent or caregiver was identified as being particularly problematic and anxiety-inducing for affected children: "*he doesn't like the separation. He hates leaving mummy*".

Participants reported that within an educational environment there were multiple factors that evoked an anxious response in their child. Being expected to complete academic tasks such as mathematics or literacy was said to cause anxiety: "*they've got children in the class that are learning to read and write so they do encourage her to try but she almost has a massive anxiety towards reading and writing, and maths*". It was also evident that children with MYT1L-syndrome were anxious about trying new tasks or attempting to develop a new skill: "*she is quite anxious… I think she feels that she can't, not that she can't achieve things but that she is hesitant to try new things because… she is scared of not being able to do them*".

At home, increased levels of anxiety impacted family relationships: "*we are trying to juggle how we let [sibling] do what she wants to do without causing [daughter] anxiety, I mean it's the silliest things, but everybody has to walk on eggshells*". Increased anxiety levels were also

reported to impact children's ability to fall asleep: "*I think her anxiety levels are very high and that might be what means she can't sleep at night. I haven't done any research but that's just what I think about it. I know that when I'm anxious it is hard for me to sleep and she's constantly anxious about something, if I tell her that we have an appointment tomorrow she will be anxious thinking that 'I have an appointment tomorrow we need to be prepared'*" and also affect quality and duration of sleep: "*She has had times that she is very anxious where she will just wake and have tantrums in the middle of the night, which is really quite difficult, we haven't had that for a while, but we did have that when she first returned to school, so we do have disturbed nights with her*". Coping strategies included parents sleeping in the same bed as their child to aid settling, described by the caregiver of an adult: "*if I sleep with her, she will tend to be less anxious and sleep*". Parents and caregivers explained that increased anxiety led to episodes of vomiting: "*him having anxiety… he would vomit*" [child] and somatisation: "*when she is anxious that is when she has a stomach-ache - it doesn't just come out of the blue*" [adult].

Multiple parents and caregivers hypothesised that anxiety led to instances of physical outbursts: "*I think the best way to describe [daughter] is, she's fearful. Um, all the time she's on red alert… it's like she's frightened all the time and so, because she's frightened, she lashes out*" [adult]. One parent explained how their adult-aged child coped with triggering stimuli, such as people visiting their family home: "*If we see anybody they have to come to our house because [daughter] has her safe spot and her room that she can retreat to after she has slammed the doors and told them to fuck off*". Parents also reported that their child was

highly variable in their ability to cope emotionally, and this was particularly challenging for them to manage, as described by the caregiver of an affected adult:

> *"She was very unsteady emotionally and a little bit unpredictable and highly variable. Sometimes she would seem really, like, like she was interacting in a very normal way and other times she would just be having outbursts and, um, there would be other times where she would seem very withdrawn which we never quite understood. One day she would be really social and the next day she would seem that she wasn't really responding to the things around her. As a parent that was hard."*

**3.3.1.4. Subtheme 1.4: Executive Functioning & Emotion Regulation**. In addition to high anxiety levels, children with MYT1L-syndrome were reported to have poor impulse control, demonstrated through the following examples: "*he's very impulsive, that's one thing, extremely impulsive and high anxiety*" [child], "*she has no impulse control and is very impulsive*" [adult]. One parent reported that medication had helped their child manage their impulsive tendencies, but was mindful that they didn't want to reduce their child's character because of the medication:

> *"It's getting the balance with the medication because we don't want to just give her medication and take away the joy, um, but we want her to be able to function as well because she wouldn't even sit still and concentration was so fleeting before the medication that we thought it would help academically as well and school have said*

*that it does help, but more with the impulse control than the sitting and concentrating - she still doesn't sit and concentrate at school."*

A lack of impulse control was also widely reported regarding food and drink: "*he's very impulsive and very… heightened… he'll want to keep drinking it and drinking it*". Most of the cohort were reported to be *"really driven by eating… it's probably [their] main driver of the day"*, which demonstrated a fixation on meal times and the consumption of food: *"she is always after food, and she is always very focussed on food and what you are going to give her for lunch or what you are going to give her for dinner and things along those lines"*. Some participants felt that their child demonstrated behaviour suggesting an inability to feel satiated: *"I don't know whether she says she is hungry because her body tells her she is hungry even if she is not, or whether it is just that she is seeking another sensory input… she's started to take food now a lot behind our back"*. Many of the poor behaviours described by participants also related to food: *"all of her tantrums were over food… breaking things and aggression because I would say no to having a snack or something"*.

Many participants reported that some of the most challenging behaviours resulted from their child being unable to regulate and manage how they feel. Participants said that when their child was tired challenging behaviours arose and became problematic, as demonstrated in the following quotes: "*Yeah, so those kinds of things and mood swings, yeah, if she's tired then there is hell to pay or if she is hungry then we all get it in the neck*", "*if she starts getting tired then she gets aggressive and her day goes kind of sideways, So, she does, she needs somebody to kind of be with her at all times*". This led to adjustments in

education to make the day more manageable: "*right now she is only at school, um, two mornings a week. So, she is there for three hours twice a week, because she is just too tired, and she can't handle it.*". Tiredness, hunger, or other basic requirements not being fulfilled was also noted to lead to problematic behaviour – the cohorts lack of ability to communicate this with parents/caregivers seems to be a significant factor linked to this:

> *"The other thing is when she gets tired or hungry or if she's got a dirty diaper or something she gets really aggressive with other kids, which I think I mentioned, so we really do have to keep a close eye on her and how she's, her temperament, and how she's – if she starts to escalate then we need to be on it."*

Compared to same age peers, some children with MYT1L-syndrome did not seem as emotionally developed, or able to manage their emotions:

> *"One of which, let's call behavioural, um, so it impacts her ability to manage anger and frustration and it impacts the degree to which she becomes angry and frustrated. Because she now knows that there is something different about her and that makes her cross and not only does it make her cross but her ability to deal with being cross or angry is probably not as well developed or as mature as her age peer group."*

**3.3.1.5. Subtheme 1.5: Perceived Autistic Traits**. Whilst not universally reported, some parents explained that they perceived some of the behaviours exhibited by their child as characteristic of autism spectrum disorder (ASD), an example demonstrated here by a

parent: "*he does have characteristics of autism where he… stims*". One specific ASD trait that respondents referenced was rigid thinking: "*With a typical kid you don't really need to be that strict, they can have candy one day and the next day they are fine to not have it, whereas with her she's 'well I had it yesterday, why can't I have it today' so it's kind of made me, it's forced me into that super strict role and needing to have things done in a certain way and very controlling and it has just really affected us*". This is also described through the following example:

> *"It's been a struggle for [daughter], one because of the inconsistency - for instance, we go to baseball games, and we don't have to wear a mask when we sit there but if we go to soccer, we have to wear a mask. I told you before, she is very black and white and she gets that if it's a rule, it's a rule, but she's like 'mum why is it a rule here if it's not a rule there?' So, a lot more explaining as we go on."*

Other difficulties, described by respondents as being linked to ASD include difficulties maintaining eye contact, ability to communicate and social responsiveness: "*He obviously has an autistic syndrome as well, so it is very difficult to get eye contact with him and connections and exchanges. We do get some exchanges and there are a lot of things happening, but it is non-verbal, of course. It is pretty difficult in any case.*" [child].

Some respondents used the term ASD, instead of MYT1L-syndrome, when explaining their child's difficulties to professionals and education providers because it was more commonly encountered and therefore more commonly understood:

> *"No one knows what MYT1L is, so I feel like for the past couple of years we've just been saying he's autistic and he has this very rare genetic anomaly that manifests as autism. Um, but you know, autism is a, it's a huge umbrella"*.

Routine was another component, frequently cited as an ASD trait, that respondents often noted as a very important aspect of their child's life: "*So, she has, she has to have routines and they have to be a certain way*". It was widely reported in the interviews that individuals with MYT1L-syndrome had a strong preference for routine, which subsequently impacted various aspects of life but seemed to be strongly directed towards food and diet – highlighted through the following examples: "*She's very routine oriented so if we make the same breakfast every day that works really well for her*" and "*I'll pick her up in the morning and one of the first questions she will ask is 'what are we having for lunch?' So, it's very much a focus for her*". In addition to diet, this routine was also notable in sleep patterns: "*When he was about 2, he would go to bed about 8pm and he is very ritualised around sleep. When he was, um, I think, under 2 I remember he would have sleeps, little siestas in the day for about 45 minutes and that's it - no longer*", and observed in play: "*But, for the most part she always, she doesn't change her interests very easily and she always wants to play the same things… She's really into her routine so you see that in her playing as well*".

It was particularly problematic for respondents to handle ever-changing routines and uncertainty throughout the COVID-19 pandemic:

> *"Well in March we had the start of the lockdown which was when everything closed and the fact that his day service closed and his respite and everything, he just spent his whole time - he's very repetitive [son] - he just spent the whole time asking me when it was going to finish and when it was going to be over and it was like stop it [son] you can't keep asking, I don't know and I would ask 'how long is a piece of string [son]? And he would just look at me because of course he doesn't know what that means so I shouldn't have said that to him."*

Challenging behaviours were more noticeable preceding changes to routine or change within education: "*She used to hit and scratch when she would get really mad because I think that she just couldn't verbalise how she was feeling. So, we always had to prep her like 6 months before we changed classrooms or changed her schedule*."; "*and the routines, as I said she used to have these sort of chart things that you stuck on – she needed to know what she was doing every day. If anything differed, she couldn't deal with that at all, and that would result in the behaviours – the hitting, the shouting, the crying and that sort of thing*".

Whilst perceived ASD traits and a preference for routine was discussed by a significant number of participants interviewed, it is important to note that some parents/caregivers did not consider that ASD traits were exhibited by their child, with some respondents noting that: "*You know, there was some unusual behaviours that seemed to be, yeah, there were some that seemed to be on the autism spectrum, but they weren't enough for her to be diagnosed with autism*" and others that: "*[Daughter] doesn't have autism, she doesn't have any diagnosis of attention, ADHD, or anything like that*".

Challenging behaviours were not only identified as antecedent to routine change, and instead were reported to be a much more consistent and significant challenge for many respondents. Behaviours made going out in public environments more of a challenge, and social norms were seldom adhered to: "*her ability to act in a socially acceptable way. Challenging behaviour has become a lot more significant from the age of 5 or 6 onwards and we, that's probably, our, and her biggest challenge at the moment. People are very forgiving about lots of things but if she hits out at other children, or swears in public, then that's not quite so socially acceptable as a child who is perhaps non-verbal, and people can obviously see that there is something the matter*" [child]. These behaviours meant that simple activities of daily living, including a grocery shop, were made more difficult:

> *"She will sit and scream. If we are at the checkout she has made it all the way through the grocery store and she is doing really well and usually she will go over to this one section and she will sit on the stairs and watch me checkout - because I have to watch her because she runs - and she will just scream and hit herself in the head and right now it's a lot of F-bombs, she swears at people, she spits at people and hits herself in the head and does a lot of hitting out. A lot towards babies, I'm going to whack your baby - it's just, she's wonderful, she lets it go and she doesn't care who is around and she does not understand that she should be embarrassed."* [adult]

**3.3.1.6. Subtheme 1.6: Social Relationships**. Parents and caregivers commented that maintaining social relationships with others was, and is, very important for their child's

development: "*School is very important for socialisation for her, because she doesn't see anybody with, I don't know how to put it, she doesn't have people around her that are like her where we live. And she wants to play with younger children still, and um yeah school is very, very, important to her*". Despite this, it is evident from the interviews that, for some individuals with MYT1L-syndrome, establishing and maintaining such relationships did not come without its challenges. The social circles of children with MYT1L-syndrome looked different in several ways to typically developing children. One example of this is the size of friendship groups and the age of peers that children were most likely to socialise with:

> *"[Daughter] does find friends and warms towards friends and they warm towards her, and she develops good friendships with a smaller circle of friends than the average child, so maybe two, three or four people - that is increasing more recently but she has had tighter groups of friends throughout her schooling. They have always tended to be, um, of a lower age, so people that she can have similar likes, dislikes, and behavioural play patterns with."*

Challenges establishing relationships with peers was also noted by other respondents: "*Making friends has been difficult for her and she really doesn't have a huge friendship circle, there are probably only one or two [people] that she has got much of a relationship with.*" [adult]. Social awareness and comprehension appeared to be a contributing factor, whereby children were not aware of social constructs including 'best friends': "*you know, she just doesn't have those friendships… she doesn't have a single friend really. This is the age that you start making those, having those friendships and to her she doesn't really realise it*

*because to her everyone is her best friend, and she is so friendly, and everyone loves her, and she loves everyone, but she doesn't really have those close relationships. It's impacted her like that*." [child].

The development delays discussed in this section also appear to contribute to challenges with friendships and socialising as developmental, age appropriate, milestones were not being met meaning individuals with MYT1L-syndrome were at a different ability level, and therefore had different interests and mechanisms of play compared to age-matched peers, as demonstrated in the following example:

> *"What has been, what has been difficult is, um, for me, it's been really hard her not making friends particularly easy that's been a really difficult thing because, again, you have these expectations for your children, and you don't want to think that your child doesn't have any friends or isn't liked or anything along those lines. I don't think it's a case of her not being liked, I think it's more of a case of she's not at her chronological age, so it makes her difficult to make friends."* [adult]

Others highlighted that their child was able to form relationships but only at a superficial level and did not seem to form friendships with peers on a deeper, more meaningful, level: "*Yeah, she has a lot of friends at school but like I said, right now I don't think that she is really, I don't think she is getting those deep relationships*". Understanding social norms was also reported to be a difficulty, with one parent reporting: "*she'll just go up to other children because she wants to play so she'll stand in their space like 'hello, what are you doing?' And*

*they're a bit like [imitates stepping back], you know, and they'll walk away or if they're in a group they will laugh*" , and another that: "*She is very friendly and she will go up to almost anybody and say hi and sometimes it can be inappropriate and she wants to get too close to their face and she wants to compliment them non-stop and it's things that, there is nothing wrong with it but it's like um, we don't really do that - stuff like that*".

In addition to development, co-morbid medical conditions, and the resultant lack of independence, were also suggested to impact social relationships and the activities that children could participate in with their friends: "*I think about what typical fourteen year olds would do, like she doesn't, well some of it is a social piece, but she doesn't sleep over and I think that some of it is that she doesn't have friends to do that with but what I'm getting to is that since she has more dependency on us especially with the brace - she wears the brace at night and she needs us for that, so that's impacted us with the scoliosis which I think is related to the syndrome*".

Many interviewees reported that their children's play styles and mechanisms of play were also contributing factors to, often challenging, interactions with others. One challenge was an inability to play independently, with one description from a parent highlighting how a sibling may have to take on a more maternal role than they would with a typically developing child:

> "*Um, she looks after him and mothers him quite a lot. Very much so, definitely mothers him. But then sometimes she likes to be, quite like most kids they like their own space*

*but then sometimes they like playing with each other. Yeah, [sibling] helps him a lot and she pretends to be the teacher and she tells him to do this, that and that and he accepts it all*" [child].

Playing alone did not appear to be instinctive, and often had to be actively encouraged by parents: "*She almost needs to transfer her attention from one person to another. It's fairly rare that she will just play by herself for a long amount of time. So, she always has to be with someone which is either me or daddy or her brother and… she has to, like, be told that she has to go and play on her own rather than with her brother, like she won't just think of it herself she kind of goes from one person to the next*". This challenge was also highlighted by other respondents: "*She just follows you around and she can't come up with independent play, so although she can do a jigsaw or she can play with Lego… she wouldn't necessarily go and instigate that so, it is that intensity of her just being there with you constantly and that's quite exhausting*".

In addition to independent play, communication difficulties meant that children were often not able to take the lead and instigate games with peers and explain the rules of a game, for instance: "*What I know with friends in school, he's got lots of people that he plays with and looks for, but he does observe a lot and he's obviously not going to start making the games because he can't explain*" [child].

It was noted that these challenges meant that, on occasion, children with MYT1L-syndrome were the victims of bullying from peers within educational environments: "*she hasn't got*

*that one friend you know like most teenagers that have a best friend, you know, she'll play with anyone who says do you want to come and play with me [daughter]. She's a sheep, if somebody says jump – she'll jump, it's like that. She has had problems with people bullying her but they're on top of that. She doesn't react, only time she reacts to anything like that is when she is at home when her and her sister are arguing. At school it's totally different and it's 'no I can't do that'*". Challenges with social interactions, in some circumstances, meant that behaviours exacerbated, and subsequently individuals became further isolated: "*his behaviours were not diminishing because he was surrounded by all these children that were 'normal' and were having birthday parties and they wouldn't invite him and that sort of thing, so he felt very different which in turn made his behaviours worse, I think*", which was also challenging for the families of individuals with MYT1L-syndrome: "*The biggest one, I think, is that she is isolating herself more and more every year and by doing that she is also isolating the rest of us, and you just feel like you are put into this little, tiny box and the box gets smaller and smaller. I think those are the biggest downs*" [adult].

Many respondents highlighted that despite difficulties establishing relationships with peers, children with MYT1L-syndrome were very able to establish relationships with, and often preferred, teachers and adults within educational environments. One parent noted that when their child "*turns up at school, she knows everyone's name in every year group, she knows all the kids and all the teachers – from the cleaner to the site manager, everybody, she knows everybody, she asks questions and wants to talk to everybody – people are quite endeared by her*". A strong preference to socialise with teachers/adults over age-matched peers was observed throughout the interviews: "*No, he can't really form friendships with*

*friends his own age. With adults, he is much, much, better with adults, and he has a lot of friendships with adults*" and "*with teachers excellent. She is always, that is actually something that we've had to work on - she does not do well with her peers. I say do well, she just doesn't, she's not motivated or interested as much in her peers as she is adults, um, and it's also adults have always paid her attention because they enjoy her*". This, in part, may be due to the professional obligations of staff in educational environments who must be tolerant of behaviours, unlike peers: "*Like, socially, he's able to make friends now, but I think it's, he's a loving kid and he likes to be around adults more than children, but I think because kids get like annoyed with him.*". Adults are also more likely to support individuals with MYT1L-syndrome than peers: "*Staff wise, she loves hearing conversations going on, she can listen to 5 conversations at the same time and pick up information from each one. She definitely has preferred adults and likes the people that do the most for her, and that is who she is drawn to*". Whilst these may be contributing factors for some to prefer socialising with adults – one parent described the act of conversing with adults, rather than peers, was easier and more manageable for their child: "*she's so great with social interacting, um, before it was mostly just with adults. You know, she was able to interact with adults so much better than her peers, now that she is at school - the school isn't really teaching her anything academically because they don't really have a one-to-one to sit with her and help her, which is fine because what it has done for her socially is amazing*".

In addition to more positive interactions with teachers at school, respondents noted that more positive behaviours were exhibited at school compared to at home: "*Really good relationships with her TA, she's very well behaved at school - no behavioural issues at all*". The

unique personalities of children with MYT1L-sydrome meant that teachers themselves acknowledged that they could be a barrier to social interactions: "*um, so, with teachers, I mean, yeah she has no problem connecting and really we have to work on that because they were giving her goals to interact with her peers and they finally said 'it's our fault' because we're the ones that, if we're having a bad day, we'll go to [daughter]. She has people that she doesn't even have as a teacher [parent begins to cry] and they're like 'if I have my [daughter] everyday then I just know it's going to be okay' because she's very consistent emotionally which as I read about the MYT1L I know that people have such different experiences*". Positive behaviours exhibited at school appeared to correlate with a more well-equipped school: "*well equipped because of an incredible teaching assistant who was allocated as [daughter]'s one on one who has maintained with her over the last three or four years and has developed an incredible bond and relationship and she has patience to teach [daughter] and has increasingly let her have time in mixed groups lessons as well*".

**3.3.1.7. Subtheme 1.7: Motor**. One of the first indications of delayed developed for many caregivers interviewed was relating to motor skills. From an early age, children with MYT1L-syndrome were reported to have limited movement as a baby, for example:

> *"So, the first one was smiling and then the arms - he was really stiff, and he has really stiff arms and the mobile above his head he was just looking and wasn't moving. He was just looking at things without moving and without wanting to reach for things - so those were the first ones. Then came sitting, was a bit delayed at sitting independently*

*and staying, we could see that his balance was, it's still not great, it's getting there, so yeah those were the first ones. The smile was the first one for us. For me at least."*

The cohort of individuals discussed in this study were all reported to have significant gross motor delays from a very early age. Delayed motor control was a contributing factor to this, when moving into a seated position, for instance: "*He can, how to say, his head, he can't have his head up straight now, but he can stay, he wants to always lie down. He doesn't have the strength to be seated. His motor skill, it is like he didn't improve. For example, I do not see him sitting in the short-term*" [child]. Crawling and standing were both found to be delayed across the cohort: "*about a year ago he started moving around. He doesn't crawl and he doesn't go from his back to his belly on his own, but he can sit straight, and he moves around like in a seated position*." [child]; "*She finally stood at a year and a half, she stood, like, on her own which is usually kind of 8/9 months kids are trying to stand, right, so it's quite a bit later. She tended to be like 6 to 8 months delayed in most of her physical development, um, yeah*".

Compared to typically developing peers, all of the core gross milestones were delayed for the majority of individuals with MYT1L-syndrome, highlighted through the following examples: "*Peers were sitting up, she didn't until she was 9 months, then she didn't crawl until she was about 13 months and then she got up on her feet by 17 months and was able to walk by 18 months but just fell all the time, she fell over her own shadow – so she was always very wobbly*"; "*Physical manifestations are some of the ones that we have spoken about, so slower in sitting, standing, walking, running - all of which she can now do, but less capably than the average person of her age. So, they are the kind of macro motor skills*." [adolescent]; "*so she*

*walked late at 2 years - 2 years and 2 weeks is when she walked - so she was delayed in all her milestones but that was a significant one*".

Whilst individuals did, albeit delayed when compared to peers, stand and walk, it was noted that delays were still present in early adulthood: "*I guess developmental weaknesses are her, yeah, I'd say some of her motor skills are still not at an [appropriate age] level and she's a little bit clumsy in some ways, um, her, yeah, her understanding of things*".

Delayed gross motor movements meant that falls and trips were commonplace and were frequently mentioned during the interviews: "*she was able to walk by 18 months but just fell all the time, she fell over her own shadow*"; "*Um, she you know, if she gets a bump or a bang or a bruise and she has had her fair share of those in the playground because her motor skills are not as capable*". This, subsequently, meant that the need to replace uniform increased: "*You know, tights, ripped knees, if you're constantly falling and you're constantly damaging things*".

Falling and tripping may be, in part, due to a lack of spatial awareness: "*she was tiny, she would fall all the time, she would run into doors – we got a diagnosis that she's dyspraxic. If she was walking in front of you, she would fall, you know, if you didn't have hold of her, she would just trip constantly*". Other respondents commented that a lack of spatial awareness was present, as described by the parent of a child: "*He doesn't know where his body's at in space, kind of thing*".

In addition to gross motor movement, fine motor skills were also delayed. Respondents of younger children reported that delays were present in fine motor skills, and hand-eye co-ordination, from a young age: "*Now he is trying to grab things more, his toys. But it's difficult to co-ordinate his sight with the object, so I have to show him first the toy and wait, wait, until he sees the toy and then give it to him and then also wait again for him to grab the toy - it is very, I need a lot of patience and time with him*".

In early childhood delays were present in school when colouring, for example: "*Things like her motor skills and particularly, yeah, gross motor skills and fine motor skills - both were behind. So, things like, yeah, you could see in terms of when kids do colouring in and things along those lines, um, she was still scribbling when other kids were quite neatly colouring in between the lines and things like that. So, she has always been behind at school*".

These delays continued into later childhood where learning how to write, for example, was also, and in some cases continues to be, severely delayed. This is highlighted in the following examples: "*He's not a typical seven-year-old, um, he's unable to like, write his name – he can't write. Um, and I think that is where the fine motor comes in*."; "*Fine motor skills are more delayed still, I would say, so writing is very slow and she's getting, she's 11 years old and she's getting it but it's probably the writing of a 5-year-old currently, so that is quite delayed*." and "*He always played and, you know, it always went well and there were never any big problems other than he can't use scissors and he can't write*" [child]. Writing may be a challenge, in part, due to an inability to correctly hold writing implements due to poor grip:

"*her grip is very odd, um, she can't grip a pencil correctly and we worked and had every type of aid and bought things to try and it's not going to happen*" [adolescent].

A delay in fine motor skills was also present when eating, and holding cutlery:

> *"Um, when it came to knife and fork that was delayed because I think she found the manipulation in terms of using them, with her motor skills, or lack of, I think she found manipulating a knife and fork to be fairly difficult. She still, she will use them now and she's fine with them now, but she still is, um, she's, yeah, she's still not, I mean her motor skills are still not up to a normal [age-level] basically so it's a little bit awkward when she uses things, but she has no problems in terms of eating independently or anything along those lines"* [adolescent]

Other activities of daily living were also impacted by poor fine motor skills, and meant that individuals lacked independence:

> *"[daughter] has trouble tying her shoes and brushing her teeth and showering, like she can do it independently but if we did it every day independently there may be issues, you know, she wouldn't be able to shave, and she wouldn't be able to, her hair, she'd get too much of a build-up of shampoo because she can't really get that out."*

In addition to delays in gross and fine motor skills, some respondents highlighted that their child exhibited stereotyped movements: "*they actually thought that she had Rett Syndrome*

*and they were pretty positive about that because of the way that she constantly held her hands up and she was stimming. She would look past you*."; "*He's very impulsive, he does repetitive things, he has some stereotypic movements, you know*".

It is worth highlighting that individuals in this cohort do possess relative strengths when considering motor development and this was one challenge when making decisions such as which school their child should attend that would meet developmental needs in other areas whilst not neglecting relative strengths:

> *" I looked at a local school called [school's name] that caters for physical disabilities and learning disabilities, but she's, she's not quite in that group and I felt that she would be held back in the fact that she loves sport and she's really good despite all of her issues when she was younger with gross motor skills. She's really good at catching a ball, throwing a ball, you know, if you were playing cricket on a beach, she's the kid that catches the ball from someone else's cricket game – she just catches it, and it's astounding. So, I really wanted her to, to have access to sport with children that are capable to the same level as her, now there will be issues with her learning the rules about going offside or whatever – but she does love football, you know, she's very, so all those things I think the school will be fine for."* [adolescent]

### 3.3.2. Theme 2: Speech, Language & Communication

It is evident from the parents and caregivers interviewed that the early communicative behaviours displayed from birth were also affected. The first indicator of atypical

development for many parents and caregivers interviewed in this study was a lack of smiling as a baby: "*I suspected that something was not quite right, and he was not really smiling… that was the first sign*". One parent reported that another atypical behaviour that their child exhibited was that "*he stuck his tongue out* [which was] *very odd looking for a baby, I'd never seen that*".

Interviewees widely reported that their child had speech delays, demonstrated in the following examples: "*his language, everything was super delayed*", "*he doesn't speak, doesn't utter syllables and doesn't babble*" [child] and "*he can't talk, he only makes some sounds, but he doesn't talk*" [child]. In place of speech children were reported to scream or babble – "*she didn't talk… always just 'aaaaah'*". For children that did eventually develop speech it was at a much later age than typically expected: "*she didn't speak properly until she was four*" and "*she hasn't met any of her milestones… she was five before she started speaking*". Although some children have developed speech, albeit later than typically anticipated, there are children in the cohort that have not developed speech as demonstrated in the following example: "*he doesn't communicate, there is very little communication or clear communication*" [child].

Parents reported that speech delays, or in some circumstances a complete lack of speech, were particularly difficult and frequently led to the child becoming frustrated:

> *"Around 18 months we started seeing that she was getting really frustrated that she couldn't communicate with us, which is developmentally kind of appropriate that they want to start talking around then".*

In addition to children becoming frustrated due to a lack of ability to communicate, one interviewee noted that "*obviously the speech is a bad thing, that's a negative point and it's very hard to live with at times*" [child] demonstrating that speech delays were problematic not only to the individual but to the wider family network. Although speech was delayed, parents and caregivers interviewed noted how significant and important it was when their child did go on to develop speech and begin to be able to communicate, and how this "*changed everything… [because] she could tell you, or at least describe pain – she could never tell you if she had tummy ache or tooth ache, she just couldn't, and that's really the only last few years where she will describe it*".

Whilst some individuals did develop speech, parents and caregivers interviewed reported that speech was jumbled, there was an inability to understand speech and problems with word selection. An example from one parent described that their child spoke in an atypical way where:

> *"He does, like twisted, he um, he like will talk backwards – not backwards but he'll say something and get it mixed up. I'm trying to figure out what that is."* [child]

In addition to jumbled, or backwards, speech there were numerous examples of challenges understanding what the MYT1L-individual was saying when they were speaking. There was a lack of understanding for two overarching reasons: speaking too quickly and a more general inability to understand words formed. Whilst some children were reported to be speaking a lot it was "*very hard to understand at times*" and "*people can't understand some of the things he says*" [child]. An inability to understand speech influenced the way that parents interacted with services, including professionals working in education. One example given by a parent was that "[*the teacher] sends WhatsApp pictures so that when [child] comes home [parent] can say 'oh, you've been gluing today' and 'you've been making a hat' because [child] explains but I can't understand… the photos make it easier*".

Participants noted that word selection was also a problem where the incorrect word is chosen during speech, for example "*she gets melon and lemon mixed up so its melonade instead of lemonade… some days it is really hard to decipher*". The ability to access words was more challenging at certain times, including during holidays or periods away from school and when in an elevated state of anxiety. One parent shared that: "*she still has a hard time accessing her words… when she is emotional or frustrated*", and another that:

> *"When she is in a state of anxiety… she struggles with words, and she struggles with you talking to her when she is wound up, so we have to limit what we say and most of the time just walk away from her until she has calmed down."*

To alleviate frustration some parents and caregivers interviewed utilised sign language to empower their child to communicate. This was widely noted to be a successful intervention to enable communication through an alternative medium other than speech:

> *"We actually started using sign language and it helped immensely with her frustration and… she picked it up so quickly. She knew all of the animals… and to this day she still uses signs here and there to support her speech."*

It is evident from the interviews that MYT1L-syndrome impacts an individual's expressive and receptive language in different ways. Many participants stated that their child was much more articulate when speaking than they were able to understand: "*she's very verbal and seems to be very articulate, but she can say a lot more than she can… process and understands back*". This was shared with other participants who said that their child was often perceived to have much stronger conversational skills by those that were not familiar with their syndrome and was a challenge to communicate with teachers because "*she looks normal and sounds normal at a superficial level – whatever normal is*" and demonstrated another example where:

> *"She's been a conundrum for teachers because when she presents to them, she speaks very well, she uses appropriate words but she doesn't always know what they mean. Like, she can, if she interacts with you long enough, she will talk at your level and then I'll say, 'so what does that mean?' and she will say 'I don't know' – but she can use the words and she is very mature in how she speaks… so her teachers often get fooled by*

*her and… when they actually go to the testing she's not comprehending it… and not able to put things together so her receptive language is very behind"*.

Although some parents noted that expressive language was a relative strength, others noted that affected individuals reverted to scripted conversation that did not follow the flow of typical conversation and instead was based on common phrases used: "*even though he can talk to people a lot of it is scripted. He knows what things you like, like he will always say to women 'I love your hair' or 'I love your lipstick' because he knows that people like these things. It's kind of a scripted conversation*" [adult].

Participants reported that repetitive question asking was commonplace where "*he'll ask the same questions over and over and over… he loves to ask questions*" [child] and that children with MYT1L-syndrome exhibited challenges staying on topic during a conversation. One parent noted that: "*she'll peter off halfway through her sentences and can't sing songs – she just can't remember the sequence of words*" [child] and another that "*she talks around what she wants to talk about and she's very specific about what to talk about… in a way that she wants to say it… she has no interest… in anybody else*" [adult]. An inability to stay on topic when conversing with others was highlighted as being problematic when forming friendships with other children:

*"The school has reported that… the older kids would come and talk to him, and they said it would be hard to converse with him, like he couldn't stay on topic. If it is about*

*what he wants to talk about, sometimes he can, but a lot of the time his mind is going everywhere."*

Imitation was utilised by individuals with MYT1L-syndrome as a tool to aid communication, as a precursor to language development: "*He does imitate some gestures like clapping, for example, or he communicates with us when we make funny noises for example, he will be happy and will do some similar things. So, I don't know, like he doesn't communicate the way that we would expect him to communicate*" [toddler].

It was widely reported by participants that, in addition to the aforementioned speech and language delays and idiosyncrasies of communication, individuals with MYT1L-syndrome were much louder than their peers and are seemingly unable to moderate the volume at which they converse: "*she's always very loud and you always just have to constantly tell her, you know, to keep her voice down*" [adolescent] and "*she has this volume level that's like always loud, just loud*" [child] . This was most problematic when in public environments where volume contravened socially expected behaviours and parents reported they had to: "*constantly tell her to… behave in a particular way, you know, if we're in a restaurant then there are restaurant behaviours compared to behaviours at home and things along those lines*" [adolescent].

### 3.3.3. Theme 3: Cognitive Ability & Profile

**3.3.3.1. Subtheme 3.1: Intellectual Disability**. For many respondents, global developmental delay was one of the first indicators that their child was not typically

developing: "*We only realised that his development was not right, let's say, around that period. You know, when he was past 6 months*"; "*We knew that there was something not quite normal going on there because she missed, well not missed but her milestones were quite late*".

It was observed from an early age that, universally, milestones were not reached when expected, and instead reached at a much later stage than peers: "*Okay, um, so I think mainly it's the delays in everything – so everything, all the milestones have been achieved quite late so far. It seems that as she's got older it takes longer for the next milestone to come and it feels a little bit, to us, that she has always been – it seems to follow a pattern that she's always about half her age developmentally, not in every area*". This trajectory was consistent for other respondents who noted that developmentally their child was not at their physical age: "*Although she'll be thirteen… I'd say that she's probably seven or eight emotionally, um, not physically, but yeah and developmentally*".

The skills acquisition of children was reported to be a slow progress: "*It is all at very, his improvements are very little, very little*." [child]; "*we are still hopeful that he can improve. He does improve but very slowly, the curve is much smoother than it should be, but he does improve, slowly but surely*". In addition to developing skills later and at a slower rate than peers, one respondent highlighted that their child had plateaued developmentally:

> *"From, say, from about seven to puberty – she hit puberty about 13 – she had a, I think, I don't know what to call it, where she suddenly became more aware and more, um, I*

*think she did her growing mentally from seven to puberty and then it stopped again. Do you know what I mean? She, sort of, like became into herself, and I think that when she hit puberty it just stopped. She started being able to make herself a drink, she started being able to go to the toilet on her own, started being able to be a little bit more independent between seven and puberty and then it just stopped and there's no developmental difference. I think that's the age that she's set at."*

These developmental delays have a profound impact on various aspects of life for individuals with MYT1L-syndrome. This includes following instructions: "*I think there's the frustration that they're starting to have now, though, that they do expect their sister of 14 to understand things more like jokes or when I give them two or three or four step commands to remember and [daughter] is like 'what's next?' And they can be like 'come on [daughter] you know this' and she really doesn't and that causes some strain sometimes*", communication: "*She can communicate, she can talk. If she was here now, she can talk very well at a superficial level, but you can't get any deeper, yeah, it's hard to describe what's not there – but there is something not there*" [adolescent] and a lack of safety awareness: "*I know my mother-in-law mentioned a couple of times that she was here and, um, my daughter, like she found her in the pool outside - so that lack of safety awareness. She does get out of the house. I haven't experienced it too much recently because we got a top lock on our door which has been really helpful… this is something that we need to address because if that top lock is not on, she will get out of the house, the other day I found her walking out on the street because I forgot to lock it so that is a major concern*" [child].

Subsequently, the individuals in this cohort lacked independence in various aspects of life and required support to undertake activities of daily living. One area that individuals lacked independence was relating to personal hygiene: "*But yeah, I guess now, our big issue is around that she's started her periods and how do you explain that to an eight-year-old who's in an older body and the hygiene that's necessary with that? So, yeah, that's our recent milestone to overcome*"; "*she has a PA and they help her clean herself when she goes to the toilet and help her in her lessons and things like that*" [adolescent]. This meant that caregivers had to remain involved in the care and support of individuals, when typically developing peers of the same age would have developed independence: "*He always, he needs me all of the time*". This lack of self-care led to detrimental health outcomes in some cases, highlighted through the following example:

> *"Dental, she has had a lot of cavities and as far as I am aware I think it is because she doesn't brush enough - I don't think that there is anything biological that means she is inclined to dental issues. It has been hard to get her to adhere to certain daily routines. So, she knows that she should brush her teeth twice a day and she knows she should brush them before she goes to bed but she kind of forgets most of the time, she is doing it but not as much as she should."* [adult]

A particular difficulty that meant independence was challenging to achieve was individuals' lack of understanding of danger and ensuring their own safety:

*"Because the other thing too, it comes to me when I talk, she is very trusting so, like, we have to talk about stranger danger all of the time and we have had to go through a lot of scenarios because she doesn't understand the grey. If I give her an exact scenario, she'll be fine, it's fine, like you never go with somebody that pulls up in a car that wants to offer you candy, okay? She gets that. Somebody comes and says you want to help me with my dog, will you get in my car? Well mum didn't say not to do that, so I'll do that because I want to help somebody. So that impacts sometimes our ability to do things independently when at fourteen she should be able to do some of those things, like I won't let her walk around the block and we live in a nice neighbourhood and we know half of the people but she's very routine so she would walk the same way every time, probably the same time every day if we let her, and unfortunately that is not very safe for people to gauge on."* [adolescent]

Whilst many in the cohort experienced developmental delays, relative strengths were also apparent. One example of this is the use of technology, highlighted through the following examples that aid communication: "*And, um, she is able to read a little bit and she uses a computer really, really, well. She has a programme that speaks to her and she types, and it talks back to her, and that's really helped with her language, to a degree, and her reading. So, she's good at that*." [adult] and "*He will be going to speech and language three times a week at the moment, and he is learning to use a tablet with ACC, with the pictures on it, so that is her mission - to get him to use that so that he can communicate at school*." [child]. The ability to use technology confidently also meant that individuals with MYT1L-syndrome were able to reclaim some independence: *"I should make sure to say that she does do some*

*things independently like we have to get on the zoom calls and she is great with 'mum I need to get on my call' and she would just get on her call and be able to do all of that*" [adolescent].

**3.3.3.2. Subtheme 3.2: Memory & Encoding**. Poor memory was a problem for several children in the cohort: "*It's her memory, she just doesn't imprint, so, um, you could do the same task with her every day and on Friday it would feel like a new task, or you could read the same book and the really common words she would recognise, she might not recognise on the first page, she will on the second page and by the end of the book she's forgotten them again – so that impacted her*". This impacted multiple aspects of life for children, including the ability to remember instructions for a long enough period to follow them:

> *"I think one of the other things as well that is difficult for her is, um, it's always been sort of understanding instructions I think has been difficult for her, so, you know, she might if she was getting an assignment or something along those lines she would understand that she has got work to do but if a teacher said she had to do a number of things she really couldn't follow several instructions together so it was a matter of we had to split it up into this is the first thing you need to do and once you've done that this is the next thing and then this is the next thing. That is still difficult for her, so you learn not to give her terribly complex instructions when you tell her because if you run too many things together, she just won't be able to remember what they are."*

This also meant that children were, in some cases, unable to retain learnt behaviours, demonstrated through the following examples: "*Um, like riding a bike – he rides a bike, but*

*he struggles. It's like he has to relearn every time and he's a little nervous to do that*" and "*there is a need for constant reminding and it's almost like it's you every time that you've got to remind her to do these things and that's difficult*." [adolescent] and unable to remember sequences, such as when singing a song: "*Um, she'll peter off halfway through her sentences and um, can't sing songs – she just can't remember the sequence of words. And, um, yeah so that's quite frustrating to her – her speech*" [child].

Despite reports of poor memory and encoding, some parents did acknowledge that their children had good long-term memory: "*but her long-term memory is absolutely fantastic. You know, she reels things off, she retains information, and she holds on to this information, but like, if you ask her what she was doing in the kitchen ten minutes ago she'll say "oh, I don't know", no idea whatsoever, you know*" [adolescent]; "*so, she'll tell you the capital city of different places around the world, she'll tell you the history of the native Americans and she'll tell you all sorts of facts that she's got from watching YouTube and she does have an interest in learning.*" [child].

**3.3.3.3. Subtheme 3.3: Numeracy**. In the classroom, participants provided an insight into the abilities of children with MYT1L-syndrome and reported that numeracy was a particular area of difficulty. To access maths "*she needs a far more basic maths package, so everything needs to be at a primary/junior school age really. If they put those packages in place, then she can access those*". Parents reported that teachers did not fully understand the level of need that some children with MYT1L-syndrome had and what accommodations needed to be made for them to succeed:

*"Um, I've had a bit of a to-do with the school in the last week actually because I looked in her maths books and they've had her doing algebra with a child that can't add up, can't subtract, can't divide, can do her two-, five- and ten-times tables but sometimes can't. So, they had her doing algebra, perimeter, things like that and you just see that even though she's in an intervention group – it's still not at the level she needs."*

Some parents found it useful for their child to be able to use assistive devices such as a calculator: "*So, they instead of teaching, um, you know, without a calculator - she's able to always use a calculator. She's not going to be expected to do it without some assistive device*." [adolescent]. Participants expressed in the interviews that their preference was for numeracy to be targeted towards understanding real-world applications of numbers such as time and money management: "*So, from an academic standpoint our focus is around what are the core things that you need to succeed in society? So, I want to focus heavy on the math and the English but what's applied, um, science and social studies are great but not priority*." [adolescent]. This would be particularly useful for supporting more independence in this cohort of children as demonstrated through the following example from one parent, whose adult-aged child struggles with time management:

*"Making sure that she gets to work on time, time management is a huge issue for her. She doesn't have a good concept of numbers and she doesn't have a good concept of time so her, um, she can have the best of intentions but when she tries to get a certain amount done in a certain amount of time, she just doesn't gauge it very well, so we*

*have to continue to work with her on that. Her [support] drives her to work and that helps to make sure that she gets there on time."*

Money management was also a problem for individuals with MYT1L-syndrome: "*she has no understanding of, she has no concept of money. They've tried but, she can't, she doesn't understand money at all. They tried, but she doesn't understand money or numbers. She can't, she can count but not reliably*." [adult] and was commonly reported by respondents as a challenge: "*He doesn't really understand money either and he gets very, very, confused with that.*" [adult]. Whilst intellectual disability may play a part in challenges relating to numeracy and counting, multiple parents reported their child was very anxious when approaching maths problems: "*they've got children in the class that are learning to read and write so they do encourage her to try but she almost has a massive anxiety towards reading and writing. Um, and maths*." and another noted that their child would not attempt to solve the problem but instead guess:

*"She, um, there are things where, um, and like I said maths is a real weakness for her - so anything to do with numeracy is a real weakness for her and she'll ask about, she'll ask a question about money or something along those lines and you'll say 'you can work it out' just work out, you know, a simple sum and you can tell that she can't work it out and she just guesses answers rather than putting any thought into it. That could be putting her on the spot and her being a little bit anxious about it or she just doesn't have any idea about what you are after to solve that problem, but certainly anything numeracy is a real weakness for her."* [adolescent]

**3.3.3.4. Subtheme 3.4: Literacy (reading and writing)**. In comparison to numeracy, one parent noted that their child was more able when looking at literacy but still had difficulties centred around fine motor skills: "*Whereas numeracy is still 5 or 6 years behind her peer group. So, there's a real struggle with the comprehension of numbers but literacy is far better. Particularly in verbal and reading, less so in writing because that involves fine motor skills as we have discussed*" [adolescent]. There seemed to be high variability across the sample in relation to reading and writing and levels of ability differed between participants, and within participants, on occasion to a significant extent:

> *"Some kids continuing to be non-verbal until a fairly late age and then others, like my daughter, um, having a lot of areas where they are seeming almost normal but still having these issues. I wouldn't say that my daughter was normal but that very often people have said that there are some areas where she seems like she is just about where she should be, whereas she has the other areas where she really does have some significant challenges."* [adult]

This experience was not common across the cohort and instead reading and writing was a challenge that most parents and caregivers expressed as a particular difficulty, as demonstrated in the following examples: "*the fact that she can't read or write yet. So, academically, she's still pre-school in what she can do*" [child], "*The downsides are all the stresses of not being able to write*" [child] and "*Fine motor skills are more delayed still, I would*

*say, so writing is very slow and she's getting, she's 11 years old and she's getting it but it's probably the writing of a 5-year-old currently, so that is quite delayed*".

These challenges meant that adjustments were made in education, including placing emphasis on life skills opposed to academics and tailoring the curriculum to a lower attainment level: "*She still can't properly read and write but she has life skills, they've taught her life skills.*"; "*So, academically, I think they set the bar really low um, but he's trying to read, like he wants to know, and he's doing pretty good, like, he'll, he's started to read like little books, and I think he's doing well. But he's still very behind*". Parents and caregivers also reported that problems frequently arose at school because teachers did not understand the challenge that children with MYT1L-syndrome faced in comparison to their typically developing peers: "*so, she went to another school that used to be a private school and it was really academic, and they didn't have a clue what to do with her even though we'd done a transition. Um, and then you could see how far behind she was, she just couldn't keep up. She could barely read and write*". This meant that individuals were often set tasks that they were unable to complete: "*Um, so, yeah, so things like they're giving her assessments and I just wonder how she could do an assessment given she can't read*" [adolescent].

Multiple parents and caregivers also said that their child had special educational needs including a diagnosis of dyslexia, which added to the challenge of participating in school and maintaining progress alongside peers: "*So, she has dyslexia as well. Um, so obviously that must've been, everything must've just been jumping all around the place for her*".

To overcome some of the challenges, one parent highlighted that the use of assistive technology was a contributor towards to their success in reading and writing:

> *"Um, as I say, her reading is really quite good and it's all down to the computer really which was all through the special school. They um, introduced this clicker which she still uses – the programme for the computer – and that really, really, did help her. She can write, type, on the keyboard and she writes reams of stuff, her spelling I can understand what it means, and most people could. She doesn't spell accurately, but you can get the gist of what she's, she'll put for phone, for example, f-o-n-e rather than p-h-o-n-e. That sort of thing, but it's understandable."* [adult]

## 3.4. Discussion

The analysis provides insight into both how heterogeneous the impact of MYT1L-syndrome is on behaviour and cognition, and how profound and extensive the impact can be for affected individuals. It also provides deeper understanding of the cognitive and behavioural profile, building on the limited existing literature, and focuses on aspects of the syndrome that are most important for caregivers. The analysis identified that the impact MYT1L-syndrome has on behaviour is far-reaching and multi-faceted. Activities of daily living, including shopping or eating in public, were often challenged by hypersensitivity to sound, light and noise, whereas the opposite was reported relating to pain where some individuals displayed a hyposensitivity to pain that was often challenging for parents and healthcare professionals alike. From a very early age some caregivers reported unusual behaviours including a lack of movement, crying and limited babbling. Challenging behaviours presented from early infancy and continued through to adulthood – including injurious and self-injurious behaviour, screaming and anxiety. Executive functioning was impacted for some children, where they were reported to have poor impulse control, particularly relating to eating, and an inability to regulate and manage emotions. Many caregivers reported traits that they perceived as being related to ASD, including a strict adherence to routine, an inability to maintain eye contact and impairments to social functioning – although it is important to note that some caregivers did not consider that their child portrayed any traits characteristic of ASD.

From an early age, in some instances, participants were reported to have limited movement and low muscle tone. These gross motor delays continued into adolescence for some, and

falling, tripping and fatigue were notable during the analysis. Fine motor skills were also impacted, which meant that tasks requiring more precise control and movements, including activities of daily living such as brushing teeth and showering, were areas whereby affected individuals required additional support. In Williams syndrome, children are inhibited by hypertonia, or abnormally high levels of muscle tone (Morris et al., 1988) whereas in this cohort individuals were described as possessing low muscle tone, or hypotonia. This finding is corroborated by existing literature where six out of nine individuals with MYT1L mutations were also reported to have low muscle tone which caused subsequent motor delays (Windheuser et al., 2020). Further research investigating the motor delays experienced by individuals with MYT1L-syndrome will be beneficial in the future. Noritz et al., (2013) concluded that the identification of motor delays at an early age allows for appropriate interventions to be put into place, potentially having a more notable impact on motor abilities when instigated earlier and enabling clinicians to pursue earlier diagnostic testing. Given the rarity of cases currently reported in MYT1L-syndrome, access to testing for others with motor delays can only be positive and in the years to come may empower researchers to understand more accurate incidence rates of the syndrome in the population.

The data also begins to unearth the extent of the cognitive impairment for individuals affected with MYT1L-syndrome. Global developmental delay was reported widely by caregivers, and universally milestones were not reached when they were expected to be. An aspect of global development delay that was commonplace throughout the analysis were multi-faceted language delays. This is consistent with a recent case series

investigating the clinical aspects of MYT1L-syndrome that found 95% of the 40 participants included had language delays (Coursimault et al., 2022). An interesting finding from the analysis is that individuals with MYT1L-syndrome were frequently reported to be much more proficient when speaking than their ability to understand, or their expressive language was superior to their receptive language abilities. Whilst demonstrating highly variable abilities, like the present cohort, the opposite effect was observed in children with FXS who acquired expressive language skills slower than receptive language, gaining expressive language skills at one third the rate expected of typically developing children and receptive language at about half the rate (Roberts, Mirrett, & Burchinal, 2001). Conversely, individuals with the maternal uniparental disomy genetic subtype of PWS were found to exhibit higher expressive language abilities when compared to receptive abilities, but other genetic subtypes of PWS are associated with significant impairments to both expressive and receptive language abilities, when compared to verbal intelligence (Dimitropoulos, Ferranti, & Lemler, 2013).

Whilst caregivers highlighted the complex and varied nature of language delays in this cohort, ways to support and nurture communication for affected individuals were also discussed. One mechanism for facilitating communication for individuals that were non-verbal and those with language delays was sign language. Another method utilised to overcome communication issues in non-verbal children is The Picture Exchange Communication System (PECS). The introduction of using PECS in education settings led to, in one study, increases in expressive language, the length of interactions with peers and the time spent engaging in play with peers that was developmentally appropriate (Jurgens,

Anderson & Moore, 2009). PECS use was also found to lead to higher imitation skills, which was noted to increase the chances that a child will develop functional speech later in life (Carson et al., 2012). Research investigating the impact of using sign language and PECS should be explored further in this sample, and the findings of other research should be prospectively applied to the cohort with the view to potentially improving language development. Caregivers reported in the analysis that many children experienced social isolation from peers, which may be linked to challenges communicating. It is well-established that the symptoms associated with NDCs increase the likelihood of social isolation from others (Currie & Szabo, 2020). Children with communication difficulties associated with ASD have been found to be lonelier than typically developing children and compared to non-isolated individuals, and socially isolated individuals were at a significantly higher risk of poorer health outcomes as adults (Bauminger & Kasari, 2000; Caspi et al., 2006; Wilson et al., 2007).

The sensory profile (subtheme 1.1.) outlined by caregivers of individuals with MYT1L-syndrome featured a hypersensitivity to sound, including being afraid of loud noises and the ability to seemingly hear sounds before others. This is consistent with WS, where children were also found to be aware of sounds before others in the same environment (Bellugi, 1988). The fear of sound has also been found to impact children diagnosed with WS as demonstrated in one study which identified that when compared to children with a range of developmental disabilities other than WS, 90% of the WS cohort and 20% of the other developmental disabilities cohort respectively exhibited a behavioural reaction to sound (Gallo et al., 2008). This suggests that a hypersensitivity to, and resultant fear of,

sound may not be a universal experience for all children with developmental disabilities and instead specific to the profile of some syndromes. Additionally, it could potentially represent the co-occurrence of other NDCs such as sporadic autism, which sensitivity to loud noises is a prominent feature of (Landon, Shepherd, & Lodhia, 2016). Research has identified that children with WS are more likely to display problem behaviours because of exposure to noise (O'Reilly, Lacey & Lancioni, 2000). Whilst causation cannot be established in the current study, the hypersensitivity to sound reported by caregivers could be an influence on the problem behaviours described. This relationship is observed in Fragile-X syndrome (FXS), where sensory issues, including hypersensitivity to sound, were found to be predictors of how frequently a child would display aggressive episodes. The same researchers concluded that the presence of sensory issues, when in conjunction with anxiety, were predictive of how severe aggressive outbursts would be (Wheeler et al., 2016).

Aggressive outbursts, for a significant number of participants in the cohort, were a core feature in the behavioural profile exhibited by individuals with MYT1L-syndrome. These behaviours were both injurious and self-injurious, involved the destruction of property and seemed to be resultant to numerous stimuli. Many of the behavioural outbursts outlined in the interviews related to one common factor - food. Incidents of problem behaviour resulted from caregivers denying requests for more food and restricting the amount of food eaten by removing food items. Moreover, children exhibited strong routines centred around mealtimes and were often noted to repetitively question when the next mealtime would be, and what would be eaten. Numerous caregivers felt like their child did not feel adequately satiated after a meal, as typically developing children would. Similarly, children with PWS

are well-documented to exhibit these food seeking behaviours and experience an abnormally high desire to consume food, known as hyperphagia (Dykens & Shah, 2003). In PWS, these behaviours have been attributed to neural differences. When looking at photographs of food, individuals with PWS were found to display greater activation in the orbitofrontal cortex, medial prefrontal cortex, insula, hippocampus and parahippocampal gyrus immediately after consuming food when compared to a control group consisting of typically developing individuals of a healthy weight (Honea et al., 2012). These findings indicate that the underlying neural networks responsible for motivation function differ in individuals with PWS. Given that mutations to the MYT1L gene are noted to be associated to a predisposition to anxiety (Blanchet et al., 2017) future research should investigate the underlying neural mechanisms to understand the cause of the hyperphagia characteristics reported in the cohort analysed in this study. In individuals affected with PWS, such research has led to better awareness of the issue and the subsequent development of tailored dietary management plans (Miller & Tan, 2020) and therefore, whilst the underlying mechanisms may differ, similar outcomes should hope to be achieved for individuals diagnosed with MYT1L-syndrome.

In addition to behavioural outbursts targeted at others, individuals with MYT1L-syndrome were frequently reported to display self-injurious behaviours, including self-hitting and hair pulling. This behaviour is not uncommon in other rare genetic syndromes, including PWS (Didden, Korzilius & Curfs, 2007). In FXS, children were found to exhibit self-injurious behaviours such as finger biting most frequently following proposed changes to routine or the presentation of a task deemed challenging (Symons et al., 2003). In the ASD literature,

self-injurious behaviour is more widely reported than any other problem behaviour, and over 50% of diagnosed individuals are anticipated to engage in such behaviour during their lifetime (Baghdadli et al., 2003). In children with ASD, a recent study identified that a high frequency of repetitive and stereotyped behaviours was a predictive factor of the severity of self-injurious behaviour, amongst other problem behaviours, later in life (Oliver et al., 2012). The Antecedent-Behaviour-Consequence, or ABC, observation tool is commonly adopted to understand what happened prior, during and after a behaviour, and considers behaviours resultant from events as a method of communication (Lam & Gale, 2000). In children with ASD, the utilisation of the ABC model identified that the application of antecedent interventions including minimising schedule change, written descriptions of daily activities and encouraging a nap after a night of disturbed sleep all led to a reduction in the self-injurious behaviours exhibited (Mesibov, Browder & Kirkland, 2002; Clarke, Dunlap & Vaughn, 1999; Horner, Day & Day, 1997). Given the successful application of ABC observations in ASD, equipping caregivers and other professionals, including teachers, with the knowledge to understand activities antecedent to problem behaviours may lead to the identification of areas evoking the behaviour, and the subsequent development of appropriate interventions to reduce the incidence. Given the wide reports of self-injury in this cohort, and that self-injury has also been found to have a deleterious impact on quality of life for the individual (Duncan et al., 1999) as well as increasing the stress and depression incidence in caregivers (Baxter et al., 2000; Lecavalier et al., 2006), research should focus on understanding the incidence of self-injury behaviours in a wider cohort of individuals with MYT1L-syndrome and assess the implications of applying such interventions.

In this analysis interviewees reported, almost universally, that affected individuals exhibited traits linked to anxiety (subtheme 1.3). In addition to problem behaviours, this included social isolation and an inability to sleep. This finding is not unique to MYT1L-syndrome, and was also reported in children with PWS, where the behavioural profile of 28 children was found to include anxious behaviours (Walz & Benson, 2002). In addition to children with PWS being identified as exhibiting anxious behaviours, the parents and caregivers of PWS children were also found to display elevated anxiety levels, amongst other behaviours, when compared to controls (Skokauskas et al., 2012). This highlights an important avenue for future research in families of children with MYT1L-syndromes, as these behaviours may also be present and highlighting such findings may lead to the development of more robust and timely interventions for families in the future. Those interviewed in this analysis hypothesised that the affected individuals exhibited anxious behaviours when there was an expectation to engage with, or complete, new tasks or work towards developing new skills. Arguably, this behaviour is characteristic of Pathological Demand Avoidance, or PDA. A term initially defined by Newson (2003), PDA is characterised by an obsessive resistance to daily requests, sudden changes in mood associated with the need to feel in control, a lack of social constraint, and difficulties with peers. Children with PDA are noted to exhibit extreme problem behaviours when encouraged to participate in such behaviours, including aggression, and are reported to be less likely to access education due to the demands of expectations laid out in an academic environment. Whilst an interesting interpretation of the behaviours exhibited by individuals with MYT1L-syndrome, those documented as having PDA were reported to have typical intelligence levels, but were unable, or unwilling, to engage. This does not seem to be the case for those

discussed in this analysis, as profound, and often life-limiting, intellectual disability is frequently reported and anecdotally seems to be linked to elevated levels of anxiety. Critics of PDA question whether it is an independent syndrome at all, or instead a collection of symptoms with varying aetiologies, and many paediatricians now consider that PDA is a manifestation of ASD (Green et al., 2018). Furthermore, some propose that PDA is an over-simplistic theory that attempts to understand very complex and variable behaviours and does not consider individual differences, including anxiety, and the influence they may on an individual's approach to activities, including the tendency to avoid challenging or uncomfortable situations (Milton, 2013).

One study, which conducted semi-structured interviews with the caregivers of children with ASDs, found that behaviours exhibited which resemble characteristics of PDA were subtly different. Descriptions of PDA would suggest that children responded 'manipulatively' in attempt to control situations and avoid compliance with tasks, whereas children with ASDs were found to instead portray 'strategic' behaviours including refusal and behavioural outbursts to distract and divert attention (O'Nions et al., 2014). This research is more consistent with the behaviours reportedly exhibited by those in this cohort which arguably are strategic attempts to divert attention away from the task at hand, as opposed to the extreme and manipulative profile outlined in the PDA literature. One key difference in the findings from O'Nions et al., (2014) and this analysis are the sample utilised, as those included in this study do not all have a diagnosis of an ASD. Although it is evident that the individuals in this sample do exhibit traits that are characteristic of ASDs, including a preoccupation with routine, rigid thinking, and difficulties maintaining eye contact and

social responsiveness (Nicholas et al., 2008), other characteristics present across the cohort are not characteristic of ASDs and suggest that the overall profile is more complex and part of a phenotype unique to this cohort of individuals.

Intertwined with the challenges typical of ASDs, there are elements of hyper-sociability present that are conventionally uncharacteristic of the profile observed in autism; '*to her everyone is her best friend… and she loves everyone*' [subtheme 1.3]. Jones et al., (2000) corroborate this finding in WS, where children displayed behaviours that amounted to an overfriendly and engaging personality. In the current study, this was not only characteristic of some interactions with peers but also present in relationships with teachers and adults. Some caregivers outlined that whilst there were social challenges with age-matched peers, individuals with MYT1L-syndrome displayed a strong preference to form relationships with those older than them, including adults such as teachers. A strong preference for adults is observed in other rare genetic syndromes, including Sotos syndrome. Numerous research studies adopting standardised measures completed by caregivers, observational and case reports have documented individuals with Sotos are more likely to have fewer friends and exhibit solitary behaviours (Anderson & Schaefer, 2000; Sarimski, 2003). In addition to this, children were also found to portray a preference for spending time with adults over peers that were nearer to their own age group (Rutter & Cole, 2008; Cole & Foster, 2021). Researchers noted in children with Sotos syndrome, the preference to socialise with adults over peers is paired with significantly elevated levels of separation anxiety leading to anxiety when removed from their preferred adult (Sarimski, 2003). Separation anxiety was present within the current analysis, notably so when caregivers were leaving their child in

an educational setting. It could be proposed that those reported on in this analysis form strong relationships with preferred adults because of both the social isolation experienced due to an inability to form relationships with peers, and to overcome the separation anxiety experienced when they are removed from caregivers. Future research should further explore the dynamics of these relationships, as one parent in the analysis hypothesised that their child formed and maintained relationships with adults over peers because adults are able to perform more activities that are beneficial to their child, unlike those around them that are of a similar age.

This analysis provides insight into potential cognitive and behavioural difficulties from caregivers that encounter and overcome such challenges daily. To translate the findings of this research into a robust and quantifiable profile, enabling more standardised cross-comparisons to other syndromes, it is important that valid quantitative methods investigate any domains flagged from this analysis. Subsequently, the second part of this research project is a quantitative analysis, which utilises standardised clinical measures. The measures used are resultant from themes identified in the present analysis and investigate domains including communication, sensory profiles, anxiety, activities of daily living and physical activity. This iterative process was a conscious decision made when designing this research, and owing to the lack of previous research, it was deemed important that parental and caregiver insights guided which domains the subsequent stages of the project should investigate further.

# Chapter 4: Life with MYT1L-syndrome: a parent/caregiver perspective

## 4.1. Introduction

In addition to the impact that a rare disease has on the affected individual, it is well-established that caregivers, siblings, and members of the wider family are also impacted in a variety of ways. Prior to understanding the cause of symptoms present, caregivers are often faced with delays reaching a diagnosis and subsequently lack information about how to meet the current care needs of their child (Grut & Kvam, 2013). This, alongside a 'diagnostic odyssey' of incorrect diagnoses, hospital appointments, and the fact that approximately 50% of individuals with a suspected rare disease remain undiagnosed, is often burdensome for caregivers and severely impacts family health (Matilla-Deunas et al., 2017; Zurynski et al., 2008). Upon receipt of a diagnosis, caregivers often experience a marked decline in their own mental health given the potentially minimal preparation they have had for life with a child who has a rare disease (Pelentsov, Laws, & Esterman, 2016). The impact of a diagnosis of a rare disease is often so profound that psychological support is specifically recommended at the time of diagnosis (Kenny et al., 2022).

Following a diagnosis, caregivers are often faced with challenges accessing health services due to a lack of connected provisions, a need to visit multiple service providers, or due to a lack of awareness of specialist centres (Genetic Alliance UK, 2016; Muir, 2016). Parents of children with Rett Syndrome reported that they experienced challenges accessing appropriate health services, faced administrative barriers to existing services, and that a significant time investment was required to effectively navigate the health system and

manage healthcare interactions (Gueita-Rodriguez et al., 2020). Challenges are often also encountered when accessing appropriate education, where caregivers often have increased communications to coordinate suitable delivery and to ensure adequate personnel are in place to support the needs (Verger et al., 2020). Supporting the complex needs of an individual with a rare disease means that caregivers often need to quit their occupation or stall the progression of their careers and subsequently face an additional financial burden (McMullan, Lohfeld, & McKnight, 2022).

The complex needs associated with providing care for a child with a rare disease may also have a detrimental impact on caregiver health. This includes psychological worry, elevated stress levels, and depression (Weng et al., 2012; Powers et al., 2002). This is also reported to be the case for siblings of children with chronic conditions or rare disease who may experience reduced coping, social support, and be at risk of a reduced quality of life (Kelada et al., 2022; McKenzie et al., 2018). However, with the implementation of appropriate and timely support caregivers and wider family members have been found to develop adaptive coping strategies and reduce isolation, stress, and burden (Senger et al., 2016; Rice et al., 2020). Despite these challenges, some research highlights that positive adaptations can occur for many parents in the form of a changed world view concerning disability and the positive contributions their children make to wider society (King et al., 2006).

The present research aims to understand from the parents of individuals with MYT1L-syndrome the different domains of impact across the lifespan, not only for them but also the wider family. Whilst there is already an established evidence-base characterising the

impact on family life, a scoping review of unmet needs suggested the need for more research to better understand, and address, the distinctive care needs of caregivers and the wider family (Pelentsov et al., 2014). This is, therefore, an important avenue for future research as it will add to the growing evidence base of how caregivers are impacted by rare disease and may lead to the implementation of appropriate interventions and psychological support where it may be most valuable. Qualitative research methods are deemed an appropriate design when understanding caregiver impact, and have been successfully utilised in other rare diseases, as they enable caregivers to share an unabridged story about how family life may be impacted by a rare disease (Fortune, Reid, & Miller, 2013; Pasquini, Goff, & Whitehill, 2021). Using the published evidence relating to family impact in other rare diseases, questions relating to the impact on family life were included in the interview schedule to guide the semi-structured qualitative interviews in the present study. Broad topics of interest included the journey to a diagnosis, impact on family life, and the care needs associated with MYT1L-syndrome. Additionally, areas including, but not limited to, finance and work, sibling experience, and access to education and healthcare services were also included. The rewards and challenges of parenting a child with MYT1L-syndrome are explored in the interview schedule through questions similar to those posed by Lalvani (2008) in their study of mothers' experiences of parenting a child with DS.

Guided by findings from the wider literature describing the parental and family impact of rare diseases, it can be hypothesised that caregivers will describe the multi-faceted challenges associated with parenting a child diagnosed with MYT1L-syndrome. It is

anticipated that caregivers will report a challenging journey to reach a diagnosis, or a diagnostic odyssey, and difficulties in domains including work and finance, access to services, and the need to remain intimately involved in the daily care needs of their child.

## 4.2. Methods

This chapter addresses a different research question (family impact) using the same qualitative interviews (**Appendix 1**), discussed in Chapter 3 (cognitive and behavioural impact), which by design were broad in scope. Topics of interest included the impact of MYT1L-syndrome on family life, financial difficulties, and the experience of caring for a diagnosed individual. Therefore, the same data collection, data preparation and analysis techniques outlined in Section 3.2. were applied. In line with the methods discussed in Chapter 3, an initial coding framework was developed based on the analysis of four interviews and was then developed into a codebook (**Appendix 4**) as further interviews were analysed, and 20% of the subsequent transcripts were analysed by MF to ensure reliability. One additional participant was recruited to the study after the first analysis was conducted and was included added to this analysis exploring family impact, meaning that 19 participants were included in this analysis relating to parent/caregiver impact (see **Table 4.1** for participant characteristics). As Europe, the UK, and the USA, have similar cultures it was deemed appropriate to include all participant data in this chapter pertaining family impact.

| | |
|---|---|
| N | 19 |
| Age in years (of individual reporting on) | |
| Mean (SD) | 12.95 (9.85) |
| Range* | 0-5 (7), 6-11 (3), 12-17 (4), and 18+ (5) |
| Sex (of individual reporting on) | |
| Male (%) | 8 (42%) |
| Female (%) | 11 (58%) |
| Relation (to individual reporting on) | |
| Mother (%) | 15 (79%) |
| Father (%) | 4 (21%) |
| Location of residence | |
| United Kingdom (%) | 8 (42%) |
| United States (%) | 4 (21%) |
| Europe (%) | 3 (16%) |
| Other (Australia, Canada, and South America) (%) | 4 (21%) |

***Table 4.1.*** *Participant characteristics – Family impact qualitative analysis*

*Individual ages are reported in range brackets to protect participant anonymity

### 4.3. Analysis

The analysis resulted in the identification of five central themes: 1) Diagnosis MYT1L-syndrome, 2) Daily impact, 3) Involvement in care, 4) Finance and work, and 5) Other family members and support networks. Subthemes accompany many of the core themes (see **Table 4.2**). Theme 1 explores the journey to reaching a diagnosis of MYT1L-syndrome and the subsequent adjustments required, with many caregivers providing insight into their experience of the diagnostic odyssey and the need to persist through multiple incorrect diagnoses. Further, many parents felt the need to reframe their expectations of when developmental milestones would be reached following the diagnosis. Theme 2 focuses on caregiver impact and the impact on caregiver relationships, where many participants felt their ability to socialise was inhibited, and relationships with partners were strained and often adopted a dynamic of working as a team to provide care for their child. Theme 3 outlines the often-intensive involvement caregivers needed to manage elements such as finding and maintaining caregiving, managing the delivery of appropriate education, and challenges relating to the health service. Finance and work, Theme 4, provides an insight into the impact of MYT1L-syndrome on finance and caregiver work, where many participants reported the need to spend more money on specialist equipment, replacing damaged items, and travel to appointments. Further, there was a significant impact for many parents on the ability to maintain work and progress in their career, due to the demands and care needs of their child. Theme 5 outlines the impact on siblings and wider family members, and attitudes towards external support and the networks that parents of children with MYT1L-syndrome have sought support from. Where appropriate, to provide additional context and protect individual anonymity, age brackets of baby (during

pregnancy, at birth and up to 1 year), toddler (1-3 years), child (4-12 years), adolescent (13-17 years) and adult (18+ years) are provided alongside participant quotes.

| Themes | Subthemes |
|---|---|
| Theme 1: Diagnosing MYT1L-syndrome | 1.1. The journey to a diagnosis |
| | 1.2. Reaching a diagnosis |
| | 1.3. Reframing expectations |
| Theme 2: Daily impact | 2.1. Daily caregiver impact |
| | 2.2. Caregiver relationships |
| Theme 3: Involvement in care | 3.1. Challenges finding and maintaining caregiving |
| | 3.2. Involvement in education |
| | 3.3. Challenges relating to the health service |
| Theme 4: Finance and work | |
| Theme 5: Other family members and support networks | 5.1. Siblings |
| | 5.2. Wider family |
| | 5.3. Support networks |

***Table 4.2.*** *Themes and subthemes relating to family impact in MYT1L-syndrome*

### 4.3.1. Theme 1: Diagnosing MYT1L-syndrome

**4.3.1.1. Subtheme 1.1: The Journey to a Diagnosis.** Many interviewees noted that the first step that began the journey to reaching a diagnosis was observing that their child was not following the developmental trajectory that is expected in typically developing children: *"we knew that there was something not quite normal going on there because she missed, well not missed but her milestones were quite late"*. These observations were at different

developmental stages for different people, with some observing that their child was not behaving as expected as a baby: *"I suspected from the start that something was not quite right… he was not really smiling – that was, kind of, the first sign"*. For most participants, the acknowledgement that their child was not reaching milestones as anticipated was when their child was reaching early infancy and was coupled with a lack of understanding about why their child was not reaching milestones as expected: *"he didn't walk until 19 months… I didn't understand why his language, everything, was super delayed"*. However, there was still the expectation present, for some, that their child was developing later than others but would still developmentally catch up with their peers:

> *"From about the age of 18 months, I think we thought she's missed a few milestones here… I just noticed she wasn't, she was slow to sit, she was slow to walk, her language development was delayed, she wasn't putting words together like the other kids were, she didn't play in the same way as the other children did. So, it was pretty clear before she was 2 that there was something going on – but I didn't realise the extent of it because at that stage you are thinking, oh this will be fine, you know, she'll catch up with it, she'll be fine."*

A small number of interviewees reported that during a period of hospitalisation, or during other interactions, healthcare professionals observed that their child's developmental progress and symptomatic profile was not that of a typically developing child and that is what prompted the search for a diagnosis through genetic testing: *"during his stay in the intensive care unit… it was like a group of signs that were telling the doctors that something*

*was happening with him, and we needed to know why [son] had all of these little problems… they said that they believed it was something genetic".*

For other participants, comparing the individual's developmental trajectory with the older sibling(s) illustrated, much earlier, delays reaching milestones: *"we first started noticing that [daughter] appeared to be doing things a little later than her siblings were, right from sitting… she had no inclination to do that and appeared to lack core strength or leg strength or even coordination, motor coordination"*. Observing when a younger sibling reached developmental milestones was also indicative, to some, that milestones were not being met by the individual: *"she was my first child… when I had another child… who doesn't have any disabilities at all, I suppose that's when I started thinking [daughter] isn't reaching milestones"*. It was more challenging for interviewees who had only one child, or where the affected individual was their first child; *"She slept through the night and during the day she was very placid. I guess I didn't notice that she wasn't doing the things that she should have been doing because she was my oldest"*; *"she was our first kid, so we didn't really know much… she was such a good, good, baby, I don't think any baby is really that good"*.

Irrespective of when interviewees acknowledged that their child was not reaching developmental milestones as expected and felt that there may be a, yet unknown, underlying cause, participants shared, almost unanimously, feeling that they were alone because of how they felt: "*it was a lonely battle until I had received the results".* In addition to feeling alone, many believed that they were incorrect or *"worrying for no reason"* feeling the way that they did: *"it's difficult because it's frustrating that you can see something and*

*someone else can't and I think that impacted me… it was 'come on people there is something here, what are we going to do?' And then them just not getting it at all"*; *"once people diagnosed it was easier for me to deal with because it was not just in my head and a gut feeling… it was oh okay, I'm not crazy – there actually is something"*. Participants noted this was a common occurrence when interacting with partners: *"her dad was just like 'oh, she'll catch up, what are you worrying about? So a lot of people thought I was worrying too much"*, and with family members when respondents shared their concerns with others: *"a lot of people in my life would make out that I am imagining things and that it's not really as bad as I think and make me feel like I'm some terrible mother that is not able to handle their kid"*; *"it always felt like I was banging my head against a wall when I was saying something isn't right, something isn't right.. he wasn't supportive, he just didn't see it. If you're not there every day then the person who is, is the person who sees it. So, it was exhausting really, it was really, really, exhausting*". In addition to delayed milestones, the explanation of why behavioural concerns may be so prevalent to others was reported to be a challenge as family members *"didn't understand him at first and didn't think anything was wrong with him, which was hard because I knew in my heart there was something… people would just say he was naughty"*.

In addition to interactions with family members, interviewees reported that they also felt alone, and dismissed, during interactions with healthcare professionals and trying to share their concerns and make progress towards finding a reason for the profile their child presented with was like *"battling against the tide"*. One participant described interactions as *"very challenging… I would take him to the [doctor], and they would tell me that nothing was wrong with him"*; *"I was worried, my husband wasn't that worried, it was only me at the*

*start where I would say he's not smiling, I don't think it's normal… the health visitor was a bit dismissive"*. This type of experience was shared by other interviewees:

> *"I kept taking her down to the doctors because I thought she was having seizures and, um, they kept saying no there is nothing wrong, you're an over-anxious mother… I just kept banging on and he kept saying you're over-anxious, there's nothing wrong."*

As part of the journey, caregivers reported that their children underwent a variety of tests for other conditions, that were often intensive and time-consuming processes: *"she had been tested for Fragile-X and Prader-Willi syndrome when she was about two years old, and they were both negative. She had a more definitive test for Prader-Willi when she was 11, which was negative"*; *"they actually thought that she had Rett Syndrome and they were pretty positive about that because of the way she constantly held her hands up and she was stimming… she came back negative, of course"*. Prior to reaching a diagnosis on MYT1L-syndrome, many participants shared that they were given multiple other, incorrect, diagnoses: *"no one knew, they said that there wasn't really much to go off… and then he was given so many different diagnoses… we saw a geneticist and a neurologist and right away he was diagnosed with a different anomaly"*. For participants whose children had received a diagnosis, other than MYT1L-syndrome, there was a shared feeling that the diagnosis did not capture the full profile of their child, and that there may be something else responsible for the characteristics present: *"I joined a support group for parents and [daughter] just wasn't the same as all the other children… I mean, yes, they can't walk, and she can't walk but, I don't know, there was always in my mind something that was different about her"*. It

was this feeling of uncertainty that led to many caregivers requesting further testing, that led to the correct diagnosis, from clinicians: *"he got an extra diagnosis of autism but, I suppose, being a parent, you automatically think there is something else going on here and he didn't actually display your typical autistic traits… that's when we requested some genetic testing… we got the results… he didn't fit into the categories of atypical autism"*. Uncertainty, specifically around the diagnosis of autism, was shared with other caregivers whose child had received a co-morbid diagnosis; *"I'm starting to think… I read somewhere that kids are misdiagnosed with autism, because this manifests as autism – the MYT1L-syndrome"*.

**4.3.1.2. Subtheme 1.2: Reaching a Diagnosis.** Interviewees provided insight into the high level of involvement required from them as part of the diagnostic process, including staying away from home to undergo tests: *"we stayed up there for a few days, they observed [daughter], they observed me and her father… and observed us as a family"*. Another aspect of the diagnostic process that was reported as time-consuming was repeated visits to see clinicians, frequently over a period of multiple years: *"we started to see a geneticist probably when she was two or three… really to rule out things like Angelman syndrome and Rett syndrome and some other syndromes, so we started with a geneticist then and really, we went to see the geneticist about every 18 months to see if there was anything new"*. For some, accessing genetic testing was an involved process: *"we had run the gamete of what could possibly be wrong with this child, actually I was the one that suggested it to the paediatrician, I was like, well, none of this is adding up can we do genetic testing?"*.

The length of time to reach a diagnosis of MYT1L-syndrome was varied amongst interviewees, with some reaching a diagnosis when their child was still a baby: *"he was 5 months old when we got the diagnosis… when I compare to other people… it was quite early to have discovered that"*, whereas for others the journey was much longer: *"she was diagnosed a few weeks ago… we've been doing genetic testing for 17 years and they just discovered it"*. When comparing participants, it had taken less time to reach a diagnosis of MYT1L-syndrome for those whose children were born more recently – likely due to the advancements in availability and accuracy of genetic testing, and the acknowledgement of MYT1L-syndrome as a condition itself. This was highlighted by those where the journey to reach a diagnosis had taken a much longer period of time: *"we've been looking for a diagnosis for about 30 years… I think the syndrome was only very recently identified and so, therefore, it would have been impossible to diagnose her sooner"*; "*she was very little, they couldn't test for this and it wasn't a recognised syndrome at all, they weren't able to do microarray at that time"*; *"microarray [testing] wasn't widely available when we first realised that [daughter] had a developmental delay of some kind"*. The motivations for seeking a diagnosis for such a prolonged period were different for interviewees who were seeking a diagnosis for multiple years, as described by one parent *"we were honestly just continuing the genetic testing because I have sons… I wanted to see if something came through me, so they were aware. I would rather know what we were fighting rather than just being blind to it"* and felt a lack of motivation to continue testing: *"it was an answer… I wouldn't have necessarily pushed".* Similarly, older participants felt that they responded much differently to reaching a diagnosis, after waiting for often many years more than younger parents might: *"I don't think it was as crushing as it can be for parents with really young children*

*because by that time, we knew she had a disability of some sort – we just had no answer for it"*; *"I should imagine for younger parents or younger children who didn't have any diagnosis at all, it probably meant an awful lot more than it did to me… I've had years of diagnoses… it was just sort of like ugh – but it was good, I was pleased"*.

Irrespective of the duration of time that it took to receive a diagnosis of MYT1L-syndrome, all caregivers interviewed felt that the diagnosis accounted for many aspects of their child's behaviour and overall profile: *"we got this diagnosis and it made sense, even the sleep habits… and the overeating… we got this diagnosis and it made sense to us"*; *"when I read the leaflet on the syndrome I thought it so completely matched [daughter], that there was no doubt about it – this was what it was because she's got a lot of the characteristics that were in that leaflet and I thought that it was so good to have a diagnosis in order to explain to others what's wrong with [daughter] to get the sort of medical attention and help that she wants"* [49]. This prospect of access to improved services and funding was a relief to other participants, too: *"having this defined, because it's attributed to a disability, it'll provide in the future and… it isn't going to be a question because we can't define it if she is going to get some benefits for medical or things like that – so that was a relief"*. The diagnosis also meant that interviewees were able to communicate to others the reasons for the behaviours and symptoms present, where they may not have felt believed or empowered to explain why their child was behaving in the way they were before: *"when people might observe [daughter] doing things different we could now say that's because she has a 2p25.3 deletion, it's a chromosome deletion and it has a reason at last… that was a relief"*.

For all caregivers interviewed, reaching a diagnosis of MYT1L-syndrome was *"more of a relief than anything… it means that we are not daydreaming or, you know, having false hopes… it has a lot to do with what we can implement for him to improve"*. Some noted that the relief was due to having a definitive reason and explanation for why their child possesses the developmental profile they do:

> *"It was, it still is, quite emotional because… we expected that we would just not have a diagnosis and this was just our [daughter], and, you know, we just wouldn't. So, when the geneticist called me, she was in tears [participant begins to cry] and she was like 'we know' and I'm like no, everything that she's been through can't be attributed to one thing, and it pretty much is".*

The diagnosis was also acknowledgement that there was a reason behind their child's atypical developmental trajectory, and confirmed that there was an underlying issue:

> *"Relieved. So relieved… I say relief because it meant that it wasn't in my head anymore, it wasn't just like me making it up like there were all these little weird things and everybody around me kept saying no, it's fine, it's fine, it's fine – you're worrying about nothing. Um and, sorry, I get quite emotional about that [participant begins to cry] because it was a really lonely feeling, you know, and nobody else acknowledging that there was something and um, I mean she looks normal and especially at that age she looked like a baby and for everybody to say that no there's nothing wrong, you're making it up – it was a huge sense of relief when somebody said, no there is something.*

*Um, even though we didn't know what it meant, it just meant that suddenly doors would be opened for further exploration and more support from doctors and generally people will stop telling me that I'm crazy".*

Alongside feelings of relief, some participants reported that the diagnosis also raised questions of why the deletion had occurred:

*"Was it something that happened? Was it something genetic from us? That was something that went through our mind. Was one of us responsible genetically? Is there anything that we did through the pregnancy that is responsible? There was a feeling of what, or who, is responsible and we looked to ourselves and to what role we might have played in that. Was it that little bit of bleeding that might have happened… could that have played a role? So, so, many different things are flooding through your mind about what is responsible."*

Upon understanding the de-novo nature of the syndrome, once the reasons underlying the diagnosis had been given, many interviewees felt relief because it marked the removal of blame: *"I thought oh my God… it kind of felt like when I read that it was nobody's fault because, obviously, when I had a disabled child you automatically think that you are the mum, you're the person that has done something wrong"*; *"it gave us an explanation for her difficulties which in a way I think is quite good in the sense that you don't feel like, oh gosh, it's because I drank a glass of wine when I conceived her or whatever you beat yourself up about. So, for us, it was an explanation"*. The diagnosis also meant that the future could be more

clearly defined when considering future pregnancies themselves: *"we were keen to know whether there was something that we needed to be aware of if we were going to have more children"*, and for siblings, too: *"having it as de-novo, and knowing that it started with her… it was a huge weight off our shoulders because of [siblings] because I wanted to know I wasn't passing it onto them and that they wouldn't have to be dealing with this – so that is good"*.

It is important to acknowledge that whilst interviewees did report feeling relief, for a variety of reasons, some reported that receiving the diagnosis also felt like a powerlessness to change their child's outcomes: *"it was just a lot to take in, and it's detrimental… because there's nothing that you can do for it, you know"*, with a need to accept that their child had a disability: *"To go back to what you were asking me about the diagnosis and knowing that it is that specific genetic disease, it really helped in as much as we, it forced us to acknowledge that [son] had a disability and that we had to live with it"*; *"I think it was one of those where before we got the, perhaps I was probably a bit naive before but before the diagnosis there was, sort of, a little bit of well she is slow but she will catch up and after the diagnosis there was a well, there's not going to be catching up as such as I think the situation became a lot more real in terms of this is what we're going to be dealing with"*. It also meant that their child's developmental trajectory was now more defined:

> *"The emotional reaction when I found out was, again, mixed. It was a relief that we know and almost excitement that we now have an explanation and that it all fits, but at the same time it was okay – she definitely has something that isn't going to change."*

Further, the diagnosis also marked an uncertainty about what the future would look like for their child:

> *"Concern was our overriding thought, concerned for what [daughter]'s future might hold and concerned that she might never be able to enjoy some of the things that her siblings and her peers group were enjoying, concerned for what that meant in terms of our family nit and what levels of support [daughter] might require in the future, or worse still at that stage we didn't know if her developmental delay was a more serious condition that could even impact her, not just her quality of life, but also length of life"*;

> *"I guess disappointment in life in general because of what that means for later on for your kid… no one knows what is going to happen really to him because there is no description of him with the exact same genotype so, like, it's, I think that is one of the frustrations. All of those unknown characteristics and genetics. It's like oh let's wait and see."*

Factors, including the format that the diagnosis was delivered, also led to feelings of upset: *"I was given the diagnosis over the phone, quite abruptly. It wasn't great and I was very upset. I think we just hadn't really thought that anything would come back and then when something did, because nobody was there when I just got this call in the middle of the afternoon it was just horrible – it's not a nice way to deliver the news"*.

All interviewees reported that they were not provided with any, or limited, information about what the diagnosis was and what it meant for the future: *"when he gave me such limited information… I was just really upset"*; *"it raised a whole set of new issues as well, in terms of the frustration that was not knowing, and then still not knowing, what that meant for her future"*. Participants shared that they felt the process following a diagnosis was not as they expected: *"we got a paper and we got a short briefing from our paediatrician consultant, um, there appeared to be no real support network as to 'we will keep you updated' or 'we will keep monitoring her' there was none of that and it was kind of 'well if you think you still need to see a paediatrician to help with her development then we can kind of keep a conversation going' but she was basically signed off and that felt bizarre because once your child has a condition surely, um, they get under someone's care and control and they tell you what happens next and they tell you what you should be doing - but there is none of that"*.

All participants noted that there was a paucity of information provided following the diagnosis, and the ability of healthcare professionals to educate them about the syndrome was *"Zero. All I get is 'watch her weight, it's going to cause trouble in the long run' and nothing else, because nobody knows anything about it, nobody"*. This was shared by other caregivers: *"the diagnosis went to the paediatrician by email, and he was the one that told me about that. He didn't know anything about it either and he had only read what was explained in the results"*; *"Not, not at all. Not at all. No one knows anything"*. This lack of information is arguably anticipated given the lack of published research relating to MYT1L-syndrome; *"I don't think the understanding is there yet and we were supposed to be seeing a genetic counsellor every few years and… we saw her once when we were first diagnosed… she*

*imparted what she knew about the 2p deletion and that the MYT1L deletion was important and the weight and the challenging behaviour and that was it… so, yeah, there isn't the specialist knowledge out there"*.

In response to the lack of information provided by healthcare professionals, most interviewees reported that they *"went online and researched everything that we could find which isn't necessarily a good thing is it, but if there is no one to ask then that's what you do isn't it"*. Many felt that sourcing information themselves was the only way that they would find important information relating to the condition: *"It's only been up to me to make myself aware and to do the research and to know a bit more about it otherwise I don't think, I don't think that, if you were a parent and it was just here is the information and then it carried on as normal. There was no we need to do this now or do this now, there was none of that... We've had to do a lot for ourselves"*. The resource required and burden of needing to find further information was also evident from respondents: *"you eventually succeed in solving because you put in the amount of work or time that is needed and that is it… I guess that it took a lot of time to find - I don't know that all parents would have that ability, the time, and the resources to do that on their own without the extra help"*. Whilst some interviewees were able to source information due to their previous experiences: *"because of our background we already knew like the gene itself and, um, where to find the information"*, most caregivers did not have the expertise to assess information for validity and reliability: *"although I read something recently… that MYT1L, they discovered it in a lot of autistic children this deletion. I don't know if this is true or not. You read so much crap on the internet that I don't know"*. A common source of information amongst interviewees was the charity UNIQUE: *"I contacted*

*Unique… and they gave us a leaflet and that's where I've learned"*; "*I think I would have got it from UNIQUE, they give a very concise one-page piece on it"*.

**4.3.1.3. Subtheme 1.3: Reframing Expectations.** A major part of the caregiver journey once a diagnosis had been achieved was acknowledging the need to adjust parental expectations in line with the development of the affected individual. The lack of information provided by healthcare professionals at the time of the diagnosis made this adjustment challenging: *"because we didn't have any information on like why would she not be potty training, I reached out to the Facebook group and everyone on there was saying 'oh between the ages of 6 and 9 years was when their child potty trained. It was like, oh okay, we had to shift our entire mindset about all that, you know"*. Interviewees also noted that adjusting expectations from those of a typically developing child was a difficult transition to make: *"when [daughter] was a new child… your mindset is built around that more average frame of reference, um, so it takes you a while to reset that and you constantly re-calibrate it, but you learn that you have to give [daughter] her own frame of reference"*; *"So, it's a long journey. I learn that it is a long and a very slow, slow, journey. I thought that at this time he would be eating by himself but it's not the case."* [child]. This was not only applicable to development, but to other aspects of life including friendships and social skills:

> *"it's been really hard her not making friends particularly easy that's been a really difficult thing because, again, you have these expectations for your children, and you don't want to think that your child doesn't have any friends or isn't liked or anything along those lines. I don't think it's a case of her not being liked, I think it's more of a*

*case of she's not at her chronological age, so it makes her difficult to make friends. That's a really difficult thing to accept and how do you deal with it? Well, you don't, I think it's one of those things that you don't really ever get over. It's always there and it's not, it's not something that you think about everyday but that never goes away."* [adolescent]

One participant noted that whilst it was necessary to adjust expectations to account for developmental delays, it was challenging to not underestimate what their child may achieve:

*"I think one of the challenges that I do have is that I definitely do underestimate her and so that's something I always have to check myself on and actually her teachers are really good at that too and they say 'yeah, you just need to let her do that' and I'm like are you sure? She wants to go on a class trip and I'm like without, I'm not going? I know that she doesn't need me, but can I just be at the hotel at night [laughs]. They're like, she's got it."* [adolescent]

Although interviewees reported that they had adjusted their expectations, seeing other age-matched peers or other children developing was widely noted as a difficulty: *"Yeah, comparing with other kids is painful because you can see that they are developing, and they are growing up"* [toddler]; *"you see children that start walking and, yeah, I'm kind of getting used to it but you see kids that you have seen when they were born and months after you see them crawling and then walking and then talking and [son] is still in his pushchair and is*

*incapable of doing that and probably will never do that. That is really painful."* [child]. Interviewees reported that another aspect of adjusting their expectations was an uncertainty of how to best support their child to develop: *"the thing that I struggle with the most as a parent is just, is what we're doing the right thing to support her? You know?"*.

Further, participants reported that when coming to terms with their child's atypical development they often felt grief for the expectations that they had for their child's future: *"you have in your mind how things are going to go, you have in your mind what they are going to do with their lives and things along those lines and for me it was a very difficult adjustment when we got that diagnosis to, sort of, readjust your expectations and we hope that it is going to be a fulfilling life for her but at the same time that adjustment of expectations was difficult and it took me quite a while to come to terms with that. I'm still not sure that I completely am, but I'm certainly much better than I was when we first found out"*. This grief was described by other participants, too:

> *"I think that there is a huge amount of grief, um, for what you've lost [begins to cry]. I say to people, and it's hard to say, um, I didn't have plans for my children, I'm not a controlling parent, I didn't think that they had to go to university, or they had to have this kind of job, it's not that, it's when things are taken away from them that is upsetting. So, it's the fact that she won't be able to go to university, will she get married? Will she be able to have children and if she does how much will I have to be involved? Indefinitely. Um, just going to high school, everything is hard. Yeah, I think that's the impact [continues to cry]. It's the grief of what you lose, not necessarily what*

*I've lost, but what she has lost. I have to remind myself, and I think that when they're younger that is much stronger, and it is more intense and more regular and that is overwhelming. That you just can't go to the playgroups and do the things that other children can do, you can't do the sports day because your child is the one that is hurt, you can't do the school plays because your child can't remember the words, um, you can't just send her on a bus with her friends because she's vulnerable, um, at 13/14 she could've been going to the cinema and having that independence where you just drop off and pick up, which she could… but she is very vulnerable, she wouldn't, she's quite risk averse but she would potentially just walk off with somebody. Um, you know, she wouldn't cross a road, she's quite nervous about things, but I think it's that, it's what, what she's lost. But she doesn't know she's lost those things and she's very happy with who she is and what her world consists of, and I mustn't put my wants and needs and desires for her onto her shoulders"* [adolescent]

### 4.3.2. Theme 2: Daily Impact

**4.3.2.1. Subtheme 2.1. Daily Caregiver Impact.** The challenges present as part of MYT1L-syndrome resulted in an often-significant impact on the parent or caregiver's ability to carry out day-to-day tasks. Some activities that were frequently reported by participants as being a daily challenge were tasks such as visiting a shop or a restaurant: *"he wouldn't be able to handle all the people – he's better with it now but I couldn't take him to the store. I remember pushing him in the cart and the noise of the cart bothered him, um, so it's difficult"* [child]; *"If we are at the checkout she has made it all the way through the grocery store and she is doing really well and usually she will go over to this one section and she will sit on the stairs and*

*watch me checkout - because I have to watch her because she runs - and she will just scream and hit herself in the head and right now it's a lot of F-bombs, she swears at people, she spits at people and hits herself in the head and does a lot of hitting out. A lot towards babies, 'I'm going to whack your baby' - it's just… she doesn't care who is around and she does not understand that she should be embarrassed."* [adult]; *"There was another time similar where [we], walked into a restaurant for dinner and… all of a sudden there was this loud scream and of course everybody in the restaurant looked … and I remember feeling very uncomfortable. It was hard to control her, you really couldn't, you know, you couldn't. It could be very embarrassing in public. Those are the times that I really remember it."* [adult]. Opposed to retreating from the public sphere, some interviewees shared that they still participated in activities with their child, but chose different environments in line with their child's needs: *"you can't bring him out to play centres because he would just pull hair… he would rob people's food and bite them and pinch them and all that sort of thing, so you would just bring him to forests, where it is nice and quiet and he runs around and, you know, um, all that sort of thing"* [adult]*; "we would only ever eat out if it was a buffet and the food was ready because sitting and waiting in a restaurant is not possible."* [child]. Participants whose children were now older reported that this experience was familiar but became less problematic as their child reached adulthood: *"When she was younger, she couldn't filter out noise, you know, you couldn't take her into a supermarket, she can be very upset or into a restaurant should become upset because of the background noise. She can cope with all of that now, that's all gone and she's able to cope with noise and going into busy places and quite enjoys it now, which is very different to what she was when she was younger"*.

Another element of impact on daily life was the need to manage the different therapies and medical appointments: *"we have different therapies all the time… [he] is in therapy every day…so that's challenging too."*; *"basically our week is structured around the different care and the physiotherapist twice a week and once with the other, then, um, speech therapy, then, etc. There are five of them plus all of the paperwork"*. As therapies were not local to many participants, transport to various therapies that individuals were enrolled in was also an impact: *"I don't want too many therapies because we spend all of our time driving in the car and going places and it takes up so much time"*.

Many participants discussed the problems that arose from their child's eating habits and diet, and the reported lack of impulse control meant that caregivers often needed to control or manage what their child consumed: *"It's a battle, we've actually got locks on our doors, like, um… it is, a constant battle – she'll get up, she, most of the time she'll get downstairs before me… I've got to fly downstairs after her because I know she'll have put three slices of toast in the toaster, and if I go in the living room it's going to be a battle to get them back off her.* [adolescent]; *"At night time, I have to get rid of everything so that he doesn't continuously eat the wrong food. I have kind of trained him to eat healthy snacks at night now… food is a huge thing, a huge thing."* [adult].

Initially accessing services, or funding, was also a challenge due to the need to complete often complicated documents: *"difficulties we encounter are the paperwork"*; *"you go into all of the new world of form-filling and trying to make sure that she is getting the support that is required"*. Further, the inability to access specialised equipment was reported to limit the

ability to participate in tasks: *"we needed a stroller, but they were all up to 50lbs [weight restriction] and we tried to get one through the insurance… they wouldn't approve it, so we were left with well do we buy one or do we wait? So, we just started not going places with her too often that required a lot of walking but that was another thing, obviously if we could've afforded it, we would've bought it and it would have been super helpful for her to have"*.

Participants also provided insight into the impact on their sleep due to their child not sleeping or having short periods of sleep: *"he was never a sleeper, um, never, not even as an infant – he would just scream non-stop, all the time. It took a lot to get that kid to sleep at night, so I had a lot of sleepless nights"*. Participants described the impact of this on their daily life*: "We have been hugely impacted because well, it's very challenging to function without sleep… it's had a negative impact on our health and our cognitive functioning because we tend to now lose words, yeah, it's taken its toll."* [adult]; *"She really was, she didn't sleep well at all, and I can remember saying to people, [daughter] doesn't sleep very well, but nobody seemed really concerned by that. I was thinking, this is really difficult because she doesn't sleep, so nobody else sleeps- and people then get very tired, and [daughter] gets very tired"*.

In addition to the daily impact, participants shared that the needs of their child also impacted the ability to travel independently: *"you know, my husband and I probably haven't done as much like trips on our own because there are very few people that we would leave her with"*. Travel as a family was also reconsidered or delayed: *"there are trips that I want to take her on, but I've been hesitant. We've always wanted to go to [location]… I probably would*

*have done it younger, with my child younger, but I probably feel comfortable now… there are just some things that you hold back on from doing".* It was also considered a challenge because of the additional planning that was required: *"we are always thinking about where we can stop to feed him because I can't do that in the car… and he needs to take his milk, so that change, we are always, all we do is think about [son]'s needs first and we adapt our plans or what we want to do - we adapt the things that we do always thinking in [son]'s needs which is difficult. If you have a normal child where you can give him the bottle anywhere at any time"*. The inability to participate in events such as going on holiday also marked a need to adjust expectations:

> *"There are things that we wish we could do. We love travelling… at some point we were seriously considering travelling around the world… and maybe we will, but it makes things a bit more complicated and there are things that you wish you could do and, of course, it is very basic of a family with a child with additional needs, but it is totally new to us."*

The multi-faceted impact on daily life meant that some participants reported the impact on family life was *"horrendous, to be honest"* and *"very stressful"*. The profile of MYT1L-syndrome resulted in participants noting *"there is a lot we can't do as a family, um, we can't go for bike rides because she can't ride a bike and she is too heavy to go on somebody else's bike. Um, we can't go for big hikes, um, we, you know, there is a lot of things that we can't do."*; *"Obviously, you couldn't go to the beach, you couldn't go on a walk because she'd be exhausted – little did we know she was hypermobile so she must've been so tired trying to*

*walk, um, she couldn't really express herself"*. Interviewees also provided insight into the impact of behavioural challenges at home: *"it's always her, and her mood and her issues that dictate what we can and can't do. So, yeah. It's been really, it's had a really big impact on our family [begins to cry]"*. Coping with challenges such as behavioural issues day-to-day was also a challenge: *"the general day-to-days for a long time were quite difficult in terms of aligning her behaviours and her interactions with other people and with her brother and things like that. It just puts a bit of a strain on everyone."*; and *"it takes its toll. The family, um, can become very stressed and can argue and can, you know, you want a break from it all. You do".*

In addition to the challenges arising from the symptoms associated with MYT1L-syndrome, it was widely reported that a lack of understanding from the general public contributed to the difficulties undertaking day-to-day activities: *"everyday difficulties are people staring… people being rude"*; *"she can't advocate for herself, um, the fact that people judge her very quickly in a negative way sometimes is hurtful and that is a down"*. Participants reported that these experiences were challenging, and the lack of understanding was from adults and children alike:

> *"I think the hardest thing is growing broad shoulders really when you're out because people are judgmental… you sometimes forget sometimes that people aren't always quite understanding and not everyone is as, you know, non-judgemental. There have been times where I've had looks, she's had looks and I think the most distressing thing for me is to see other children's reactions to her when we might be in a playground*

*because she'll just go up to other children because she wants to play so she'll stand in their space like 'hello, what are you doing?' And they're a bit like [imitates stepping back], you know, and they'll walk away or if they're in a group they will laugh. Children understand about difference but they're not as tactful as adults are about it."*

This lack of understanding meant that caregivers felt that they needed to explain their situation to others: *"there is an ongoing social impact I think where you find yourself explaining to people around you that [daughter] might come across a little bit different to someone of her typical age, um, so that is an impact on how you, you know, how you would address social situations"*. One interviewee noted that *"we've just got a green lanyard… with the daffodil on them… she's just got one of them and that's been an actual godsend… that has helped quite a lot, people understand"*.

It is important to note that despite the various challenges that MYT1L-syndrome may pose to families, many interviewees described developing a resilience that enabled them to still participate in activities: *"Like, there are lots of things that we can't do, but we do them anyway most of the time*."; *"So we all did things, but it was all, family life is not normal when you've got somebody like [daughter]"*. One interviewee also described that a key part of living with MYT1L-syndrome was adjusting their expectations of what family life looked like:

*"I never thought we were going to be this family. I thought we would be camping all the time and I thought were going to be travelling and doing all these things – and we're not. It definitely guides how you are as a family, but instead we're having tea*

*parties and we spend our Sunday's crafting, and the kids are in the sun jumping and giggling… and that's fine. It dictates your life, but it doesn't have to be negative. I think that is important to say to new parents who are panicking about the diagnosis."*

Many participants shared that the inability, or added difficulty, participating in daily activities resulted in feelings of isolation: *"I kind of isolated us because his behaviours were so challenging – so we lived in like a bubble [cries] and didn't go many places. And I'm not like embarrassed of him, but it was like too hard to take him places and I didn't want people to talk bad about him"*; "*You are very isolated [begins to cry]. Um, and that's the same with all kinds of disabilities and genetic conditions isn't it, you are all in your own little bubble"*; *"Nobody visited because he pulled everybody's hair, he scraped their faces he did all of those behaviours. You would go from a normal household to a locked in household"*.

The feelings of isolation were, for many, specifically relating to social isolation: *"I don't want to say that we ended up losing friends, but you don't bond with people as much if you have a child that is always screaming and that needs all of your attention because you can't visit, you can't talk to somebody else when you're busy taking care of your child."*; *"If somebody came to the front door and I went to the front door he would get up on the table and go to the toilet, people stopped visiting and there is no two ways about that. I think that every special needs family will tell you that, your circle of friends diminishes rapidly because he pulls their hair, and he pushes hot tea on top of them and they don't want to bring their children"*. One participant reflected that as their child became more isolated, it impacted their ability to socialise, too: *"she is isolating herself more and more every year and by doing that she is also*

*isolating the rest of us, and you just feel like you are put into this little, tiny box and the box gets smaller and smaller. I think those are the biggest downs"*. The ability to maintain a social circle was also challenged by the increased demands relating to the care and support of the child with MYT1L-syndrome:

> *"I think nowadays, people are more understanding of disability, but if you go back… it was really quite difficult - and so, we didn't socialise much. We didn't have the friendships as a family that we would have built up otherwise, it just wasn't, it was just too difficult. It was just easier not to go out, not to have adult friends, you know, we became very organised around [daughter], because it took every inch of everybody's capacity to try and deal with that"*.

Some participants provided insight into how living with MYT1L-syndrome impacts existing social relationships:

> *"What worries me is that I need to do something different for my mental health, I need to do something. For example, I went out with some friends…and when we were having our conversation and all of my topics were about his medication or condition, I didn't have another conversation topic - it was all to do with the therapy. I was able to relate to the conversation, but it was always about the therapy or about [son]"*.

On the contrary, one participant felt that they had forged stronger social relationships because of their friend's involvement in care: *"I'd say that I have a probably even stronger*

*friend network where they do stuff with her. I have a friend tomorrow who is going to walk… with her… [begins to cry], so it's probably helped some of my friendships. They probably like her better than me [laughs]"*.

**4.3.2.2. Subtheme 2.2. Caregiver Relationships.** Many participants provided insight into the impact of the care needs relating to MYT1L-syndrome on the relationship between caregivers, the initial challenge to overcome was coming to terms with having a child with a disability after having a routine and typical pregnancy: *"we don't have anyone in our family with a disability, so this was totally unexpected for us"*. Coming to terms with the diagnosis was a challenge for many caregivers and presented difficulties in caregiver relationships: *"it is very painful to have a child with additional needs and there are tensions in the couple… there is tension between us, and we are trying to get over it"*.

Participants also reported that differing opinions of how to best support their child had caused tension in relationships: *"You know, a lot of the time we were told to ignore her swearing and it's like how long do you ignore it when she's shouting things at people? So, yeah, that's where we have a strain - having no time out and not always knowing how to deal with a child like [daughter] I suppose"*; *"You have to constantly be really strict, and I don't think that he really understands that. With a typical kid you don't really need to be that strict, they can have candy one day and the next day they are fine to not have it, whereas with her she's 'well I had it yesterday, why can't I have it today' so it's kind of made me, it's forced me into that super strict role and needing to have things done in a certain way and very controlling and it has just really affected us, but it's the only way that our life will be okay"*.

One participant noted that the caregiver relationships had been *"put on a complete back burner and we have become more of co-parent caregivers because I tend to sleep with [daughter] more than I tend to sleep with my husband because it is just the lack of sleep, if I sleep with her, she will tend to be less anxious"*. Other interviewees also described that the transition of their relationship to one of *"co-workers, like, you know, we're a great team but we don't get any time together and it does put a strain on our relationship"*, and there was a reduced ability for caregivers to undertake activities independently: *"The spontaneity of not being able to do what you want to do - when you get to 18 you should be gone and, you know, you should just be able to go out but, um, no"*.

The additional strain put on caregiver relationships, for some, led to the eventual breakdown of relationships and subsequent separation: *"we just got divorced. Um, it had, I think, it put a strain on our relationship"*; *"well, yeah, I think that it was probably one of the causes of the divorce – really"*. Additional strain was added to relationships for multiple reasons, including acknowledging the developmental delays: *"It was really, really, hard when she was a toddler. It was really hard. It probably was one of the factors that broke the marriage, um, because I could see that something was wrong and my husband… just didn't"*, and how caregivers should best support their child: *"We were separated probably for a lot of reasons; I think that difficulty being on the same page about [daughter] was one of the factors"*. As stated by other participants, it is important to note that interviewees did not wholly attribute the impact resulting from MYT1L-syndrome as the cause of caregiver separation, instead it was viewed as an additional challenge and variable to manage: *"I*

*guess my relationship with my ex-wife, [daughter] certainly wasn't the reason that we separated and divorced but it definitely was an added factor in it. I would never, I'm not blaming [daughter] in anyway but if you put an added strain on a relationship that was already under a lot of strain, so, yeah, it has had an effect"*.

Aside from the direct impact of MYT1L-syndrome on caregiver relationships, participants also reported how their experiences had informed their views when considering future pregnancies: *"keen to know whether there was something that we needed to be aware of if we were going to have more children"*. Understanding the potential impact on future pregnancies was one of the ways that interviewees felt healthcare professionals were able to support them: *"They could help us in relation to our decision as parents to have another, if we want to have another child, they can help us with information. For example, the possibility of that happening again - to have a child with the same condition or not. They could help us with that information, but they couldn't do anything for [son]. So, the genetic part there, I didn't receive the information. Nothing"*. One participant also reflected on how knowing about MYT1L-syndrome antenatally may have informed their decision to continue with the pregnancy: *"I feel like I've talked about a lot of things – but I don't know if I've covered everything. You know, with this pregnancy … one of the things people asked me was whether I wanted to do genetic testing and I know this is a big question in the genetics community. I don't think that [MYT1L-syndrome] is a genetic issue that is worth testing for in the sense of abortions"*.

### 4.3.3. Theme 3: Involvement in Care

**4.3.3.1. Subtheme 3.1. Challenges Finding and Maintaining Caregiving.** Interviewees provided insight into how difficult identifying and maintaining external caregiving was:

> *"There was nobody who I could get, who would look after [daughter] in the way that I would have wanted them to do. It's very difficult to get the right support workers, and it's very difficult, unbelievably difficult - and I tried… I did absolutely everything... to find that full time support and care is very, very difficult and they turned over quite a lot, obviously, you know, they went on and did other things"*.

This was a common experience that many other participants shared as being a difficulty: *"It's been hard to keep nannies, too. They didn't want to, they didn't come out and say it, but he was a lot of work"*; *"Um, I think, um, as [daughter] has got more difficult to handle, as a little girl she was quite cute and people would look after her and it's still acceptable to change nappies but as soon as she got to about five or six and got a lot heavier and started to become a lot more challenging in behaviour, still needed nappies on and still needed help then asking people to care for her is very difficult"*. This challenge also applied to finding respite services: *"Um, difficulties accessing services - we have difficulties with that. We have had difficulties finding care, like respite"*.

**4.3.3.2. Subtheme 3.2: Involvement in Education.** For most caregivers interviewed a significant amount of thought had to be invested in choosing the correct educational environment for their child, with many considering: *"what will be the right school*

*environment… Will it be a mainstream school or a special educational school?"*. The challenge identifying an appropriate environment was observed across all age groups, from nursery: *"we're a bit worried about putting him into nursery because we know that he doesn't need the constant attention, but he always needs someone."*, to school: *"she didn't get into the school that she'd been in for nursery… she went to another school that… was really academic, and they didn't have a clue what to do with her even though we'd done a transition"*, and higher education: *"they couldn't cope with [daughter] at college... they couldn't cope with her, so she wasn't able to continue to go to college"*.

One caregiver described that the cognitive and behavioural profile related to MYT1L-syndrome meant that specialised education may not be appropriate, but mainstream education would be too challenging:

> *"In terms of special schooling… it's a difficult one because she's not, um, I guess when you look at the kids that go into special schools, you're probably looking at kids with cerebral palsy and things along those lines who are potentially quite physically and mentally disabled or handicapped and she's not really like that. So, she's sort of, and again this is one of our frustrations, she sort of falls somewhere in between a kid that clearly needs that special education and a kid in mainstream education. She fell sort of in between that gap."*

This frustration was shared with other interviewees who felt that, because they were not in a suitable educational environment based on their needs, their child was not receiving the

most appropriate education: *"You move classes in high school, you have different teachers, they don't know you as well, um, they don't know the kid in the class who's struggling as easily. Um, so, yeah, so things like they're giving her assessments and I just wonder how they could do an assessment given she can't read?"*; *"we sent him to a "normal" school… they didn't want to take him because of his difficulties, but they did take him. It was really just like babysitting him and they used to ring me, I knew when the phone would ring… in the morning it would be school asking me to take him home so I wouldn't answer it. No, you know he is entitled to an education like everyone else, he's going to stay there"*.

The inability to identify an appropriate educational environment meant that caregivers often had to maintain increased communications, in comparison with the typical frequency of communication a caregiver of a typically developing child may have: *"The teachers are in daily contact through a written diary, um, and I just, you know, they are constantly on the phone, and they catch up with me quite often"*. Participants reported that the need to be in contact with school more frequently stemmed from needing to explain the developmental profile of their child:

> *"I have to, um, be a part of most first time interactions with people that are her teachers… or anything like that, um, because there's a miss and sometimes if they don't realise it, for instance we had an example of somebody that had known her for two years… want [her] to do homework one day… she can't grip a pencil correctly… and this person who had known her for two years, I said 'well how did it go today' and she said 'well we went to do some of [daughter]'s homework after school and she was*

*just giving me a tough time and she wouldn't hold her pencil right and she wasn't trying very hard and she was just, you know, she was acting' she said something like 'she just wasn't doing the work' and… I looked at her and I said, she's trying her absolute hardest… that is [daughter]. Of course, she felt horrible, but that's when I really realised that there is just this big disconnect that could be a real disadvantage for her."*;

*"I looked in her maths books and they've had her doing algebra with a child that can't add up, can't subtract, can't divide, can do her two-, five- and ten-times tables but sometimes can't. So, they had her doing algebra, perimeter, things like that and you just see that even though she's in an intervention group – it's still not at the level she needs. So, it's a slowly, slowly process to get the school to understand and to get that to filter across to each of her teachers."*

Interviewees, in addition to academic expectations, also found that they needed to communicate with education providers to realign expectations around diet and eating: *"I was talking to day-care providers, and I was trying to make sure that she wasn't over-eating at school. It is very hard with a child, as you may know, because school environments, everybody wants to give kids sweets - it's just, it makes them happy, right? For most kids it isn't a big deal but for [daughter] it definitely is a big deal"*; *"He came out of school the other day with four cans of soda, a king-size candy bar, a bag candy and I was like this isn't appropriate to give a child. That's why I had to refresh their memory about this genetic*

*anomaly, I was like there's a risk, you know, for obesity and we have to watch how much he eats"*.

For some participants, the inability for their child to communicate with them about their attainment at school meant that communicating with school was often the only way to find out information relating to their progress: *"We, every day, she sends WhatsApp pictures so that when [son] comes home I can say 'oh you've been gluing today, and you've been making a hat' because he explains but I can't understand. I've used the photos to make it easier for myself"*.

**4.3.3.3. Subtheme 3.3: Challenges Relating to the Health Service.** Many interviewees reported that the length of time required to reach a diagnosis, and therefore during the period of time that they did not have a diagnosis, meant that they were unable to access key services: *"we'd never been able to really understand what it [the syndrome] was… that made it very, very difficult, because people didn't really know, you know, there wasn't a diagnosis and so that prevents you accessing resources that you could otherwise, you know, get access to"*. or that they needed a diagnosis additional to MYT1L-syndrome to access appropriate services: *"most of the schools are for kids with autism and unless you have an autism diagnosis you can't attend that school… right now she is getting a low-quality therapy because she doesn't have an autism diagnosis".*

Following the journey to reaching a diagnosis, many participants reported that they continued to have challenges accessing the correct health services:

*"The geneticist was a great woman, she was brilliant, and she sent a letter to my GP, and nobody has ever mentioned it afterwards. Really, he should probably have been sent to an endocrinologist to get his bloods checked for his metabolism, for his dietician, all of that should have been done. I think, I don't know who should've referred him but somebody I think should have… I don't know what is the normal line that happens with this MYT1L, where do they go? What happens? What is the follow on? I don't know."*

Accessing routine check-ups was also problematic, with caregivers reporting that they had to be very involved in ensuring that appointments took place: *"She is supposed to have kidney scans um every year… it was always me who would have to chase anything and say 'oh [daughter] needs her kidney scan this year' and then they [GP] would have to chase it"*.

One caregiver provided insight into the tenacity required to access the correct services: *"We have had to fight our corner quite a lot, we're very lucky that we are quite articulate, and we can find our way around the system, but I don't know how that would leave people who are very unaware about what is out there or unaware of their own child's needs. I think the support is there, but you do have to fight for it"*. The feeling of needing to 'fight' on behalf of their child to access services was commonly reported by participants: *"Just fighting to get something recognised, you know, there's something wrong. It's just been one, long, constant battle with things like that"*; *"So, it's been really parent driven and I feel like if it, if it was um, someone who wasn't as kind of pushy as I am – I don't know that she would've got that much*

*service because again she looks fine, she has a genetic deletion, but someone actually said to us once that a genetic deletion doesn't mean anything, we need to know specifically what she needs or what you want to be done. So, you almost have to go to the medical professionals and say, like the paediatrician, we need a genetic blood test, you know. It's been a lot of fighting for things that I think she needs, but it's rarely come from the medical professionals"*.

Caregivers shared that they believed the ability to access services may not have been as challenging if their child had been diagnosed with a more well-recognised condition, opposed to a rare genetic syndrome: *"if it was Cerebral Palsy I'd have this, that, and the other chucked at me but, because it's not… one of the mainstream illnesses like downs or anything – I get, you know… I have to fight for everything constantly."*; "*because her deletion is really not particularly understood there is not, the support… in some ways, it would have probably been easier if it was a diagnosis like autism because there is probably more support for more commonly recognised syndromes and there are things that you can do. With [daughter], because she doesn't fall into an easily categorised basket, I think it has been difficult to find as much support that she could've used or that we would've wanted and that has been a little bit frustrating as well"*.

Many participants commented that they saw multiple healthcare professionals for a variety of reasons, including comorbidities: *"she's seen, I'd say every three months there's a whole slew of appointments and then they kind of "okay", we're all done with those and then everyone wants to follow-up – there's always a lot of follow-ups. Um, there's a lot of not doing anything I've noticed, which is quite frustrating because she's little"*. A common complaint

was that the health service was not connected and often resulted in conflicting advice: *"The health service is challenging, honestly. We tend to have specialists for different things… none of them really talk to each other and it is really like they are only looking at one specific area… it seems like we are trying to put out fires rather than manage the person as a whole"*. Despite seeing multiple healthcare professionals, many commented that they had minimal interactions with healthcare professionals relating to the diagnosis of MYT1L-syndrome: *"I don't think we've really, yeah, I don't think there has been a lot of interactions with doctors in particular about her syndrome particularly"*.

When participants did see clinicians, some reported that it was the first case of MYT1L-syndrome that the healthcare professional had encountered: *"So, the geneticist again said that [daughter] was the first in their practice and this is a nationwide children's hospital"*. Given this, and the lack of published literature relating to the syndrome, caregivers reported that the ability of healthcare professionals to educate them about MYT1L- was *"Really none. You know, they really weren't able to educate us at all on that. Again, that sounds like I'm being critical, but I guess it's just one of those where there isn't a lot of information out there so [shrugs] it is what it is"*; *"Not at all {laughs}. I think that I've learnt more from Google. Um, yeah, no – I don't think that anyone has spoken to me about the genetic syndrome other than the geneticist that we met once, and he gave me a brochure"*.

Interviewees unanimously reported that, instead, they had educated healthcare professionals about the syndrome: *"It's me educating them, I always when I go and see somebody new, I download one of them UNIQUE papers and give it to them. That's all I can*

*do"*; *"I've sent them the leaflet that UNIQUE sent to me, and I've sent that to the consultant psychiatrist… the GPs have got it written down in their record so that they also understand it, and I'm making sure that everybody recognises that she has got this syndrome, these features do actually exist"*. Participants shared that they expected this, given the rarity of the condition, but felt that healthcare professionals should have access to better resources: *"I feel like I am telling health professionals about [daughter] rather than them telling me about her, it's the other way around. I go to see the dietician and I am explaining to them what the chromosome deletion is and what it means… which is fine because I've a living and breathing 2p deletion child so I'm going to know a little bit more. I think more information for professionals would help really because they would then automatically know the problems that a child is going to have"*. Instead of educating caregivers on information relating to the syndrome itself, some participants felt that clinicians focussed more on managing the resultant difficulties:

> *"I think it's the case that they learnt to deal with [daughter]'s personality and what she needed at a personal level just based on her personality and things along those lines but in terms of the actual syndrome itself I really don't think that they understand that at all to be honest. I'm not sure, I'm just trying to think whether we would've provided them with the information that we had at the time, I'm not sure we would have told them that the microarray test has come back with this result but in terms of what that meant or what they needed to do, I'm not sure that there was anything specific for that, for that syndrome. It was more just that this is [daughter] and we will deal with her on a personality basis."*

Some participants reported that monitoring their child's development was an important part of both communicating changes to healthcare professionals and as a coping strategy for themselves: *"I also have a sheet in my computer where I, um, I have a graphic with our day-to-day activities because everyone says that I have to do a lot of things at home with him… For my mental health I did this spreadsheet with all the hours of the day, and I put there with a colour when he is asleep and when he is awake because I felt really bad when I couldn't do one of the things that I should, the day goes, the day comes to an end, and I start thinking that today I wasn't able to put him in the standing frame or do a lot of things and that helps me and also the doctors because I also indicate there all the seizures in the exact hour that it occurs"*.

Other interactions with healthcare professionals involved discussing the use of medications, where some participants felt that it was important to exert some caution relating to the use of medication to manage their child's condition: *"We have to be really careful with meds with her because most sleep meds and anti-depressants cause weight gain, so we have been really careful"*; "*it was very depressing because he had a new medication… he would be awake for about 5 or 6 hours a day out of 24 hours… it is a bit worrying and, I mean, last year when he would be awake for like 6 hours a day it was very worrying and we were very concerned*. The lack of information relating to the aetiology of the syndrome also made some caregivers concerned about the use of medications:

*"as a child, I would for her on her behalf, resist a lot of medication because I didn't think that was reasonable, because we didn't know what we were dealing with, and my concern was, if you give… a drug to a person who we don't really know what's going on with this brain development here, you might suppress something that could be really important in developing the brain. So, you know, I was very much one that didn't really want to give her a lot of drugs early on, because that just wasn't in what I thought was the best thing at the time. If I'd known what the syndrome was then, then maybe we could have done things differently. Who knows?"*.

As children outgrew paediatric services, some participants provided insight into their experiences transitioning to adult services: *"We are just getting ready to go into adult services so we are having to switch all of our doctors around - and we will see how that goes. You do find that they were really good to her and kind when she was young, but I'm starting to notice that she is getting a, they are treating her differently now she is going to be an adult - they are less patient, less hopeful, less kind and it's just kind of, yeah"*; *"As soon as she's turned 18 [services are] all taken away again and we've had to go into adult services"*.

### 4.3.4. Theme 4: Finance and Work

Most participants shared that they had encountered additional costs due to the needs stemming from MYT1L-syndrome; "*lots of sensory toys, lots of, you know, stuff to support her with her learning. We had to buy a lot of nappies when she was, um, with the continence team because they would only provide us with three and she needed ten because her bowels are so awful, so we had a big expense… because… we were having to buy the big adult ones. So,*

*yeah, that was quite a big cost and luckily, we are only using them at night"*. Other parents also shared that the cost of items such as nappies due to incontinence was a difficulty: *"because she wasn't potty training and because she's so large we ended up having to buy like these really big kid pull-ups that were super expensive, like the diapers were really expensive"*. Incontinence was also noted to cause other costs, including needing to replace household appliances faster than expected: *"Her incontinence, um she was doubly incontinent at one time… my dryer is on its way out at the moment again, like it never stops, the washing machine is always on, several times a day. You know, she's wet her pants or she's, yeah, she says that she's dribbled in her pants"*, and needing to replace items of clothing: *"when she was wetting, we would replace school shoes all the time because obviously she was wet, it'd run into her shoes, she'd be standing in them all day and they're going to be smelly"*.

Participants also reported that they needed to replace items of clothing damaged due to motor delays: *she goes through them pretty quickly, destroys them pretty quickly I should say… she's always falling or sitting so she destroys her clothes a lot… so yeah, it has been quite expensive"*, and also due to behavioural outbursts: *"the next one is property destruction… every time she would get mad, she would break chairs… she would throw things, um, she broke our TV stand because she threw an object at it and it shattered and another time she was mad and… she went and broke all of the glasses in our kitchen"*. Additional equipment was also reported to be an extra cost: *"we got her a different bike where there are three wheels rather than two - so there are extra costs that go into that."*; *"he needs a standing frame - well he needed a lot of equipment that I started, that I learn about them now, but I didn't know that they existed, a postural chair and a standing frame and a lot*

*of things"*. One participant also noted that when purchasing equipment: *"Um, yeah - everything costs a fortune for her… everything is bumped up because its 'special needs'"*.

Another cost was relating to care and respite: *"she just had these terrible tantrums and was just really demanding… we decided that she should go into a nursery and that we'd find the money just so that I had an afternoon a week as a break"*; *"she does respite care with [daughter] and we pay for that. We would probably have her to do it more if it wasn't so expensive really. It's probably once a holiday and once a term-time and she will take her out, so we've got that."*; *"we have people in the house that we are paying more than I would be making if I was out working and we can only have them in a couple of hours here and a couple of hours there"*.

To facilitate and encourage their child to become independent, some participants provided insights into the types of costs that they encountered as their child reached adulthood: *"helping to fund rent and her apartment because I want her to be in a safe and healthy apartment and that is not cheap"*. Other participants were already considering how they would navigate their child progressing into adulthood, and the costs attached to that; *"for her financial future we're already talking about buying a house near us, like a small home, because we think she can live independently but I want her within walking distance of our house"* [17]; *"Where is she going to live? What is going to happen? I think that [daughter] is probably going to be living in a residential home at some point… it's all out of pocket"*.

Participants that lived in geographies where healthcare had to be paid for, or required insurance, reported that there were also additional costs relating to access to health services or therapies. For some, this was initially due to the lack of a diagnosis: *"he wasn't given a real diagnosis – so sensory processing disorder, it isn't in the DSM – so insurance wouldn't cover any therapies for him. So that was an impact."*, and for others this was to access different medical specialists: *"We've also had access to any doctors that I've wanted because we could pay for it"*. The costs of trying novel therapies in the hope of improving outcomes for their child was also a financial impact: *"it's an alternative therapy… so we pay for things for her to help and I think we'll possibly look at paying for occupational therapy if we think that we need to because the sensory things aren't getting better for her really. It's knowing what will help her the most really*"; *"some of the therapies, she saw an occupational therapist for a number of years and things along those lines have probably been additional costs"*. Caregivers also experienced additional costs travelling to various appointments: *"we used to have a lot of interactions with… [hospital], which is about 90 miles away."*; *"Every time you go for an out-of-town appointment that costs you money in gas, and then you end up having to get lunch or whatever and, um, yeah, it's been quite expensive"*.

Some participants provided insight into the financial support that they had received towards these costs: *"I wouldn't say that I've had financial hardship because of um [daughter]'s disability because of [daughter]'s benefits. I've always used them for [daughter], so if she needs anything, she gets it."*; *"the speech and language is paid for, everything is paid for by the government, or the health and social services"*. Whilst participants shared that this financial support did help to purchase much needed equipment: *"we get… disability living*

*allowance… we didn't get it for a long time but, now that we do get it, it does make a difference, it does, it does for those kinds of things. Sometimes you think should you get it, but I was thinking recently, her high school, would I, even now it's extra stuff because she's started her periods and then she's bled all over her school skirt, yeah, it's just – it is constant. It just moves to a different arena of what she needs as she gets older. So, you know, this week my husband went out and bought a maths, a special maths toolkit that's really good for children that have no maths concepts… It's those kinds of things that gives you the ability to do things that you wouldn't be able to."*, others noted how challenging accessing the support had been: *"I've really fought hard to get the funding that she has needed. There have been additional costs, but I have been able to find ways to cover those"*. The challenge to access financial support was a common experience amongst interviewees:

> *"But it is very, very hard, I think, and very exhausting… the whole disability benefits system is very difficult. I had to go to a tribunal to get [daughter] [financial support], because I thought she needed it, and they said, no, you know, she doesn't, she's not, and I went to a tribunal, and we won. So, you know, it was all of that it's really hard to do, whilst looking after somebody who wants to eat all the time, who doesn't sleep very much, whose behaviour is very unpredictable. It's difficult."*

In addition to the financial impact of needing to purchase equipment, or access services, caregivers also shared the impact on their ability to maintain employment. Around half of those interviewed shared that they were no longer able to sustain employment due to the care needs relating to their child with MYT1L-syndrome: *"But, for her whole life we have*

*always had a parent stay home. It was just too hard to try and figure something else out"*; *"Well, I gave up work for a number of years when I had [daughter]…I gave that up, because I thought this isn't straightforward, you know, this doesn't look straightforward here - something's not right"*; *"I didn't work, I was unable to work because he was very, very, needy and… I couldn't find anyone to watch him… he had so many different therapies so that impacted me going to work"*.

Interviewees that were still in employment shared the flexibility that was needed to provide the support their child required: *"I found that she couldn't cope with after school care, she'd just be too exhausted… I work that around the fact that I need to take her to the bus in the morning and then I pick her up in the afternoon and then I'm home – so her healthcare is priority really, and her care is"*. For some participants, this meant working different shift patterns or number of hours per week: *"I've had to work night jobs; I can't work a day job and I'm never going to be able to work a day job because what happens when she leaves education?... I have to get back for them, early morning… and get them ready and put them on the bus to school or drive them to school. I'm like a zombie most of the time"; "Yes, so I can only work part-time really… I start after the school run and finish early enough to be back… I had to give up the career I had because it just wasn't doable"*.

Another challenge was the need to attend medical appointments and other services whilst balancing employment: *"so all of my vacation time and a lot of my sick time was used to go… nearby cities because you don't have all the specialists in your own city, um, so I even got reprimanded at work for using too much sick time for my daughter's appointments"*; *"I was*

*having to take time off to take her to the doctor... There were comments made by my boss… she was concerned that too much of my time and attention was taken up by [daughter]"*. Caregivers shared that another area of impact was the ability to advance in their career: *"I had another job offer… which I had to refuse because I was a bit worried about, I mean they asked me to move… I was thinking about all of the doctors' appointments and having to switch everything and I thought no I need more time to organise that"*; *"I missed out on some promotions and it's been obvious that I haven't been doing as much career advancement as my co-workers who, you know, are in the same position and their resumes are continually building and mine is pretty much stagnant because every lunch hour and every coffee break is spent talking to a doctor or emailing somebody"*.

Despite these challenges, some participants shared that maintaining, or returning to, employment was an important part of their ability to cope: *"I thought it was very important to work and to have that independence for me… So, I did a lot of different things to try and enable me to continue working"*; *"I haven't work for a year, more. That is what worries me… I need to do something different for my mental health, I need to do something"*. A small number of interviewees also shared that their experiences of MYT1L-syndrome had influenced their decisions relating to the sector of employment: *"in that way it's worked in a positive way for me because having [daughter], I went into um social work…. I would never have done that without [daughter] to be fair"*; *"In a positive light one of the reasons that I'm in the job I'm in today is because of her"*; *"I ran a youth club for lots of people with special needs - I got into that area and set up a support group for parents"*.

### 4.3.5. Theme 5: Other family members and support networks

**4.3.5.1. Subtheme 5.1. Siblings.** In addition to the widely reported impacts on finance and work, an impact was also felt for many in their family relationships. Interviewees reported a multi-faceted and varied impact on the siblings of affected individuals. For many caregivers, experiences with older siblings meant that atypical development was more quickly identified in the affected individual: *"we realised that his development was not normal, and we have a daughter [who is older, so] we have a good point of reference"*. In contrast, the birth of a younger sibling who overtook their older sibling developmentally highlighted concerns: *"when I had another child… who doesn't have any disabilities at all, I suppose that's when I started thinking 'oh [daughter] isn't reaching milestones'"*. For caregivers in either of these scenarios, who had more than one child, and irrespective of whether they were older or younger, seeing developmental differences was often challenging: *"as I see [my] two typical developing children growing, that's been emotional at times because… they were running up the stairs one foot after the other and [daughter]… had two feet on each step, especially coming down the stairs… I would find myself catching my breath like 'oh, that's what typical looks like'"*.

The atypical development, and associated care needs, reported by caregivers meant that, for many, affected individuals required much more attention than their typically developing siblings: *"[sibling] used to get left out quite a lot because I spent a lot of time with [daughter] and going to appointments and driving here, there, and everywhere… [sibling] missed out on playdates and things like that"*. One parent reported that the reduced attention siblings received growing up led to feelings of diminished importance: *"[son] told*

*me in recent years… that he always felt like he wasn't important to me – he is, but he never felt he was [begins to cry]"*. To overcome this potential issue, some caregivers sought additional, paid for, care services to ensure that they could spend quality time with their other child(ren):

> *"I suppose when my other children were young… he would have demanded a lot of attention and would have got a lot of attention, which means that they don't get as much as him - but then I made a conscious choice that he would have a home support person to take him out so that we could give [siblings] more time, which we did"*.

Whilst caregivers reported that challenging behaviours were targeted towards them, this was often also the case for siblings: *"she's quite aggressive with her brother and she is constantly hitting him, pinching him"*; *"with her siblings, she has expressed a lot of anger and frustration and that has sometimes been physical"*. Siblings were also reported to copy the challenging behaviours exhibited by the affected individual: *"[sibling] watches [son] and I think he mimics some of the behaviours and I was afraid of that"*, which for some caregivers presented difficulties when ensuring fairness in the standards expected of their children: *"and how to deal with it when you've got two other children in the home and not appearing to deal with it too differently, particularly with the hitting because [sibling] hits and we give him the message that he shouldn't but [daughter] is constantly hitting everybody in the house and he is growing up with that… it's how we best support her but also the [siblings] at the same time"*. Another way that caregivers felt they needed to adapt their parenting style was when disciplining siblings whilst being aware of the sensory profile associated with MYT1L-

syndrome: *"with [sibling], if I was cross, I used to have to say come on, let's go into the hall [calmly] and then go into the hall and tell him off and then come back and pretend everything is fine"*.

Caregivers considered that the complex additional needs of individuals with MYT1L-syndrome did impact siblings in many ways, some of which were negative. This included missing out on activities: *"[sibling] missed out on a few playdates and things like that – as she has got older, she wants to do her own thing anyway. I can't say that it's easy for [sibling] because I still don't think she understands"*, or caregivers being unable to watch, and encourage, when they took part in activities: *"even going to watch her brothers play football, typically I am carrying her off the field screaming and we sit in the car and I miss a lot of, I've missed a lot of the boys games and they stopped having friends come over to the house because [daughter] was having a temper tantrum"*. Another area of impact for siblings was the lack of respite they had from their sibling with MYT1L: *"her younger sister is the one that struggles the most in that… she's with [daughter] every night, she doesn't get a break and she just follows you – she just follows you around and can't come up with independent play… it's that intensity of her being with you constantly and that is quite exhausting really"*. Interviewees believed that it was important that they appropriately managed this as, their other children were growing up, to protect how siblings perceived their affected brother/sister: *"I think that as the other two get older, it's about managing then that they don't feel resentful towards her, and they feel that they can have time out from her and stuff without a big fuss"*. Many caregivers also felt, very strongly, that it was important to protect their other children from any caregiving responsibility: *"I was very aware when they were*

*growing up, I never wanted [sibling] to, I never asked him to help with [daughter] because [sibling] was a child and he shouldn't be helping me"*. Even so, some interviewees still felt that siblings felt that, one day, they may need to provide care and support: *"I encouraged [sibling] to go off and have his own life, you know, he's not got to live his life any way incumbent because of [daughter]… but I think he lives with the prospect that [daughter] will be his responsibility when I'm not able to look after her"*.

When asked about the impact that the challenges have had on relationships between siblings and the affected individual, some parents felt that the relationship was non-existent: *"they don't really have a relationship now… it's sad really"*; "*he doesn't want to be around her and he doesn't really like her, it's so heart breaking to see that he is happier without her there"*. Conversely, other parents felt that siblings had adopted a maternal approach to the relationship: *"even though [sibling] is younger… she babied her, very much looked after her… very protective"*; *"she looks after him and mothers him quite a lot. Very much so, definitely mothers him"*. In some instances where the sibling(s) were older than the child with MYT1L-syndrome, parents felt that there was a diminished impact: *"I'd go on to say that from a sibling perspective there is not a big impact on them because they have always known [daughter] as she is, so actually you don't differentiate whether your sibling is an average child or a slower developing child because they've always been like"*.

Irrespective of the impact on relationships with siblings, and challenges that they may have needed to overcome, parents all believed that there had been some positive impacts on their other children: *"her brother has learned to be… responsible. He's learned that he has to*

*be a bit of a role model and that he has to help her and I see that translating into his other relationships… like at school he got commended quite a few times… for being such a good helper"*. Other caregivers also felt that siblings had matured earlier than peers because of the circumstances presented at home: *"he's matured early and happened to be a very caring person… he is very accommodating and [their relationship] may be strengthened by the fact that he has empathy for her condition"*. Siblings were also reported to, in some cases, have unique insight into how to best support their brother/sister: *"he can see [behaviour] from a different perspective to me and he'll often say 'well, the reason [daughter] is doing this is that' and… that is what is causing it. He's really good at seeing the world through her eyes and he's absolutely excellent at managing her"*.

**4.3.5.2. Subtheme 5.2. Wider family.** In addition to those in the family home, extended family members were also impacted. Like primary caregivers, in the period prior to a diagnosis of MYT1L-syndrome most in the extended family did not understand what was wrong with the affected individual: *"before [the diagnosis] I don't really think anyone understood it… my family, you know, they didn't understand it"*. Caregivers reported feeling more equipped to explain developmental delays and other symptoms to family members after receiving a diagnosis, and many felt that family members began to understand the potential longevity of the issues: *"it gave them a reason… when she was little a lot of them were convinced that it was just something she would grow out of"*. For many, however, even after a diagnosis understanding was minimal, despite caregivers *"trying to educate everyone"*, with many of those interviewed believing that there should be a better way to educate families about the syndrome:

> *"Relating to family, I would love to think that there was a greater way of educating family - bringing it to life a little bit without having to use those proxies of an unknown condition. Something a bit more helpful than a white paper to try and describe the condition, um, I understand the value that white papers might have in academia, but they aren't the most family friendly bit of education. So, something that would bring that alive for initially parents but then for family would be valuable, and that doesn't seem to be in place"*

Understanding the cause of the syndrome was also challenging, with some family members attributing the blame to parents: *"they didn't really understand… they said 'it's just because you were too old to have a kid'… and no, that wasn't why"*. Further, the wider family was reported to not understand the behavioural phenotype associated with the syndrome and believed that poor behaviour was a result of parenting: *"they put the blame on me, like 'you just don't know how to deal with her' and that kind of thing"*. Not understanding the extent of the challenges present also meant that the expectations wider family members had of children with the syndrome were not appropriate: *"I can't trust [family members] with her to like go somewhere because they're like 'oh, she's fine, she's old enough' and actually, no, she could potentially walk off with a stranger or get lost because she would lose her way, and they don't understand that"*.

It is potentially this lack of understanding that meant some parents felt that their wider family treated their child differently to others: *"knowing from fairly early on that she isn't*

*academically inclined, and she isn't going to get into university and that sort of stuff there was maybe a little bit of a lack of interest from their point after we found out what was going on"*. Others hypothesised that family members did not demonstrate an interest for other reasons: *"none of the extended family contacted me and asked me about it or what [MYT1L-syndrome] was. It's weird, isn't it? They're kind of afraid, I always think that they are afraid… to come near to you, I don't know really, maybe they feel that they might catch it"*. This placed a stress on relationships with wider family members for some and meant that contact broke down: *"it was like too hard to take him places and I didn't want people to talk bad about him. So, yeah, there's been family… and the relationships just [continues to cry] – it impacted relationships."*; *"We honestly don't have a lot of family support. [Daughter] has been really challenging so, um, we have lost a lot of family and friends over the years. So, I think, um, you know, I think that they are happy they don't have to worry that their kid is going to get it or their grandchild, but not a lot of input"*.

On the other hand, some caregivers interviewed felt that they relied heavily on the care that their family, primarily grandparents, provided: *"I couldn't have done it without my parents, they used to help me with [daughter] and look after her"*. Challenging behaviours, however, meant that this was not always possible: *"their grandparent… she couldn't handle them, and I think it was too stressful for her to be around them, so she hasn't seen them in a while"*.

**4.3.5.3. Subtheme 5.3. Support networks.** As, for many, there was a lack of support from wider family members, caregivers often relied on support from external networks. This included respite care that meant siblings were able to receive more focussed attention: *"we*

*applied for some respite so that [sibling] can have her space and we can have space away from her, too"*. Respite care was also seen as a valuable resource to have time alone as a couple, for some parents, and contributed to the maintenance of their relationship: *"we have respite… he and I are going to have a drink and it brings you right back, it reminds you that you love each other"*. Others, however, reported that accessing such support was a challenge: *"she will be going into respite care, which I've been screaming for, for the last twelve years. So, we're just waiting for that"*. Further, not knowing where to access appropriate services was cited as a difficulty: *"It is the not always knowing the right people to ask and what to ask for. Um, that information is not always forthcoming to start with I don't think"*. The COVID-19 pandemic also meant that support previously in place was withdrawn *"he had a little bit of respite but that stopped with the COVID, and he did have a home support person that took him out but that has stopped as well. He doesn't have anything now really"*.

External support was an important element to coping as a parent of a child with a rare disease, with some caregivers accessing counselling or similar support: *"Um, I'd probably say that I had a bit of a breakdown… I had post-natal depression and then a very difficult child, having had a very difficult pregnancy. So, I had some counselling then."*; *"I did see a therapist for quite a long time as [daughter] was growing up… it was an important part of my support system. It meant I had someone to talk to each week about whatever was stressing me, and I could get some level-headed advice on parenting"*.

An additional source of support, for most caregivers interviewed, was from other families who have a child with MYT1L-syndrome, many of which were signposted to a family support

group on social media by the charity UNIQUE. This was considered a meaningful support network, where caregivers could learn from others who may be in similar situations: *"I was part of the group on Facebook and just connecting with all of those parents and learning about things they are going through, I'm like wow. A lot of people in my life would make out that I am imagining things and that it's not really as bad as I think and make me feel like I'm some terrible mother that is not able to handle their kid, but seeing everyone else going through the same stuff was like wow, okay, they are all having the same behaviours and the breaking of the chairs, and the smearing across the walls and all of that"*. In addition to learning from others, parents felt it was important to share their experiences for those with younger children diagnosed with the syndrome: *"I do try to let people know that, you know, there is hope for a lot of things for your child - they may not go to university and may not get a college degree and most of them don't get a regular high school degree but there is still a lot that they can do, and they are going to go through a lot of normal development as well"*. Although most caregivers felt that having access to a platform that facilitated interactions with other families was useful, others felt that they were not able contribute: *"I thought, I'd have really welcomed the knowledge that I could've possibly shared, but I thought I just don't have the emotional strength… I didn't want another person needing me"*, and others felt that the heterogeneity observed in the syndrome meant that comparisons with other children were of limited use: *"each case is very different... it depends what part of the gene is missing and how the kids are being brought up… I want to focus on [son] and who he is rather than looking at other children".*

## 4.4. Discussion

This analysis outlines the multi-faceted, and highly variable, impact that MYT1L-syndrome has on numerous areas of family life, both for caregivers and wider family members. Whilst there is a paucity of research in this area directly relating to MYT1L-syndrome, this chapter provides insights that are consistent with the, often well-established, literature base that exists within other rare genetic syndromes exploring the impact on family life. The analysis identified that, in Theme 1, for all those interviewed, diagnosis was a long, challenging and often very involved process to overcome. It was seldom reported that being given a diagnosis of MYT1L-syndrome was an easy journey, and many participants felt that they needed to advocate for progress to be made on behalf of their child, in some cases for many years, to achieve a valid and final diagnosis. Upon the diagnosis, unanimously, respondents felt relief. This was often paired with a feeling of confusion about what the diagnosis meant and a lack of information pertinent to the prognosis of the information that they had been told. After the diagnosis, the impact on the parent/caregiver themselves was complex and individual. Many caregivers reported needing to reframe their expectations relating to what their child could, and would, achieve, and the milestones they may reach. Theme 2 found that poor sleep quality and quantity, feelings of isolation, and a breakdown in relationships were all commonplace in the analysis, with caregiver relationships and wider family relationships impacted alike. As reported in Theme 3, caregivers often felt they needed to be initially, and remain, more involved in many facets of their child's life – including education, healthcare, and other areas such as personal care, diet, and encouraging independence. This increased need to be involved, in turn, often hampered the ability for

respondents to progress in their careers or remain in employment at all, as discussed in Theme 4. In addition to the financial impact of not working, or working less hours, an often-significant financial component was present in other areas of life including needing to pay for, or travel to, appointments and therapeutic interventions, the cost of additional equipment in line with developmental needs, and the cost of replacing damaged or broken items. Theme 5 described the impact that was also often felt in the wider family, where siblings were reported to receive less attention, and needed to be protected from caregiving responsibilities and were, in some cases, thought to be more mature and well-rounded because of overcoming the challenges presented. Similarly, members of the wider family network needed to be protected from behavioural outbursts and often treated the affected individual differently.

Each theme will now be discussed in more detail. For many of those interviewed, the journey to a diagnosis was a long and arduous process. Some individuals in this study reported that the time that it took their child to receive a diagnosis was often many years of appointment attendance and exploratory testing. This finding is consistent with the literature in other rare genetic diseases, where the average length of time to reach a diagnosis, in rare diseases generally, is reported as 4.8 years in some research (Engel et al., 2013), but has been widely reported to take over a decade in some cases (Molster et al., 2016; Heuyer, Pavan & Vicard, 2017). In fact, it is well-recognised in the published literature that individuals, and families, of most rare diseases often experience long waits prior to receiving a diagnosis for their condition which, in the academic literature, has been termed the ‘diagnostic odyssey’, and involves often extensive and expensive testing at multiple

institutions (Marwaha, Knowles & Ashley, 2022). Is it important to note that participants were recruited globally in this research, and therefore access to diagnostic resources may not be consistent between countries. In line with this, the length of time undiagnosed is likely much longer for low- and middle-income countries given the limited resources and specialist knowledge (Conradie et al., 2021).

Whilst many interviewees reported long periods of time to reach a diagnosis, in line with previous literature, others noted that the journey to diagnosis was much shorter and, on occasion, received within months of their child's birth. This may reflect the transition from classic clinical practices to the advent of more robust molecular testing methods and an openness from clinicians to undergo genetic testing (Dawkins et al., 2018; Ramos-Fuentes et al., 2020). Additionally, recent regulatory and economic incentives meant that the pharmaceutical industry also demonstrated an interest to invest in rare diseases, where they had previously demonstrated hesitancy due to low returns on investment (Melnikova, 2012). Further, the progress being made to excel the reliability of early molecular diagnosis could feasibly shorten the diagnostic odyssey and facilitate more effective genetic counselling as a single test has the ability to screen for hundreds of genetic disorders (Li, 2023).

Irrespective of the time elapsed from symptom-onset to receiving a diagnosis, respondents felt, in addition to upset and confusion, overwhelmingly a sense of relief when being told that their child had MYT1L-syndrome. This is in line the experiences of parents with children diagnosed with other rare diseases who felt that a diagnosis would enable them to cope

better with managing their child's complex care needs, and without a diagnosis they were unable to prepare themselves for challenging situations which may arise (Pelentsov et al., 2015), but is not consistent with most qualitative investigations of rare disease diagnoses that suggest parental responses include primarily denial and anger (Anderson, Elliott & Zurynski., 2013; Strehle & Middlemiss, 2007). Further, and consistent with a qualitative study investigating 22q11 deletion syndrome (Dimond, 2014), some caregivers in the present study felt that the de-novo nature of the mutation safeguarded them from blame and meant that their actions had not influenced the resultant diagnosis. Parents also reported experiencing a complex grieving process, which is a well-documented element of parenting a child with intellectual disabilities (Cadwgan & Goodwin, 2018). It is thought that grief is complex for parents of children with such disabilities, including the concept of 'disenfranchised grief', where loss is not recognised by others – such examples include parental grief about lost hope and dreams they had for their child which will not materialise due to their disability (Duc, Herbert & Heussler, 2017).

Respondents in this research also reported that they were, in some cases, given multiple incorrect diagnoses by healthcare professionals before receiving the MYT1L-diagnosis. Further, it was the seemingly the tenacity and persistence exerted by those interviewed that led to their child's eventual correct diagnosis, despite often not being believed by clinicians or feeling that their suspicions relating to the idiosyncrasies were incorrect. In other rare diseases, most people were found to receive at least one incorrect diagnosis prior to securing a correct diagnosis, and those with a rare disease who have difficulty accessing information relevant to their condition were found to be two to five times more likely to

have been given an incorrect diagnosis (Muir, 2016; Dong et al., 2020). In line with participants in this study, caregivers of individuals with rare diseases are widely noted to search for, and access, information online due to the paucity of information delivered by their clinician (Morgan et al., 2014). In addition to being provided with poor information, caregivers of children with other rare diseases have also reported feeling invalidated when sharing their concerns with healthcare professionals during the diagnostic process (Jacobs et al., 2019; Shropshire, 2017; Maxfield et al., 2021).

Caregivers also felt that this impacted their social life, where friendships often broke down due to time constraints or the complexity of their child's care needs meaning that opportunities were limited. In the wider literature, parents report an inability to socialise with friends, a decrease in spontaneity and freedom, and feelings of isolation (Speraw, 2006; Coffey, 2006). Consistent with some reports in this analysis, other research has identified that the parents of children diagnosed with NDCs have reported experiencing stigma and taboo when interacting with the families of neurotypical children (Currie & Szabo, 2020), and children diagnosed with other rare diseases have also been found to experience stigma and bullying (Adams, 2002). Other relationships were also seemingly impacted by the syndrome, including caregiver relationships with their spouse. As is the case in other rare diseases, caregivers interviewed reported that, whilst not directly attributing it to the syndrome, the additional challenges and strain presented had contributed to their relationship breaking down resulting in separation (van Scheppingen et al., 2008; MacLeod et al., 2017). Other participants reported that their relationship felt more like one forged with a colleague, than a romantic one, and that there was a marked

decline in quality time spent with their partner. Research in a cohort of caregivers of children with PWS identified that romantic relationships are severely affected due to the care needs of the affected individual and that conflict within relationships had a marked increase (Kayadjanian et al., 2018; Parish et al., 2004). In addition to coping with the various impacts of the syndrome on relationships, caregivers also reported that they dealt with a huge amount of grief, relating to multiple areas, including their child's health, missed academic opportunities or uncertainty about what their child may achieve in the future. Parents of children with rare disease syndromes often endure cycles of grief and seldom does the grieving process resolve – in fact, it may re-emerge upon new symptoms arising (Hobdell et al., 2007; Kolemen et al., 2021). Whilst not quantitively assessed in this study, caregivers frequently reported that they felt stressed, upset, and low when navigating these challenges. It is well evidenced in the literature that parents of children with rare genetic syndromes experience a detrimental impact on their quality of life (Zenman, Cassano, & Adrian, 2013; Mori et al., 2019), and challenging behaviours in PWS were identified as a significant contributor to caregiver burden (Kayadjanian et al., 2018). Parents reported that social support was lacking which is consistent with findings in other rare diseases (McMullan, Lohfeld & McKnight, 2022). In the present study, parents reported accessing support groups on social media in lieu of other social support and mostly found that they were useful and enabled them to overcome some of the challenges they faced by learning from others in similar situations. Qualitative research has found that this is also the case in other conditions, where parents strongly perceive that there is a positive benefit, however quantitative studies provide inconsistent evidence of the positive effects of accessing such

peer support networks (Shilling et al., 2013). It would, therefore, be valuable for future research to further investigate the efficacy of accessing online support groups.

A limitation of the present study is that it only focussed on the experiences of parents and caregivers of individuals with MYT1L-syndrome and did not seek the views of healthcare professionals or clinicians. A recent survey of 927 practicing clinicians identified that whilst 93% has been involved in making a diagnosis of a rare disease, only 20% felt very confident when making such diagnoses (Rohani-Montez, 2022). Paediatricians, specifically, were also found to have low experience levels when diagnosing rare genetic syndromes, and this knowledge gap is further exacerbated by the limited availability of standardised guidelines and specialist knowledge in community hospitals (Greulich et al., 2013; Stoller, 2018). Over 94% of physicians reported they had insufficient, or poor, knowledge relating to rare disease and less than 5% felt that they were able and prepared to care for such patients. This is despite over 80% of those surveyed believing that rare genetic syndromes were a serious public health issue (Walkowiak & Domaradzki, 2021). Whilst uncertain, it is unlikely that the knowledge base or experiences of clinicians differed when diagnosing MYT1L-syndrome compared to other rare genetic syndromes and therefore it is appropriate to consult the wider literature to identify the education needs of healthcare professionals. This research, and the existing body of evidence, therefore, highlights a need for standardised guidance relating to the diagnosis of rare genetic syndromes, as well as a need for increased teaching and knowledge exchange about managing such conditions. One way this could be achieved is through specific teaching modules relating to rare diseases during medical education (Domaradzki & Walkowiak, 2019). The shortcomings of medical

education in relation to rare genetic diseases reflects a wider research gap between gene discovery and phenotyping, such as natural history studies.

Given gaps in formalised medical education relating to rare genetic syndromes and a low confidence from clinicians when delivering a diagnosis, as demonstrated in the aforementioned research, it is unsurprising that respondents in the present study frequently experienced challenges when interacting with healthcare professionals. All participants felt that, following the diagnosis, clinicians were not able to educate them with all, or any, of the information that they needed to best support their child and understand their developmental profile. The information that caregivers sought from clinicians was in line with the published literature in other rare diseases, including wanting to know more information, generally, about the syndromes (Graungaard & Skov, 2007; Lim et al., 2012), understand the prognosis and expected outcomes of the diagnosis (Eatough et al., 2013), and how to best support their child in the long-term (Palisano et al., 2010). Whilst participants did report that they felt doctor's lacked basic knowledge about MYT1L-syndrome, as found in other conditions (Hickenbotham, 2016; Weng et al., 2012), they were also sympathetic to the ultra-rare nature of the syndrome and, therefore, were understanding that the information provision was lacking. Due to a lack of coordinated health services, many caregivers also felt that they needed to repeat information when seeing different healthcare professionals and that information was not appropriately transferred between services, also found in other conditions (Baumbusch, Mayer & Sloan-Yip, 2019). Given the low levels of information provided during appointments with healthcare professionals, following a diagnosis, many caregivers in the present study

reported that they felt like they had the burden of educating themselves and becoming an expert on the syndrome, so that they could navigate the care pathway efficiently and appropriately support their child. Many participants in the present study sought information via online web searches and through patient information forums. This is commonplace within other rare diseases; a survey of 516 parents found that 99% searched for information online relating to disease characteristics and 82% noted that their understanding increased because of seeking information online (Tozzi et al., 2013). Conversely, and whilst not explicit within the current analysis, some parents of children with rare diseases have reported actively avoiding online information and felt that seeking information online left them feeling confused (Kirk & Glendinning, 2004). Whilst information is routinely sought following a diagnosis, the expanse of information available relating to rare diseases online may, in part, be responsible for faster diagnoses being given, as caregivers may seek information online and match symptoms observed to established syndromes (Bouwman et al., 2010). Few parents reported that they were navigating the transition from paediatric to adult healthcare, mostly due to the age of the children that parents were acting as the information proxy for. Those that were experiencing this said that they felt as if services they had fought for previously in paediatric services were now being taken away from them as they moved into adult care, which is corroborated by research highlighting that a large portion of individuals diagnosed with a rare disease are underserved and frequently experience health disparities during the transition process (Sandquist et al., 2022).

The lack of clear information from healthcare professionals relating to the expected relative strengths and weaknesses of affected individuals, based on the diagnosis received, meant that identifying a suitable educational environment was a clear challenge for many caregivers interviewed. Some interviewees noted that their child had a negative and detrimental experience attempting to navigate an unsuitable educational environment, which is recognised in the wider rare disease literature (Santos Luz, Santos da Silva & DeMontigny, 2016). The challenging developmental, and behavioural, profile of MYT1L-syndrome meant that schools were often not equipped to cope with behavioural outbursts or the need for an adapted curriculum, which has also been observed in other syndromes associated with behavioural challenges, including PWS (Schwarts et al., 2021). This influence of this inability to cope may be reflected in the fact that children with rare diseases often experience higher levels of absenteeism, an inability to access educational facilities (Veger et al., 2020). As reported previously, children with MYT1L-syndrome appear to experience challenges forming and maintaining social relationships. Given this, and that children with rare diseases have shown higher levels of bullying, depression, exclusion (Sentenac et al., 2011; Adama et al., 2021), it is critical that educational institutions are viewed as appropriate, welcoming, and safe spaces. Globally, teachers have reported that there is a lack of information available to them outlining how to best support children with rare genetic syndromes, and as such an important area of work for the future may be empowering education providers with an increased information provision relating to overcoming barriers to participating in education (Iacono et al., 2019). To overcome issues, many interviewees noted that they likely had more communications with their education provider, when compared to a typically developing child. Fostering these relationships with

providers is important as caregivers of children with other rare genetic syndromes have reported that a lack of, or disjointed, communication with school led to difficulties (Foster et al., 2022).

The need to advocate for their child in education, and other environments, was a strong theme in the current analysis and the time requirements of which meant that respondents often experienced a profound impact and felt that they could not undertake regular day-to-day activities. Multiple facets of life were impacted for the present cohort including reduced sleep quantity and quality, and an impairment to daily life including an inability to visit the shops and eat dinner at a restaurant as a family - factors which are also present in other rare diseases (Hartshorne et al., 2009; Mighiu et al., 2022; Kirk & Glendinning, 2004). This daily impact was often further exacerbated by participants needing to attend a variety of appointments relating to the syndrome, which is consistent with research that highlights how parents of children with rare diseases often felt that their home, family, and day-to-day life becomes medicalised (Belzer et al., 2022). Another key challenge reported by caregivers in this analysis relates to managing food and diet, where many parents needed to monitor and moderate their child's food intake levels and restrict access to certain foods. PWS is strongly associated with an inability for affected individuals to feel satiated, or hyperphagia, and families have also reported the need to restrict access to food and manage diet, and consequently this domain was rated the highest priority area for future research by PWS families, and was deemed the treatment area with the largest potential benefit (Tsai et al., 2018). In addition, coping with the behavioural demands associated with MYT1L-syndrome meant that caregivers often needed to reorganise their life and prioritise

caring for their child, consistent with Rett syndrome which is also commonly associated with behavioural outbursts (Leonard, Cobb & Downs, 2017; Lim et al., 2013).

Although many families experience challenging behaviours as children develop and grow, some parents, including those of children with rare genetic syndromes, have reported that sustaining employment outside of the home supports improved mental health (Lauvrick et al., 2006), which was also reflected in the current study. However, many respondents also noted that they could not work due to the demands of the syndrome, some of which displayed a clear yearning to return to employment, with the benefits to their mental health at the forefront of their thought process. Most interviewees reported that they either felt unable to work at all or had to adjust their working arrangements, which was one of the most significant costs in response to coping with the syndrome incurred for many participants, which is found in many other rare diseases (Gill et al., 2021). Interestingly, many of those interviewed in the present analysis were women (n=15; 79%). This is consistent with other qualitative research exploring rare diseases, where participants are predominantly female and primary caregivers (Murphy et al., 2007; Ludlow, Brown, & Schulz, 2018). Most female participants in the present study reported that they were the ones who felt that they needed to adjust their work schedule whilst, for some, their male counterpart remained in full-time employment. This is consistent with research which identified that mothers, mainly, were the ones who either decreased their employment or left the workforce entirely to provide care for their child (Baumbusch, Mayer & Sloan-Yip, 2019), which may indicate that women disproportionately carry the burden of care in rare diseases. For those that did remain in employment, many reported that they needed to take

all available annual leave, or reduce their working hours, to manage the demands of care. This is reflected in the wider literature where 34% of caregivers were found to reduce their working hours and 34% ceased employment entirely (Pelentsov et al., 2016). In the present study, those that remained in employment also reported that they felt, compared to other employees, they had not advanced as much as they may have or had explicitly declined a promotion, consistent with research that identified that 26% of 1,406 caregivers in the United States had actively declined a promotion due to a lack of capacity (National Alliance for Caregiving, 2018). Additional costs relating to the syndrome, in the present study, included travel to appointments, a need to pay for therapy, the need to purchase additional, or specialist, equipment, and the cost of replacing damaged items – all of which are reflected as being core to the experience of parents of children with other rare diseases in the wider literature (Uhlenbusch et al., 2019; Carpenter et al., 2018; Urbanowicz et al., 2011). Many interviewees in this study, in line with previous research, reported experiencing challenges accessing financial support and those that did receive financial support reported that it was not nearly enough to cover the costs associated with the syndrome (Zurynski et al., 2008). Those with access to a health system, such as the NHS, that does not rely on direct payment to access services still reported that they had paid for private services or tried experimental therapies to encourage their child's development or control their symptoms. For those in health systems where insurance is a necessity, participants shared that the health insurance policy was seldom enough to cover the costs of related healthcare needs and often relied on out-of-pocket expenses – this is also the case in other rare diseases (Pasquini, Goff & Whitehill, 2021).

Those in the wider family, in the present study, were also impacted – particularly siblings, many of whom were reported to receive less attention than the affected individual and were considered to have participated in less social activities than they would have otherwise. A qualitative study examining the impact of seven rare diseases found that, due to the burdensome care required for the impacted child, many parents felt guilty because siblings were left out and had to 'fit in' with the care requirements (Pelentsov et al., 2015). Whilst not explicitly explored within this study, previous research has identified that siblings experience anxiety and depression and an important part of coping as an unaffected sibling is to overcome isolation and build connections with other siblings who share similar and unique experiences (Dinleyici et al., 2019; Malcolm et al., 2014). Conversely, and consistent with caregiver perceptions reported in the present research, the siblings of children with intellectual disabilities were found to have higher levels of psychological growth compared to those without (Findler & Vardi, 2009). The neurotypical siblings of children diagnosed with ASD have also been found to exhibit higher levels of empathy and love, in addition to feeling overlooked in the family, encountering problem and aggressive behaviours, and have an impacted mental health – which demonstrates the need to research positive affect in addition to any challenges faced (Leedham, Thompson, & Freeth, 2020). It would be valuable to understand the perspectives of the siblings of individuals with MYT1L-syndrome to understand how they consider they are impacted and implement appropriate support strategies. Future, longitudinal, research would also be valuable to understand how impact differs across the lifespan of siblings.

This analysis provides insight into the complex and varied impact of the needs associated with MYT1L-syndrome on caregivers, siblings, and the wider family of affected individuals. The experience reaching a diagnosis is consistent with the published literature exploring the journey to a diagnosis in other rare diseases, where families experience a diagnostic odyssey, multiple incorrect diagnoses, and often face conflicting and challenging emotional responses when a diagnosis is reached. Caregivers were also found to need to remain hands on in the management of education and healthcare, and the toll of this was reported to impact relationships, including with partners. Increased costs were also associated with the need to travel to healthcare appointments, in addition to purchasing specialist equipment to meet the needs of their child, and for many there was also the financial impact of not being able to maintain a full-time job because of the time requirements to manage care needs effectively. Caregivers also considered that siblings were impacted but it is important to note that, in addition to challenges such as receiving reduced attention and encountering problem behaviours, some positive attributes including higher levels of empathy and helpfulness were attributed to growing up alongside their sibling with MYT1L-syndrome. Further research should investigate how to best support the families of children with rare disease, and how to support other family members including neurotypical siblings. Additionally, it is important that information about the syndrome is easily available and in an appropriate format to share with wider family members to remove the burden of educating others, which is often placed on parents.

# Chapter 5: The impact of MYT1L-syndrome on behaviour and cognition: a quantitative analysis

## 5.1. Introduction

The findings of the qualitative research, outlined in Chapter 3, provide useful insight into how parents perceive that MYT1L-syndrome impacts their child's cognitive and behavioural abilities. This included to domains including communication, traits associated with ASD, and the presence of behaviours consistent with ADHD. Exploring these domains further using standardised measures of assessment is important to understand the severity of impairment present in diagnosed individuals and may lead to the identification of a syndrome-specific phenotype. As discussed in Chapter 1, there is a paucity of research investigating the cognitive and behavioural phenotype of MYT1L-syndrome. Whilst case reports in MYT1L-syndrome, as outlined in Section 1.3.4. have observed that individuals diagnosed with the syndrome demonstrate language delays, intellectual disability, and behaviour disorders (Coursimault et al., 2022), there is a lack of evidence indicating which domains of language, for instance, are impacted and what relative cognitive strengths and weaknesses individuals with the syndrome possess. Understanding these individual strengths and weaknesses, in addition to the behavioural profile of a syndrome, can help towards effective diagnosis and the implementation of appropriate and timely interventions.

Given the lack of research at present defining the cognitive and behavioural phenotype in MYT1L-syndrome, it is appropriate to first look to other developmental conditions and rare diseases to see how cognitive and behavioural phenotypes were established and how an

enhanced understanding of these domains has guided targeted, and syndrome-specific, interventions. Standardised questionnaires have been widely used in many rare diseases and syndromes affecting development, leading to the delineation of distinctive cognitive profiles. Further, Waite et al. (2014) propose that cross comparisons of the phenotypes of different genetic syndromes are beneficial and have the potential to identify syndrome-specific behaviours, and behaviours which may be present across syndrome shared pathways, which may lead to better outcomes when developing effective and more wide-reaching interventions. One such rare genetic syndrome is Prader-Willi syndrome (or PWS), which is one of the most widely acknowledged genetic syndromes noted to cause obesity (Khan et al., 2018). PWS is a relevant syndrome to refer to in the context of MYT1L-syndrome as the CNV and SNV carriers that clinically present in MYT1L-syndrome overlap with those in PWS, and therefore it is treated as a clinical differential from MYT1L-syndrome (Blanchet et al., 2017). PWS is a NDC with a prevalence varying between 1 in 10,000 to 1 in 30,000, noted to affect males and females and all races and ethnicities equally (Bohonowych et al., 2019). In addition to being a well-documented cause of obesity, PWS also has established links to intellectual disability and speech delays, a behavioural profile including tantrums, compulsivity, stubbornness, and autistic traits (Cassidy et al., 2012). Research suggests that this characteristic behavioural profile is present in early childhood for 70-90% of diagnosed individuals (Dykens, Cassidy & King, 1999).

Sotos syndrome, estimated to impact 1 in 14,000 people, is a congenital overgrowth disorder with diagnostic criteria including intellectual disability (Cole & Hughes, 1994; Sotos et al., 1964; Tatton-Brown & Rahman, 2004). Research conducted by Lane et al. (2017)

utilised the Social Responsiveness Scale, second edition (SRS-2) to investigate the behavioural profile of Sotos syndrome based on the presence of autistic traits. They identified that 83% (65 participants) of the sample met the clinical cut-off score for behavioural symptoms relating to autism. Further, higher scores on the SRS-2 were evident in childhood, compared to those in early adolescence and adulthood. The cognitive phenotype of Sotos was also investigated by Lane et al. (2019) utilising the British Ability Scales (BAS3). Using these scales, a consistent cognitive profile was identified across the sample and relative strengths and weaknesses were identified. Strengths included verbal ability, but quantitative reasoning and non-verbal reasoning ability were identified as relative weaknesses.

Cognitive and behavioural profiles have also been established in other genetic syndromes that are associated with ID. Moss et al. (2012) conducted behavioural phenotyping research in Cornelia de Lange syndrome, which is estimated to be prevalent in 1 in 40,000 live births and characterised by a developmental delay (Beck & Fenger, 1985; Jackson et al., 1993). They identified, using the Autism Diagnostic Observation Scale (ADOS), that 65% (13 participants) met the clinical cut-off score for autism. Compared to idiopathic autism, participants showed less stereotyped speech, more eye contact, and less repetitive behaviours. FXS is a trinucleotide repeat disorder, a common inherited form of ID, and often leads to poor language development and hyperactivity (Hagerman et al., 2017). The cognitive profile was investigated using numerous intelligence and neuropsychological tests (Van der Molen et al., 2010). Participants were found to have relative weaknesses in short-term verbal memory and verbal-reasoning, but relative strengths in vocabulary.

Individuals with Williams syndrome (WS) are also noted to have a characteristic set of relative cognitive strengths and weaknesses, as assessed by standardised measures of language, cognition, and executive functioning. This includes within-group variability of intellectual abilities, with some individuals scoring within the severe intellectual disability range to others scoring within average intelligence ranges (Mervis et al., 2000). Further, whilst individuals with WS may develop speech later than peers, expressive language is a relative strength in comparison to other language domains (Udwin & Yule, 2005). Individuals diagnosed with another syndrome also associated with varying levels of intellectual disability, Down syndrome (DS), are noted to possess the opposite language abilities where expressive language is typically a relative weakness in comparison to receptive language (Martin et al., 2009). It is important, therefore, to explore the cognitive and behavioural phenotype of individuals diagnosed with MYT1L-syndrome, as whilst the syndrome is also associated with intellectual disability – the relative strengths and weaknesses of the cognitive profile are unknown and may differ from other syndromes, as illustrated in WS and DS. It useful to compare the cognitive and behavioural profile of individuals with MYT1L-syndrome to those possessed by individuals in other syndromes, allowing for the application of established interventions already proven effective in similar domains of impairment.

The cognitive and behavioural phenotyping of these individuals also has important implications. Establishing the behavioural profile of people with a genetic syndrome more broadly may help with their clinical management and assist parents or caregivers by

outlining care needs, for instance understanding that aggression or tantrums may be a consequence of frustrations relating to their illness. Understanding the cognitive profiles of people with genetic syndromes also has meaningful and important implications within the education sector as teachers can tailor resources and teaching styles to reflect the relative abilities identified.

This study aims to define the cognitive and behavioural phenotype present in individuals with MYT1L-syndrome using a series of caregiver-reported standardised measures. Based on the insights provided by caregivers outlined in Chapter 2, and by researching widely used quantitative measures of cognition and behaviour in the published literature, six standardised questionnaires were selected to further investigate the cognitive and behavioural profile of MYT1L-syndrome. Domains of interest are communication, adaptive behaviour, social responsiveness, sensory profiles, attention-deficit hyperactivity disorder-related behaviour, and anxiety. These are also domains of interest discussed in the clinical case reports and individual case studies of children with MYT1L-syndrome outlined in section 1.3.4. Profile analyses will also examine the disparity between the relative strengths and weaknesses of individuals and enable the assessment of whether these differences are more pronounced than within the general population. These atypical developmental trajectories are present in individuals diagnosed with ASD (Woods et al., 2019), and given the associations between MYT1L-syndrome and ASD discussed in the published literature, the profile of individuals diagnosed with the MYT1L-syndrome may present similarly. Additionally, statistical analyses will be conducted to examine the relationship between standardised score measures and age. Whilst the scores for each measure are standardised

for age, this will enable the examination of whether difficulties are more or less present at younger or older ages. This will be useful to ascertain whether there is any indication that the challenges associated with the syndrome change across the lifespan, as present in other conditions. For instance, a study of 92 individuals with WS identified that social skills and adaptive functioning improved and behavioural difficulties had declined as individuals got older (Elison, Stinton, & Howlin, 2010).

Based on the qualitative insights described in Chapter 2, it can also be hypothesised that individuals in this study will possess impairments within language domains, but this will likely vary between individuals given the heterogeneity discussed in expressive and receptive language abilities. It is also likely that individuals will demonstrate impairments to sensory processing, and have elevated anxiety levels compared to a normative sample. Given the perceived autism spectrum disorder traits reported by some caregivers in the qualitative research, it is also expected that impairments will be present in social domains such as peer relations, communication, and social awareness. Problems accessing education, impulsive tendencies, and attention-related challenges would also suggest that individuals will score lower than typically developing children on measures indicative of attention-deficit hyperactivity disorders.

## 5.2. Methods

### 5.2.1. Ethics

All participants received written and oral information about the study and had to provide written consent to participate. Participants were also made aware of the right to withdraw

from the research at any time. Ethical approval was obtained by the University of Sheffield Ethics Committee (reference number 035843).

### 5.2.2. Participants

The parents and caregivers of individuals with a clinical diagnosis of MYT1L-syndrome, classified through a 2p25.3 deletion, were eligible to participate irrespective of their geographic location. The inclusion criteria for participation were that parents/caregivers were aged over 18 years of age, were primarily responsible for providing care to the affected individual, and were able, and happy, to provide informed consent. Participants who took part in the qualitative interview study were invited to participate, alongside the recruitment of new participants via parent support groups listed on Facebook. After participating in the research, participants were invited to pass on study information and researcher contact details to other MYT1L-syndrome families that may have been missed through other recruitment methods.

The sample consisted of 24 parents of individuals with a genetic diagnosis of MYT1L-syndrome, confirmed by genetic test report. See **Table 5.1** for participant characteristics, and sample sizes for each of the standardised questionnaires used. Note that only participants who, at the time of data collection, were within the recommended age range of each measure are included in the table, and data collected from participants out of the recommended age range of each measure are described in the results and detailed in the appendices for completeness.

| *Standardised measure* | *VABS-3* | *SRS-2* | *SSP-2* | *CCC-2* | *Conners 3* | *SCAS-P* |
|---|---|---|---|---|---|---|
| **N*** | 24 | 24 | 15 | 12 | 7 | 7 |
| **Age in years** | | | | | | |
| Mean (SD) | 14.57 (9.50) | 14.57 (9.50) | 8.18 (3.15) | 8.43 (2.98) | 9.3 (2.64) | 9.3 (2.64) |
| Range | 3.5-34.9 | 3.5-34.9 | 3.5-13.6 | 4.2-13.6 | 6.1-13.6 | 6.1-13.6 |
| **Sex** | | | | | | |
| Male (%) | 8 (33%) | 8 (33%) | 6 (40%) | 4 (33%) | 2 (29%) | 2 (29%) |
| Female (%) | 16 (67%) | 16 (67%) | 9 (60%) | 8 (67%) | 5 (71%) | 5 (71%) |
| **Location of residence** | | | | | | |
| United Kingdom (%) | 11 (46%) | 11 (46%) | 6 (40%) | 5 (42%) | 4 (57%) | 4 (57%) |
| United States (%) | 5 (21%) | 5 (21%) | 4 (26.5%) | 3 (25%) | 2 (29%) | 2 (29%) |
| Europe (%) | 4 (16.5%) | 4 (16.5%) | 4 (26.5%) | 3 (25%) | 1 (14%) | 1 (14%) |
| Other (Australia, Canada, and South America) (%) | 4 (16.5%) | 4 (16.5%) | 1 (7%) | 1 (8%) | 0 (0%) | 0 (0%) |

***Table 5.1.*** *Participant characteristics – Quantitative study*
*******Please note that only participants that were within the recommended age range of each measure are included within this summary. Data collected from individuals out of the recommended age range are included in the appendix for completeness.*

### 5.2.3. Data collection

Due to COVID-19 restrictions, and because of the global recruitment strategy adopted, all data collection had to be conducted online. In line with licensing permissions of the individual standardised questionnaires used, the data for three of the measures were collected via questionnaire using Qualtrics (Conners 3, SCAS-P, and SRS-2), and the remainder of the data was collected via a follow-up online video call via Google Meet where the researcher, LS, read aloud questions, which was accompanied by the question typed on-screen (VABS-3, CCC-2, and SSP-2). Following data collection, each measure was scored in line with the relevant scoring manual and further statistical analysis conducted using SPSS where appropriate. Each participant was allocated a participant code (beginning at #1, then #2 etc.) and data was only identifiable via these codes following data collection to ensure anonymity.

### 5.2.4. Measures

The standardised measures used in this study (see **section 4.2.**) include assessments of adaptative behaviour (Vineland Adaptive Behaviour Scale. Third Edition), communication (Children's Communication Checklist), anxiety (Spence Children's Anxiety Scale), ADHD (Conners 3), sensory processing patterns (Short Sensory Profile 2), and social impairments potentially associated with ASD (Social Responsiveness' Scale, second edition).

## 5.3. Results

### 5.3.1. Vineland Adaptive Behaviour Scales, Third Edition (VABS-3)

Scores for the adaptive behaviour composite (ABC), and communication, daily living skills, and socialisation domains are presented in **Table 5.2**. Domain and ABC scaled scores that are lower are indicative of more impaired adaptive behaviour, where scores <70 in each category indicate impaired adaptive ability (see **Figure 5.1** for the domain-level scores for each participant). Within this cohort, participants' overall scores indicate that all participants have at least borderline impairment in adaptive ability, with most falling into the borderline, mild, or moderate impairment categories (see **Figure 5.2** and **Figure 5.3**). Most participants scored within the borderline impairment or mild impairment categories in all domains. The daily living skills was the only domain that some scores fell within the profound impairment category. Impairment appears to be most evident in the communication domain.

| VABS-3 | N | Mean (SD) | Range |
|---|---|---|---|
| *Adaptive behaviour composite* | 24 | 63.16 (11.98) | 38-84 |
| *Communication* | 24 | 60.66 (12.90) | 38-86 |
| *Daily living skills* | 24 | 62.45 (19.21) | 20-88 |
| *Socialisation* | 24 | 64.62 (14.52) | 32-85 |

***Table 5.2.*** *Summary of VABS-3 standardised scores for MYT1L-syndrome*

A one-way repeated measures ANOVA was used to determine whether there was a statistically significant difference between the mean scores of the communication, daily

living skills, and socialisation domains. There were no outliers, and the data was normally distributed in each of the domains, as assessed by a boxplot and Shapiro-Wilks test ($p > .05$). The assumption of sphericity was met, as assessed by Mauchly's test of sphericity, $\chi^2(2) = 3.64$, $p = .162$. The mean participant scores on any of the three subdomains did not lead to any statistically significant changes to the overall adaptive behaviour composite score $F(2, 46) = 1.676$, $p = .198$, partial $\omega^2 = .018$. This indicates that there is no effect of subdomain on overall adaptive behaviour composite score, and that the adaptive behaviour profile of the cohort is statistically flat. A sensitivity analysis conducted using G*Power (Faul et al., 2009), with power =0.95 and alpha=0.05, indicated that the minimal effect size of 0.34 could be detected with a sample of 24.

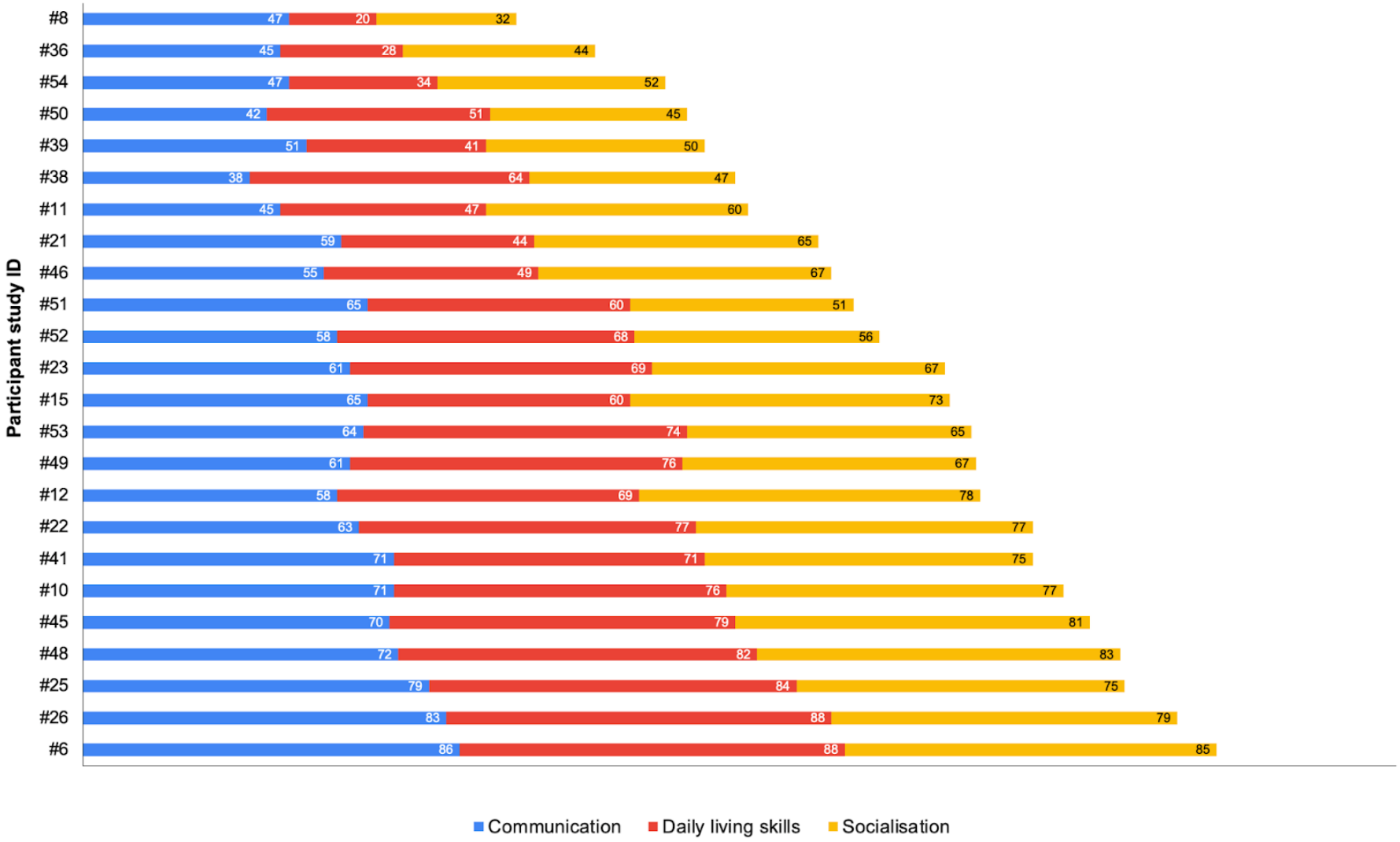


***Figure 5.1.*** *Standardised VABS-3 domain-level scores for each participant, ordered by lowest to highest score.*

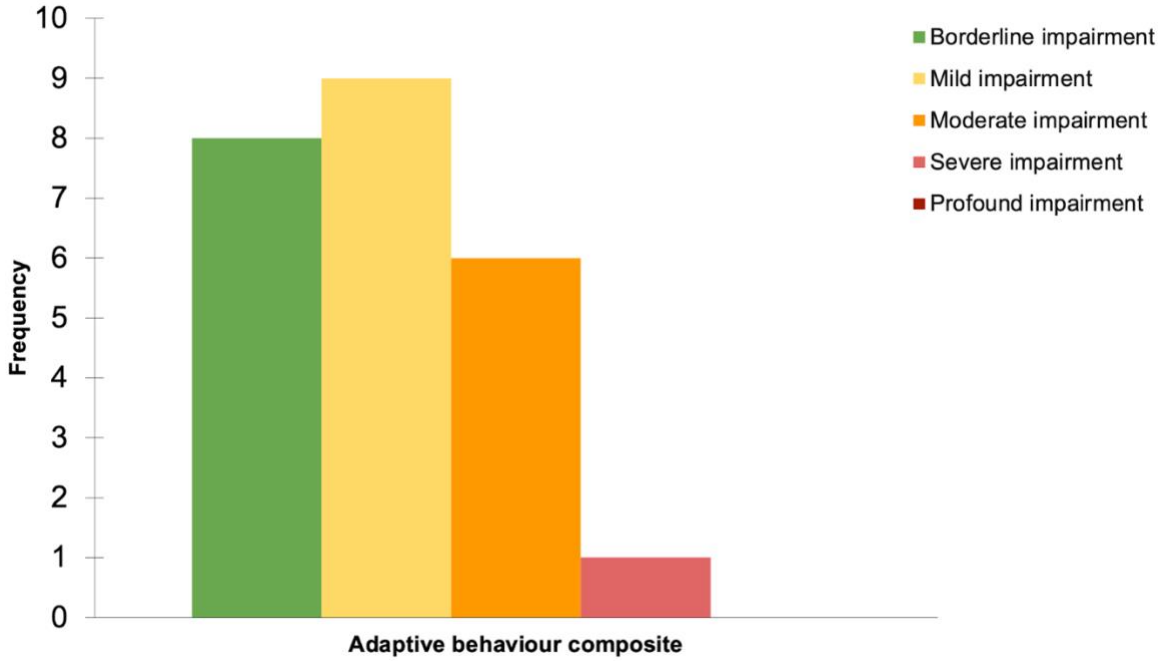


***Figure 5.2.*** *Frequency of individuals scoring within the borderline, mild, moderate, severe, and profound impairment ranges for the VABS-3 ABC score*

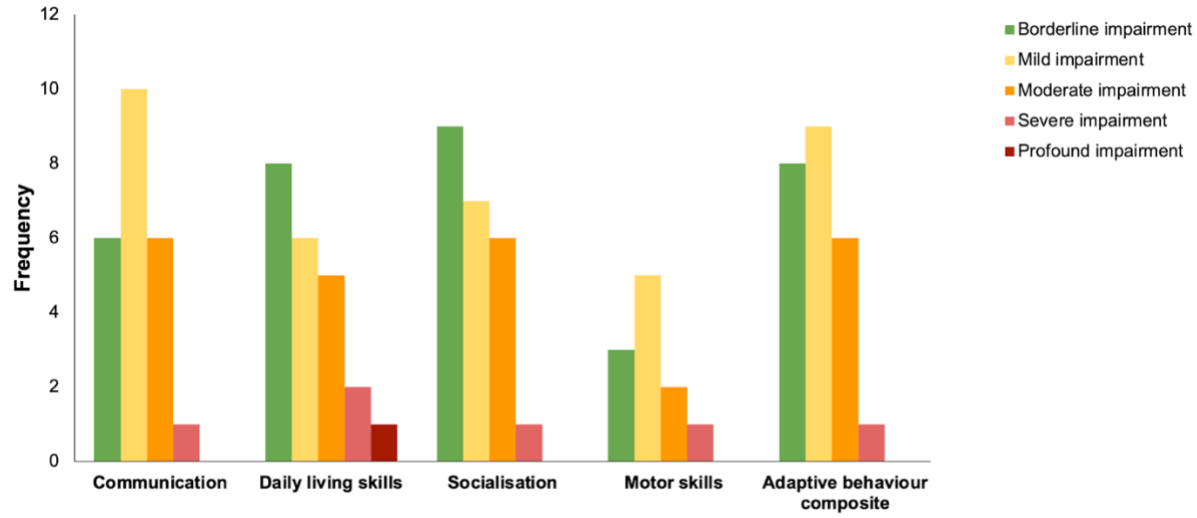


***Figure 5.3.*** *Frequency of individuals scoring within the borderline, mild, moderate, severe, and profound impairment ranges for the VABS-3 domain scores*

#### 5.3.1.1. The impact of age on adaptive behaviour in MYT1L-syndrome

To examine whether participant age was related to adaptive behaviour, a Spearman's rank-order correlation analysis was conducted. To examine whether participant age was related to adaptive behaviour, a Spearman's rank-order correlation analysis was conducted. This statistical test was chosen as it is suitable for determining the strength and direction of the monotonic relationship between two continuous variables. Note that whilst VABS-3 scores are standardised for age, this analysis enables the examination of whether adaptive behaviour difficulties are relatively more or less apparent at younger or older ages. There was no statistically significant correlation between participant age and adaptive behaviour, $r_s(22) = -.328$, $p = .118$ (**see Figure 5.4**).

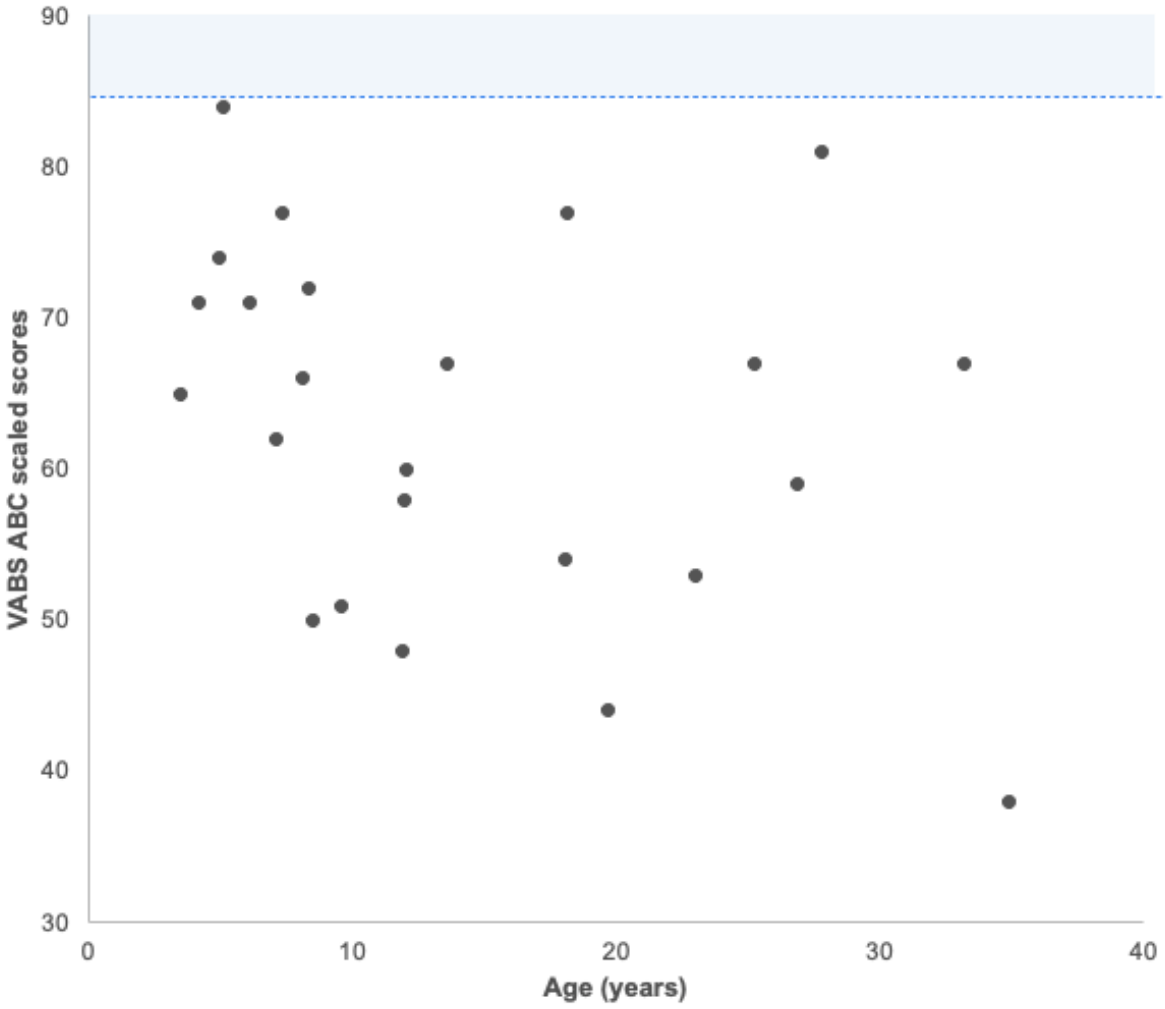


***Figure 5.4.*** *Scatterplot of VABS-3 ABC scaled scores and Participant age (years). The blue dashed line and shaded area indicates a score of 85 and above, which is considered an 'adequate' score.*

### 5.3.2. Social Responsiveness Scale-2 (SRS-2)

Participant SRS-2 total standard scores (sum of all subscales), DSM-5 social communication index standard scores (SCI; sum of social awareness, social cognition, social communication, and social motivation), and treatment subscale standard scores (social awareness; social cognition; social communication; social motivation; restricted interests and repetitive behaviours (RRB)) are outlined in **Table 5.3**. Higher scaled scores on the total SRS-2 and DSM-5 SCI scales, and treatment subscales indicate a higher severity of autism-

related social impairment, where the cut-off score is ≥60 (**Figure 5.5** illustrates the treatment subscale scores for individual participants). Mean scores fell within the moderate and severe impairment ranges for SRS-2 total, DSM-5 SCI, and all subscales apart from the social motivation subscale where participant scores ranged but fell mainly into within normal limits (n=6), mild impairment (n=4) or moderate impairment (n=11). Within the restricted interests and repetitive behaviours domain most participants fell in the severe impairment category (63%), which represents the most severe level of impairment of all the domains, indicating most participants were impacted to show stereotyped behaviours or a limited range of interests. **Figure 5.6** and **Figure 5.7** present the frequency of individuals scoring within the different impairment ranges for SRS-2 total t-score and the treatment subscales.

| SRS-2 | N | Mean (SD) | Range |
|---|---|---|---|
| *SRS-2 total score* | 24 | 77.37 (13.21) | 52-110 |
| *Social communication index (SCI)* | 24 | 75.75 (12.45) | 53-108 |
| *Social awareness* | 24 | 72.29 (14.68) | 38-100 |
| *Social cognition* | 24 | 76.04 (12.73) | 52-104 |
| *Social communication* | 24 | 75.66 (11.74) | 53-105 |
| *Social motivation* | 24 | 66.25 (11.19) | 47-95 |
| *Restricted interests and repetitive behaviours (RRB)* | 24 | 80.66 (15.79) | 50-112 |

***Table 5.3.*** *Summary of SRS-2 standardised scores for MYT1L-syndrome*

A paired-samples t-test was used to determine whether there was a statistically significant mean difference between restricted interests and repetitive behaviour (RRB) scores and DSM-5 social communication index (SCI) scores. A boxplot revealed no extreme outlying scores, all difference scores were <3SD from the mean. The assumption of normality was not violated, as assessed by Shapiro-Wilk's test ($p$ = 0.788). Participants scores were higher in the RRB domain ($M$ = 80.66, $SD$ = 15.79) compared to the DSM-5 SCI domain ($M$ = 75.75, $SD$ = 12.45), $t(23) = 2.948$, $p < .007$, $d = .602$). This indicates greater abilities in the DSM-5 SCI domain (comprised of social awareness, social cognition, social communication, and social motivation) when compared to the RRB domain, suggesting higher levels of impairment to restrictive and repetitive behaviours. A sensitivity analysis conducted using G*Power (Faul et al., 2009), with power =0.95 and alpha=0.05, indicated that the minimal effect size of 0.77 could be detected with a sample of 24.

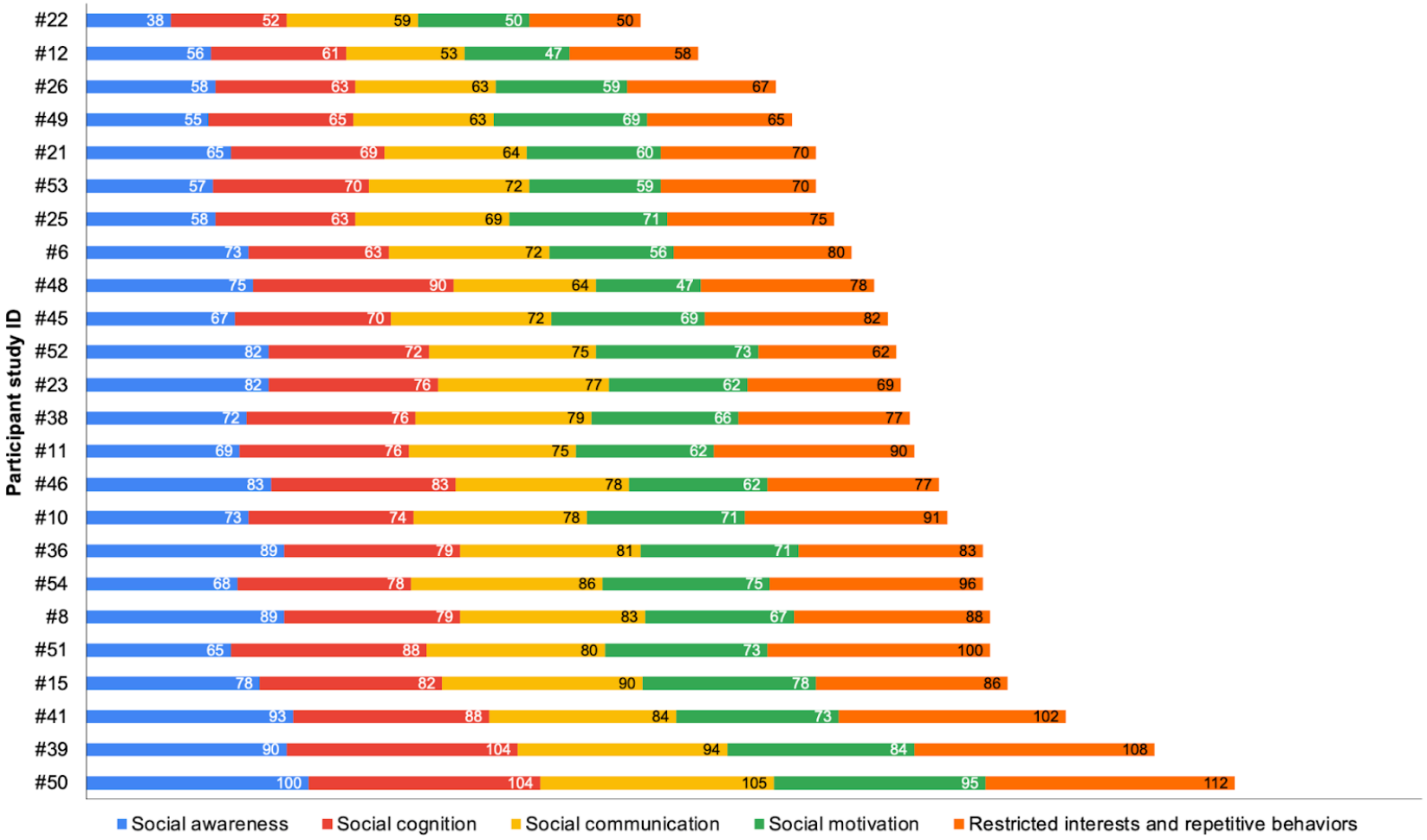


***Figure 5.5.*** *Standardised SRS-2 treatment subscale scores for each participant, ordered by lowest to highest total score.*

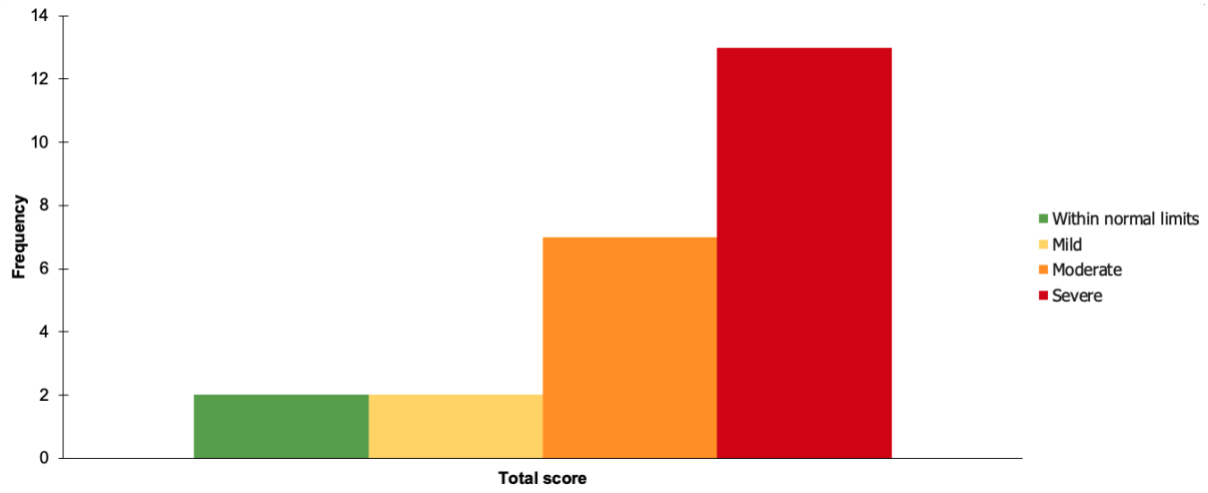


***Figure 5.6.*** *Frequency of individuals scoring within normal limits and mild, moderate, and severe impairment ranges for the SRS-2 total t-score.*

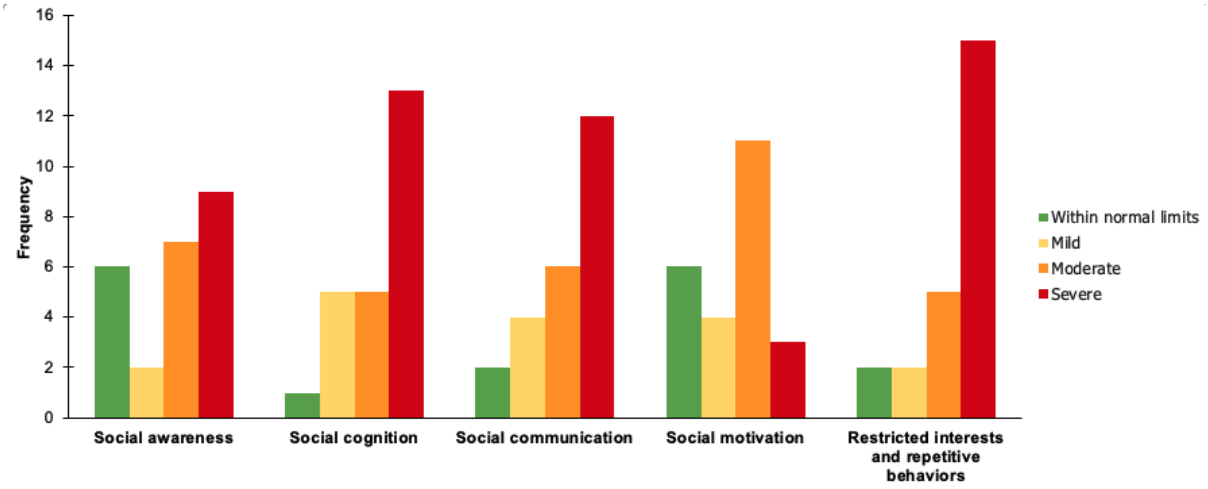


***Figure 5.7.*** *Frequency of individuals scoring within normal limits and mild, moderate, and severe impairment ranges for the treatment subscales.*

#### 5.3.2.1. The impact of age on social behaviour in MYT1L-syndrome

To examine whether participant age impacts social behaviour, a Spearman's rank-order correlation analysis was conducted. Note that although SRS-2 scores are standardised for age, this analysis allows for the investigation of whether social behaviour difficulties are relatively more or less apparent at younger or older ages. There was no statistically significant correlation between participant age and social behaviour, $r_s(22) = -.149$, $p = .486$ (**see Figure 5.8**).

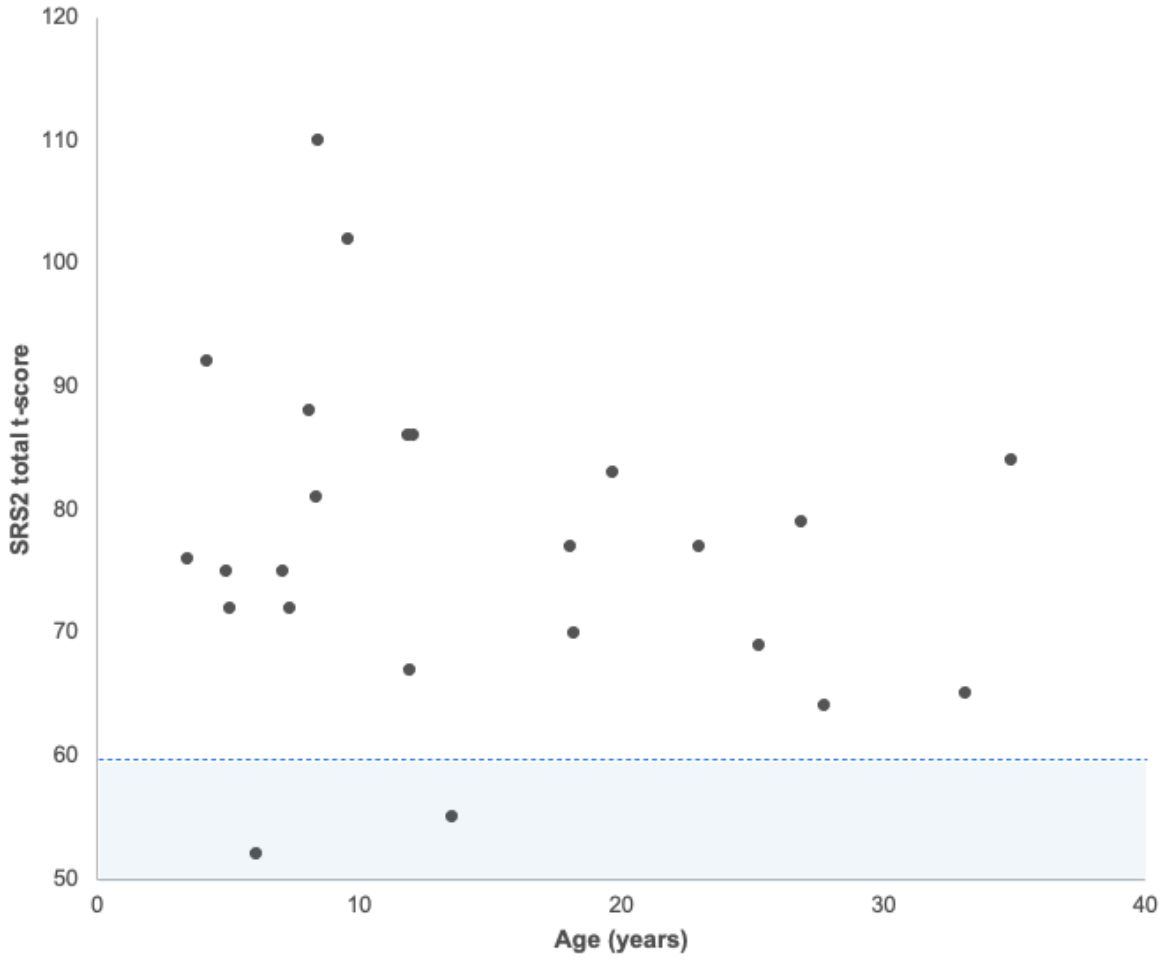


***Figure 5.8.*** *Scatterplot of SRS-2 total t-scores and Participant age (years). The blue dashed line and shaded area indicates a score of 59 and below, which is considered 'within normal limits'.*

### 5.3.3. Short Sensory Profile-2 (SSP-2)

The distribution of raw scores for each domain are presented in **Figure 5.9**. Participant scores in all four domains (Seeking, Avoiding, Sensitivity, and Registration), and on both composites (Sensory and Behavioural), were highly likely to fall in the 'much more than others' range, though there is an indication that individuals with MYT1L-syndrome demonstrate heterogeneity in their sensory profiles as in all domains some participants scored within the 'just like the majority of others' range. Of all domains and composites, participants scored in the 'much more than others' range most frequently in the behavioural composite (**Figure 5.10** presents the division of scores in the different ranges of the four domains and the two composite scores of sensory and behavioural). Data was also collected from individuals who were out of the recommended age range and has been included in this thesis for completeness (see **Appendix 5a** for the raw scores for each domain). Similar to the in-age range individuals, participants were more highly likely to fall in the 'much more than others' range as seen in individuals within the age range (see **Appendix 5b** for the division of scores in the four domains and the two composite scores of sensory and behavioural). A profile analysis was not conducted on the sensory profile of individuals with MYT1L-syndrome due to a lack of statistical power.

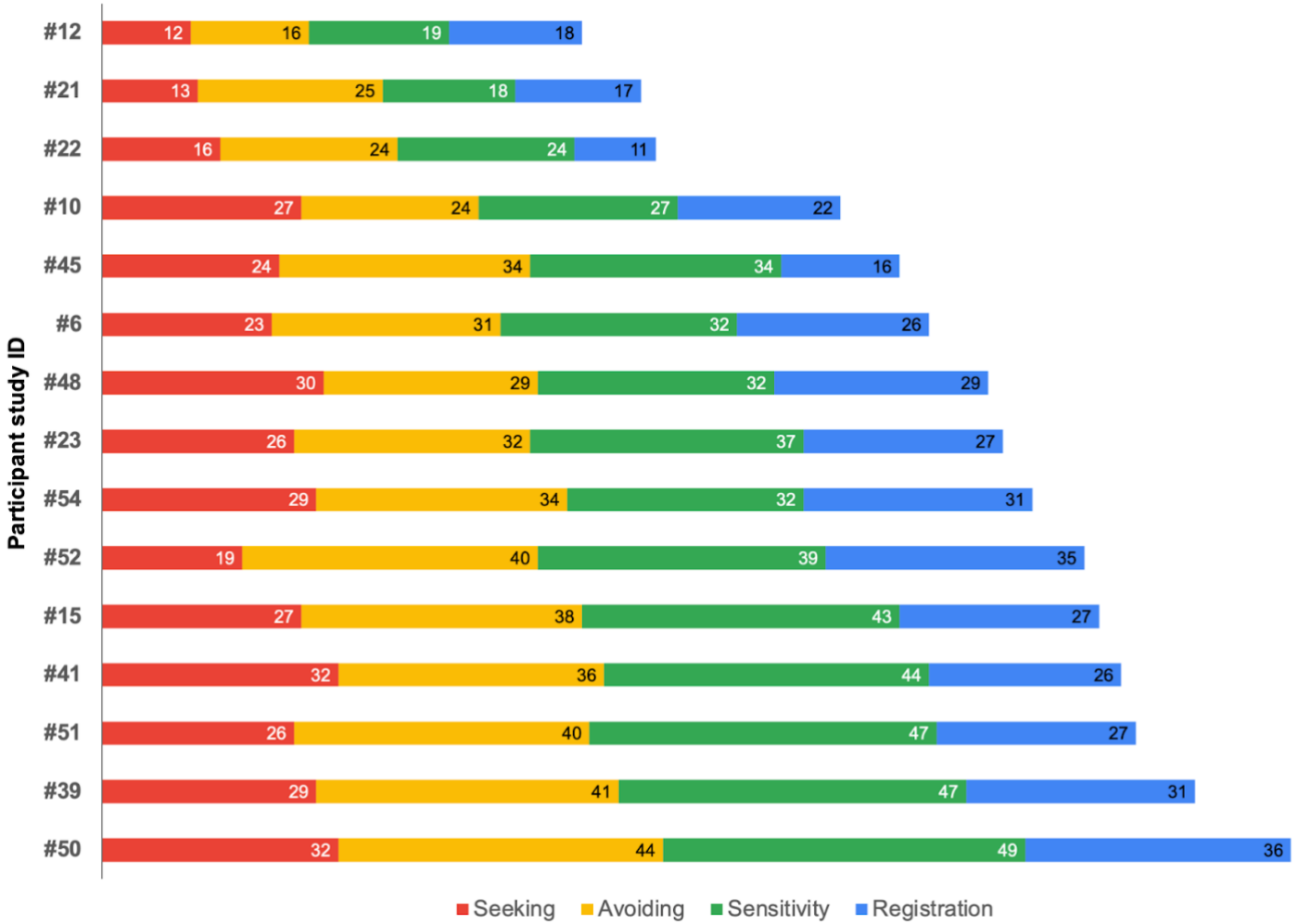


***Figure 5.9.*** *Raw SSP-2 domain scores for each participant, ordered by lowest to highest total score.*

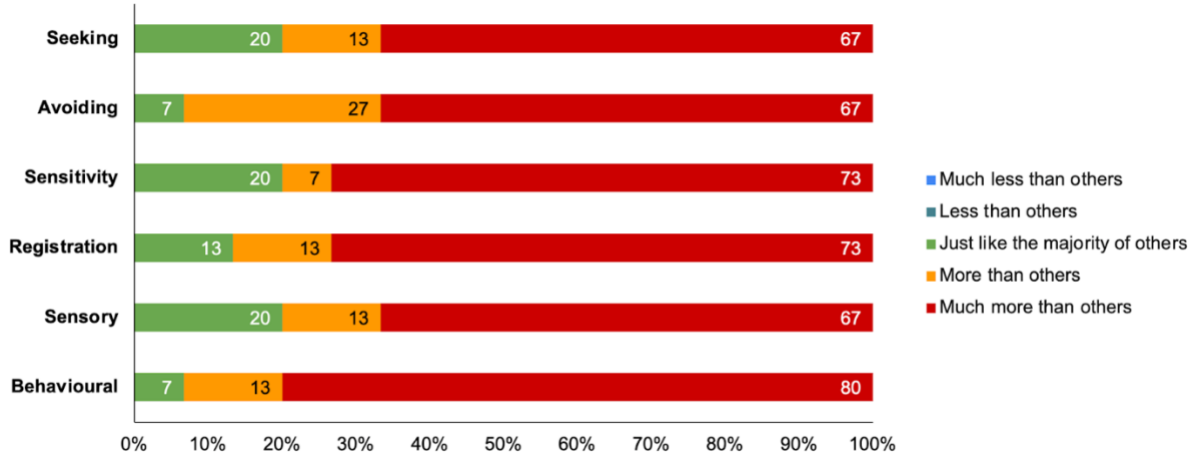


***Figure 5.10.*** *Sensory profile of MYT1L-syndrome (%).*

### 5.3.4. Conners 3 ADHD scale - Parent Short

For each of the questionnaire subscales: inattention, hyperactivity/impulsivity, learning problems, executive functioning, defiance/aggression, and peer relations, t-scores were used to identify impairment levels in the cohort (see **Figure 5.11**). Most participants scored within the 'very elevated score' range on the inattention, learning problems, and executive functioning subscales (86%, 100%, and 71% respectively). There was variation in participant scores on the hyperactivity/impulsivity (57% 'very elevated score' and 43% 'average score') and peer relations (57% 'very elevated score', 14% 'high average score' and 29% average score') subscales, and heterogeneity on the defiance/aggression subscale, with almost a third of participants scoring a 'very elevated score', and almost half of participants scoring an 'average score' (29% 'very elevated score', 14% 'elevated score',

14% ‘high average score’, and 43% ‘average score’). A profile analysis was not conducted on the Conners 3 scores due to a lack of statistical power because of low sample size.

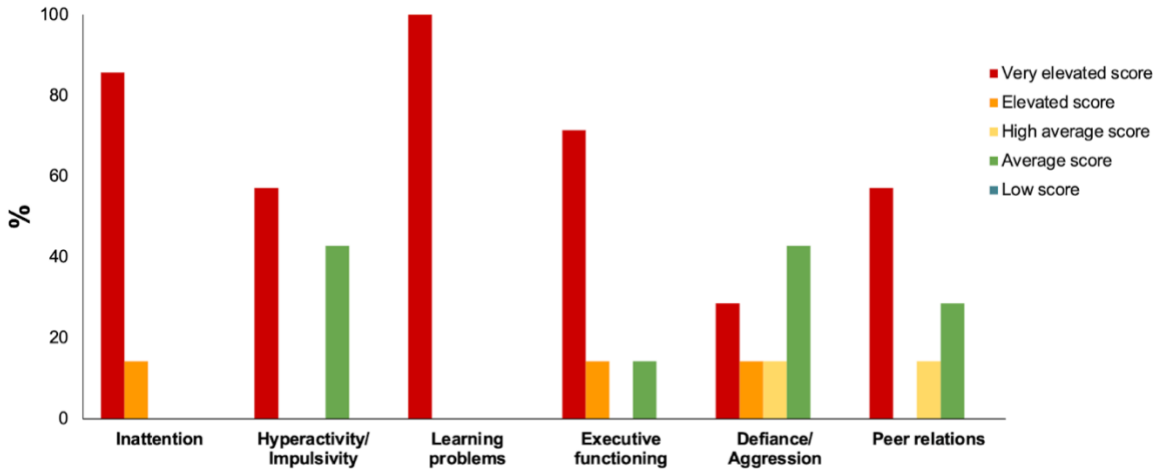


***Figure 5.11.*** *Conners 3 subscale scores (%).*

Data was also collected from participants (n=7) who were out of the recommended age range (6-18 years) of the measure (see **Appendix 5c**). All participants scored within the ‘very elevated range’ on the inattention, learning problems, and peer relations scales. Similar to the scores of those in the age range, there was variation in scores on the hyperactivity/impulsivity scale (57% ‘very elevated score’ and 43% ‘average score’). There was also the most contrasting variation in scores on the defiance/aggression scale (29% very elevated score, 29% ‘high average score’, and 43% ‘average score’). Although the majority of participants were still in the very elevated score range, in contrast to participants in age, there was some variation in the scores on the executive functioning subscale (57% ‘very elevated score’, 14% ‘elevated score’, and 29% ‘average score’).

### 5.3.5. Spence Children's Anxiety Scale - Parent (SCAS-P)

Participant SCAS-P total t-scores, and subscale t-scores (panic attack and agoraphobia, separation anxiety, physical injury fears, social phobia, obsessive compulsive disorder, and generalised anxiety disorder/overanxious disorder) are presented in **Table 5.4**. A t-score of 60 is approximately one standard deviation above the mean, and represents the 84th percentile, scores ≥60 are indicative of clinically significant elevated levels of anxiety. Most participants with MYT1L-syndrome (n=7) demonstrated elevated levels of anxiety in the panic attack and agoraphobia subscale. In contrast, the majority of participants scored within normal levels of anxiety for the remainder of the subscales (see **Figure 5.12**). Data was also collected from participants who were out of the recommended age range (6-18) of the SCAS-P (n=7; total t-scores and subscale scores are presented in **Appendix 5d** and **Appendix 5e**). There was variation in the scores in the out of age cohort, where 2/7 participants scored within elevated levels for the total t-score, 3/7 for panic attack and agoraphobia, 4/7 for separation anxiety, 2/7 for physical injury, 0/7 for social phobia, 3/7 for obsessive compulsive disorder, and 2/7 for generalised anxiety disorder. A profile analysis was not conducted on the level of anxiety of individuals with MYT1L-syndrome due to being underpowered.

| SCAS-P | N | Mean (SD) | Range |
|---|---|---|---|
| *SCAS-P total score* | 7 | 52.32 (9.69) | 41-64 |
| *Panic attack and agoraphobia* | 7 | 59.97 (7.76) | 51-70 |
| *Separation anxiety* | 7 | 59.43 (9.03) | 51-70 |
| *Physical injury fears* | 7 | 46.00 (10.31) | 40-68 |

| | | | |
|---|---|---|---|
| *Social phobia* | 7 | 47.00 (8.43) | 40-63 |
| *Obsessive compulsive disorder* | 7 | 57.00 (6.73) | 50-68 |
| *Generalised anxiety disorder/overanxious disorder* | 7 | 54.14 (10.95) | 40-70 |

***Table 5.4.*** *Summary of SCAS-P standardised t-scores for MYT1L-syndrome*

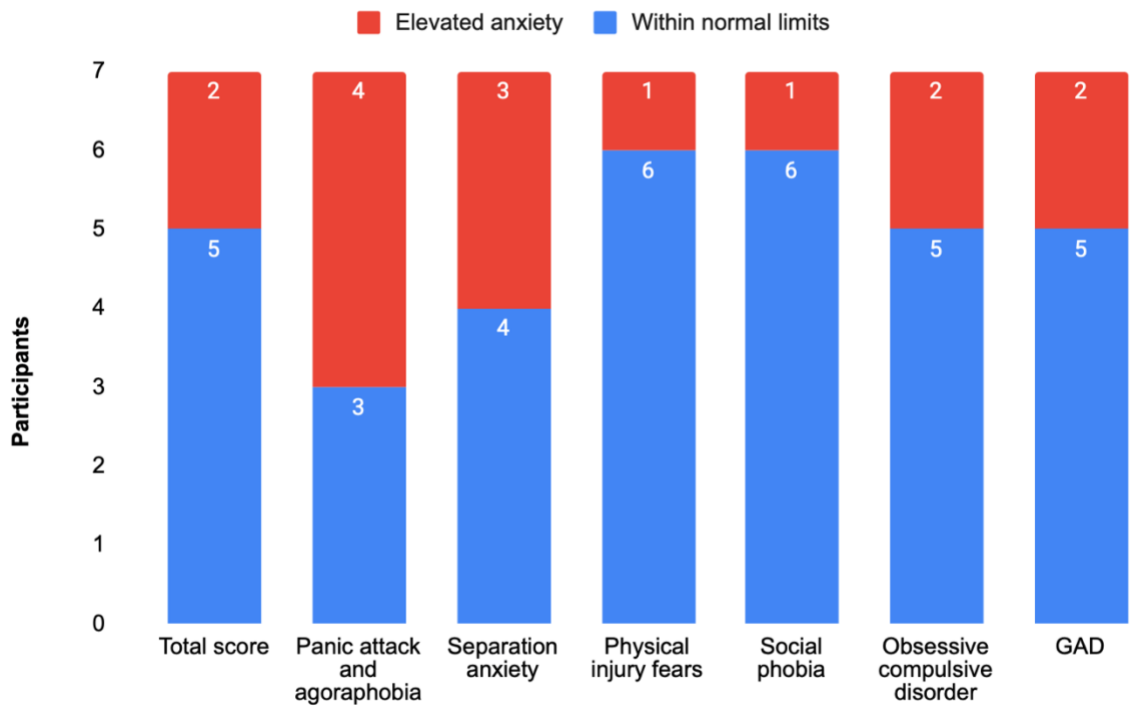


***Figure 5.12.*** *Frequency of participants scoring within normal limits and elevated levels in the total t-score and treatment subscale t-scores.*

### 5.3.6. Children's Communication Checklist - Second version (CCC-2)

General communication composite (GCC), language structure (speech, syntax, semantics, and coherence subscales), pragmatic language (inappropriate initiation, stereotype language, use of context, non-verbal communication, social relations, and interests) scores are presented in **Table 5.5**. GCC scores ranged from 8-75, with 66.67% of the cohort scoring

<55, indicating significant communicative difficulties. Data was collected for eight individuals who were out of the recommended age bounds for the CCC-2 and were aged between 18-35 years old (see **Appendix 5f**). For these participants, standard scores were computed using the highest reference age category available in the CCC-2 normative data (16 years 11 months). GCC scores ranged from 0-50, with 100% of the cohort scoring <55, indicating difficulties in communicative abilities. This demonstrates that whilst the majority of participants in the in-age group scored within the range that indicated significant impairment, all participants who were out of the recommended age range scored within this category.

| **CCC-2** | **N** | **Mean (SD)** | **Range** |
|---|---|---|---|
| ***General Communication Composite (GCC)*** | 12 | 41.50 (22.83) | 8-75 |
| ***Language structure*** | 12 | 9.08 (5.88) | 0-19 |
| *Speech* | 12 | 2.17 (2.12) | 0-7 |
| *Syntax* | 12 | 1.00 (1.35) | 0-3 |
| *Semantics* | 12 | 2.75 (2.14) | 0-6 |
| *Coherence* | 12 | 3.17 (2.04) | 0-6 |
| ***Pragmatic language*** | 12 | 13.25 (7.28) | 3-24 |
| *Inappropriate initiation* | 12 | 3.92 (1.78) | 2-7 |
| *Stereotyped language* | 12 | 3.75 (1.91) | 0-7 |
| *Use of context* | 12 | 2.08 (2.43) | 0-7 |
| *Non-verbal communication* | 12 | 3.50 (2.61) | 0-8 |

| | | | |
|---|---|---|---|
| *Social Relations* | 12 | 2.58 (3.48) | 0-10 |
| *Interests* | 12 | 4.42 (1.73) | 2-7 |

***Table 5.5.*** *Summary of CCC-2 scaled scores for MYT1L-syndrome*

#### 5.3.6.1. Language structure in MYT1L-syndrome

Mean scores for the components of language structure in the MYT1L cohort, comprising speech, syntax, semantic, and coherence were all 2SD or more below the normal for typically developing children (see **Figure 5.13**). Within the language structure composite, 1/12 individuals scored 'borderline functioning' (17-24) and 11/12 individuals scored as 'impaired functioning' (<17). This indicates that the majority of MYT1L individuals in the cohort have impaired language structure abilities (see **Figure 5.14**). All participants out of the age range also scored 2SD or more below the norm (see **Appendix 5g**), where 2/8 individuals scored 'borderline functioning' (17-24) and 6/8 individuals scored as 'impaired functioning' (<17). Individual language structure composite scores are presented in **Appendix 5h**).

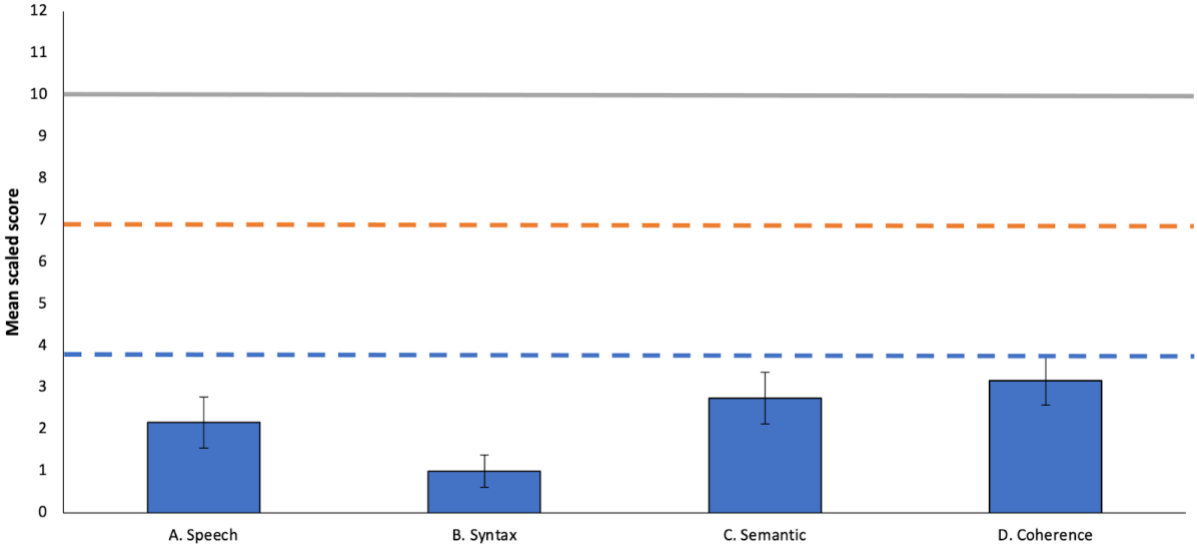


***Figure 5.13.*** *The means and standard error of the scaled language structure subscales (speech; syntax; semantic; coherence). The mean score for each subscale for TD standardised norms = 10, SD=3, and the grey line indicates the standardised mean for the norms of individuals who are TD, the orange dotted line highlights 1 SD below the mean of TD norms, and the blue dotted line highlights 2SD below.*

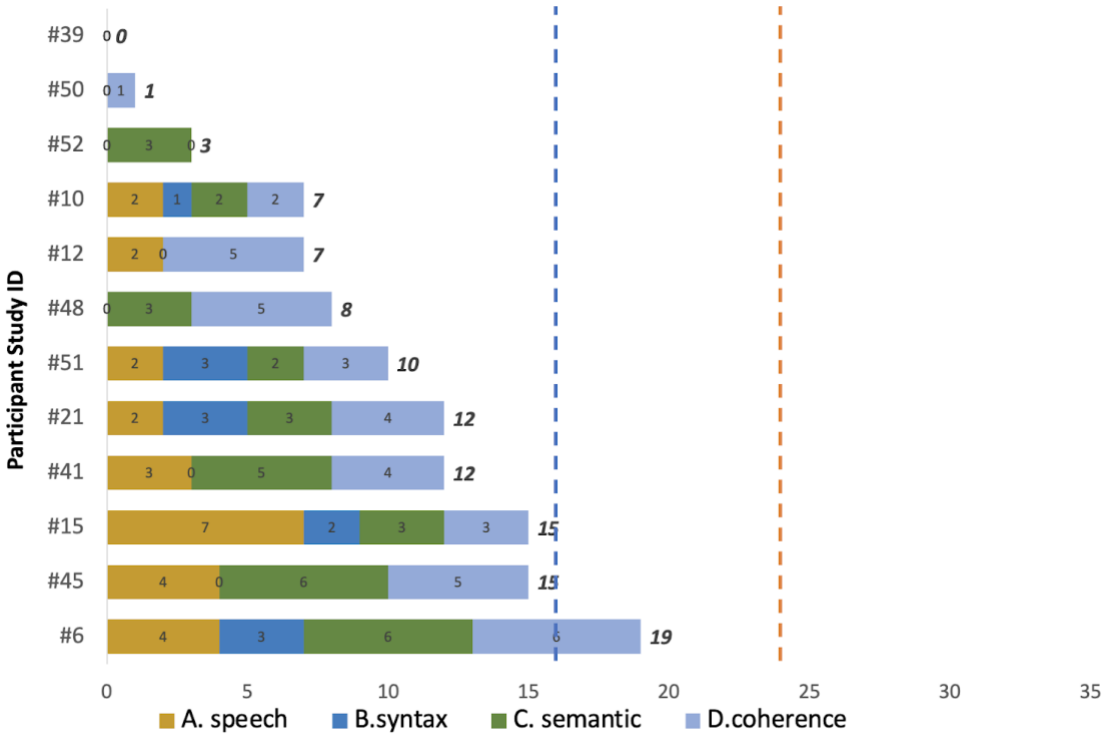


***Figure 5.14.*** *Coloured bars represent each of the language structure subscales (speech; syntax; semantic; coherence). The language structure composite score is visible in bold italics to the right of each coloured bar. Scores >24 represent 'typical functioning' (represented by the orange dashed vertical line), and scores 17-24 represent 'borderline functioning' and scores <17 represent 'impaired functioning' (represented by the blue dashed vertical line). In order of lowest to highest total score.*

#### 5.3.6.2. Pragmatic language in MYT1L-syndrome

Mean scores for the components of the pragmatic language composite in the MYT1L cohort, comprising inappropriate initiation, stereotyped speech, use of context, and nonverbal communication were all 2SD or more below the norm for typically developing children (see **Figure 5.15**). Within pragmatic language, 4/12 individuals scored 'borderline functioning' (17-24) and 8/12 individuals scored as 'impaired functioning' (<17), indicating that most individuals have impaired pragmatic language abilities, with some on the borderline of

impairment (see **Figure 5.16**). Similarly, participants out of the recommended age range also scored 2SD or more below the normative data (see **Appendix 5i**), where 8/8 individuals scored 'impaired functioning' (<17). Individual subscale scores are presented in **Appendix 5j**.

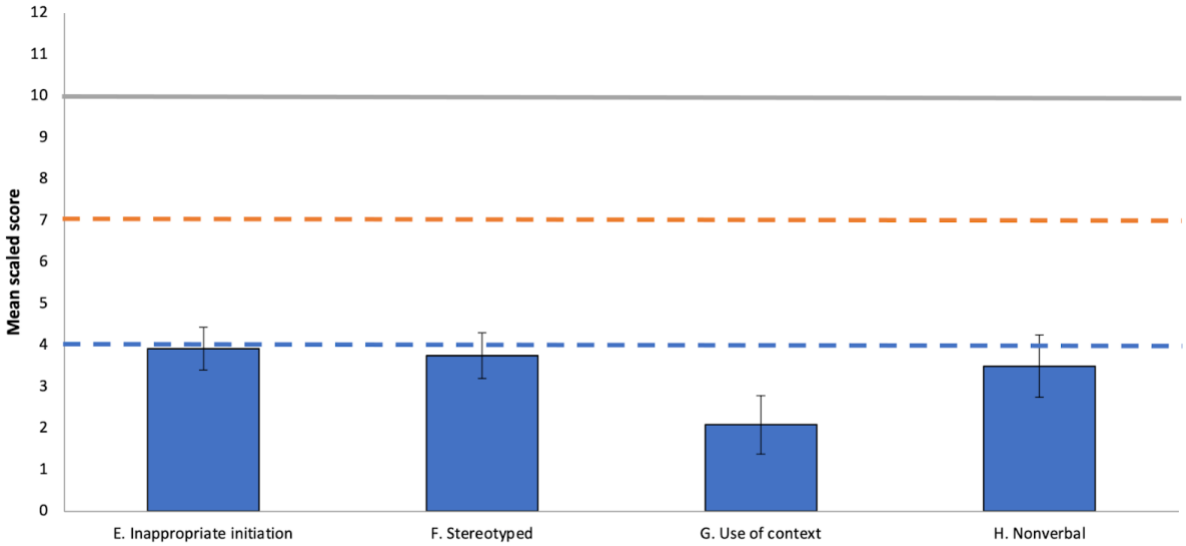


***Figure 5.15.*** *The means and standard error of the scaled pragmatic language subscales (inappropriate initiation; stereotyped speech; use of context; nonverbal communication). The mean score for each subscale for TD standardised norms = 10, SD=3, and the grey line indicates the standardised mean for the norms of individuals who are TD, the orange dotted line highlights 1 SD below the mean of TD norms, and the blue dotted line highlights 2SD below.*

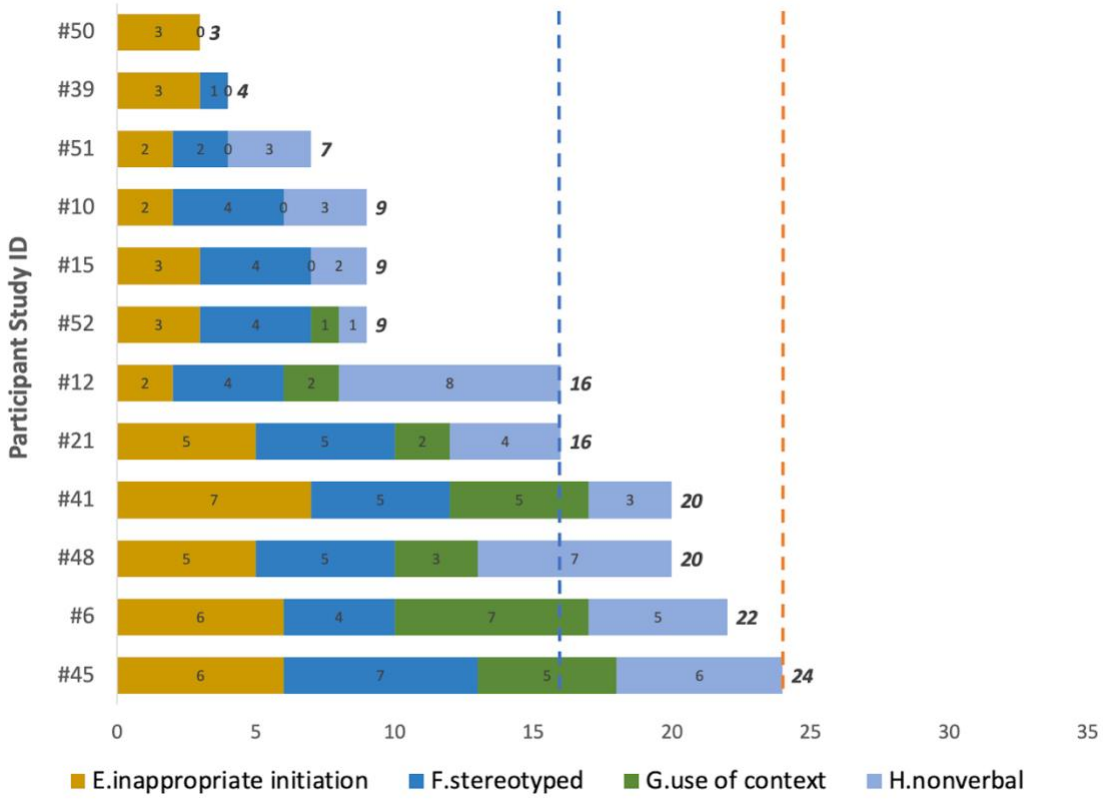


***Figure 5.16.*** *Coloured bars represent each of the pragmatic language subscales (inappropriate initiation; stereotyped speech; use of context; nonverbal communication). The pragmatic language composite score is visible in bold italics to the right of each coloured bar. Scores >24 represent 'typical functioning' (represented by the orange dashed vertical line), scores 17-24 represent 'borderline functioning' and scores <17 represent 'impaired functioning' (represented by the blue dashed vertical line). In order of lowest to highest total score.*

### 5.3.6.3. Autistic features in MYT1L-syndrome

**Figure 5.17** illustrates the mean scores for the components of autistic features, comprising social relations and interests, in the MYT1L cohort. Both of which were 1SD or more below the normative data for typically developing children. This indicates that there is varied impairment, with social relations 2SD below the normative data and interests 1SD below

(see **Figure 5.18** for individual subscale scores). For participants out of the age range, both social relations and interests were 2SD or more below the normative data (see **Appendix 5k** and **Appendix 5l**).

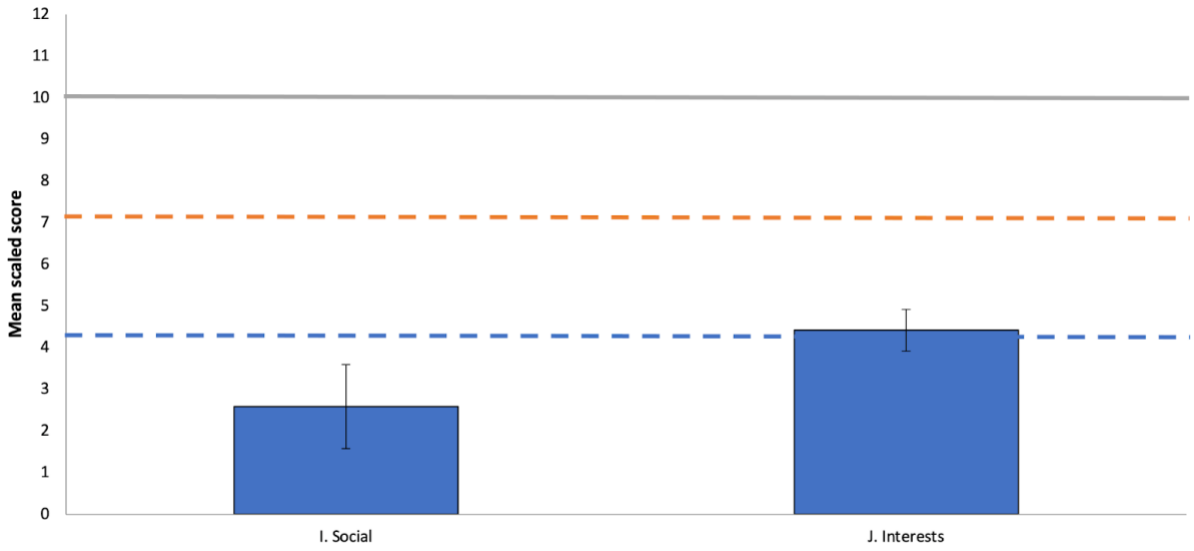


***Figure 5.17.*** *The means and standard error of the scaled autistic features subscales (social relations and interests). The mean score for each subscale for TD standardised norms = 10, SD=3, and the grey line indicates the standardised mean for the norms of individuals who are TD, and the orange dotted line highlights 1 SD below the mean of TD norms, and the blue dotted line highlights 2SD below.*

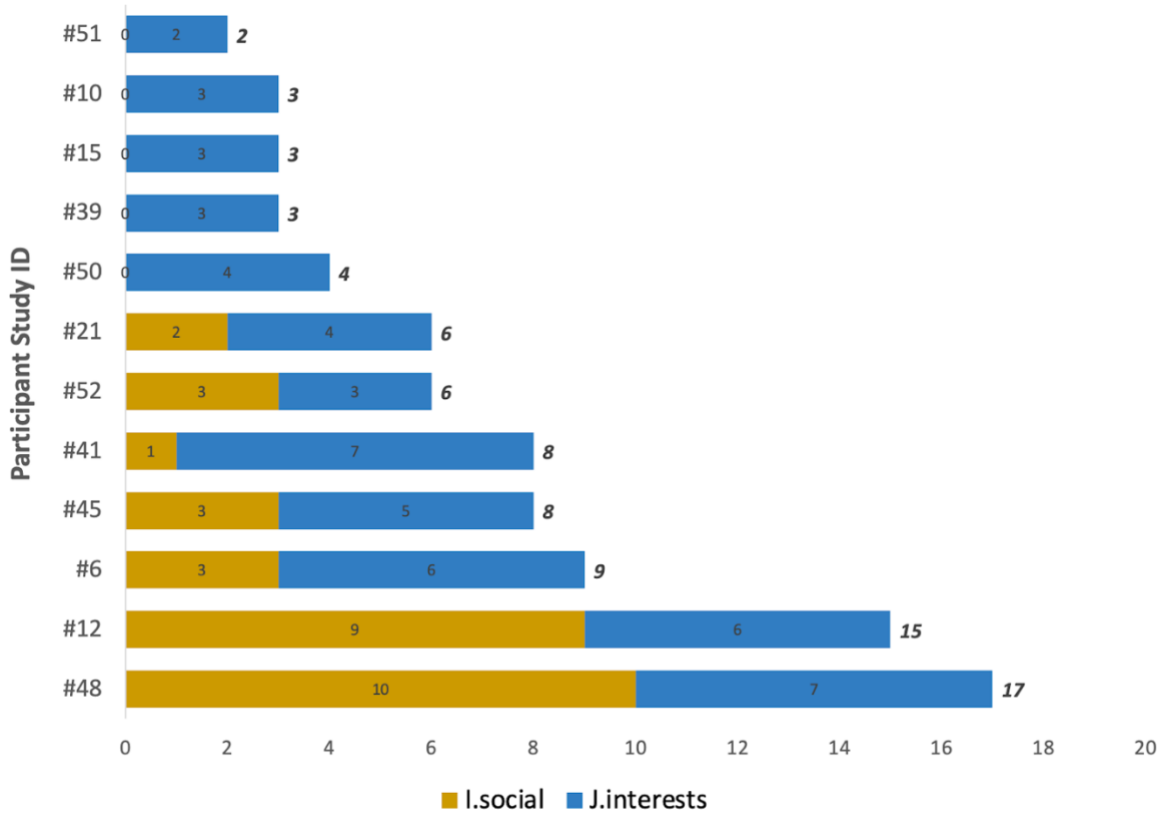


***Figure 5.18.*** *Coloured bars represent each of the autistic features subscales (social relations and interests). Ordered by lowest to highest total score.*

## 5.4. Discussion

This study quantitatively assessed the cognitive and behavioural phenotype associated with MYT1L-syndrome. Specifically, social impairments (SRS-2), adaptive behaviour (VABS-3), attention-deficit hyperactivity disorder-related behaviours (Conners 3), communication (CCC-2), sensory processing patterns (SSP-2), and anxiety (SCAS-P) were assessed using standardised measures. This is the first in-depth characterisation of cognition and behaviour in MYT1L-syndrome using standardised measures of assessment in 24 diagnosed individuals (range 7 – 24 individuals, dependent on the recommended age range of each measure). Individuals in the present study were found to possess severe impairment in the following domains: social cognition, social communication, and restricted interests and repetitive behaviours; sensory profile, including sensitivity and registration; attention-deficit hyperactivity disorder-related behaviours; language structure, and pragmatic language. Further, borderline to moderate impairments were present in relation to adaptive behaviour and few participants demonstrated elevated anxiety levels.

As assessed by the VABS-3, all participants in the present study had impaired adaptive functioning. Most participants (16/24) scored within the mild, moderate, or severe impairment ranges and 8/24 participants scored within the borderline impairment range on the overall ABC composite. This, alongside the scores reported in each of the subscales, demonstrate that whilst impairment is present in all individuals included in this study, the extent of the impairment is highly variable. Scores were most varied in the daily living skills subscale where participant scores fell within all categorised impairment levels, ranging from borderline to profound impairment. The use of the VABS-3 in the MYT1L-syndrome

cohort reported in this study does appear to have captured the heterogeneity of impairment present, however this was not the case for other syndromes such as Dravet syndrome where a recent study found that most individuals (21/25) in the study scored the lowest possible composite and subscale scores (Lo Barco et al., 2022). This floor effect means that little information is provided regarding the variability of impairment in the sample and does not allow for the investigation of individual strengths and weaknesses based on the cognitive and behavioural profile reported. Although the floor effect is not apparently present in the current study, the selection of standardised measures enabling appropriate insight into an individual's developmental profile is an important consideration for future research. Given the associations between MYT1L-syndrome and ID described in clinical case reports, discussed in Chapter 1, it may have been expected that a higher number of participants in the cohort would demonstrate more severe impairments to adaptive behaviour, as identified in other syndromes including Angelman syndrome (Micheletti et al., 2016). There is, however, conflicting evidence regarding the relationship between intelligence and adaptive behaviour, and one study found that correlations between intelligence scores, collected through the Wechsler Intelligence Scale, and adaptive behaviour impairments, scored through the composite and subscale scores on the VABS, did not correlate in individuals with ID, and that associations were similar to those found in the general population (Saleem, Beail, & Roache, 2019). Understanding the relationship between different domains of impairment is an important area for future research, and it would be valuable to undertake intelligence testing in a larger cohort of individuals diagnosed with MYT1L-syndrome alongside adaptive behaviour testing.

Autism-related behaviours, as measured by the SRS-2, were all within the moderate to severe impairment ranges, and the most severely impacted domains were social awareness, social cognition, social communication, and restricted interests and repetitive behaviours. Whilst this measure is not a clinical diagnostic tool for ASD, it is a useful indicator for the presence, and severity, of autism-related behaviours. Over half of the cohort (54%; 13/24) had SRS-2 total scores at the level of, or above, the threshold which is considered severe and strongly associated with a clinical diagnosis of ASD. A systematic review, which identified 168 papers, explored the prevalence of ASD in numerous genetic disorders, and reported estimated prevalence rates of 61% in females with Rett's syndrome, 43% in Cornelia de Lange syndrome, 30% in CHARGE syndrome, and 12% in WS (Richards et al., 2015). Compared to these estimated prevalence rates, the incidence of ASD behaviours in MYT1L-syndrome appears higher than in many other rare genetic syndromes, and potentially more common than in Cornelia de Lange syndrome and WS. Interestingly, prevalence also appears to be more common than in CHARGE syndrome, a genetic disorder implicated in the same pathway as MYT1L-sydrome. Although based on a small sample size (n = 24), the findings in the present study, when compared to the wider literature, suggest that profound impairments to social responsiveness, and the elevated presence of autism-related behaviours, are associated with MYT1L-syndrome.

Statistical analysis indicated that adaptive behaviour scores and autism-related scores (collected by the VABS-3 and SRS-2, respectively) did not correlate with participant age in the present study. As age increases, a loss of skills has been identified as core to the cognitive profile in other syndromes, including Phelan-McDermid syndrome (Dille et al,

2022), and because the present study collected data at only one time-point, it may be more appropriate to adopt a longitudinal design when assessing the relationship between domain impairment and age. Dille et al., (2022) combined both cross-sectional and longitudinal data in a cohort of 24 individuals (age range: 6 - 56 years) to successfully recognise a distinct model of neurodevelopmental regression in Phelan-McDermid syndrome - including motor function, psychosocial adaptation, and communication. It would, therefore, be advantageous to undertake a study emulating a similar methodological design to assess any changes to the developmental profile of individuals with MYT1L-syndrome across the lifespan.

Communication abilities, as measured using the CCC-2, were indicative of significant communicative difficulties, with mean composite scores for both language structure and pragmatic language falling mostly within the impaired functioning category and 67% of GCC scores falling within the significant impairment range. In relation to language structure, almost all participants scored within the range of impaired functioning (11/12) and the remaining participant scored within borderline functioning (1/12). Examples of structural language include the influence of word arrangement on sentence meaning, semantics, and coherence. Compared to pragmatic language, more impairment was present in language structure. However, impairments to pragmatic language were still evident, and 8/12 individuals scored within the range of impaired functioning, and 4/12 borderline functioning. Pragmatic language refers to social language skills such as eye contact, body language, and the appropriateness of interactions. Pragmatic language difficulties are also well-documented in other genetic syndromes including FXS (Tager-

Flusberg et al., 2005; Keysor & Mazzocco, 2002). Co-occurring ASD in such genetic syndromes may be linked to pragmatic language impairments, as individuals with ASD are also noted to experience impairments to numerous facets of pragmatic language including turn-taking, appropriateness of interactions in context, and the inclusion of irrelevant information in conversation (Choi & Lee, 2013; Paul et al., 2009; Diehl, Bennetto, & Young, 2006). A study comparing FXS-associated ASD and idiopathic ASD found that multiple similarities were observed in relation to pragmatic language impairments (Klusek, Martin, & Losh, 2014). This has important implications in MYT1L-syndrome, given the high incidence of autism-related behaviours reported in this study, and future research should seek to understand how the MYT1L gene may be implicated in the pragmatic language phenotype associated with ASD. Research has also identified that individuals with pragmatic language problems exhibit a wide variety of behavioural problems, including hyperactivity and a lack of prosocial behaviours (Ketelaars et al., 2010). Given the reports of problem behaviour discussed in Chapter 3, routine screening of pragmatic language problems in children diagnosed with MYT1L-syndrome may lead to the early detection of those most at risk of developing behavioural problems and enable the implementation of appropriate and timely interventions.

Although a small sample size, and not within the recommended age range for the measure, individuals aged over 16 years in the present study all possessed GCC scores indicative of significant impairment, alongside also falling 2SD or more below the normative sample average on the composite scores. These scores indicate that, descriptively, older participants with MYT1L-syndrome possess more impaired communication profiles.

Changes to communication abilities have been observed across the lifespan in multiple genetic conditions where, in WS, expressive language skills have been found to develop more quickly than receptive language skills (Van Den Heuvel et al., 2016). Further, language and speech development have both been found to be delayed, but school-age children and older have been reported to be understandable in context (Masataka, 2001; Mervis & Velleman, 2011). Whilst this does not appear to be the case in MYT1L-syndrome, the further exploration of language profiles may lead to the elucidation of how language abilities may change in affected individuals across the lifespan.

As characterised by the SSP-2, differences were also present in the sensory profile of individuals diagnosed with MYT1L-syndrome. However, in all quadrants, some participants scored in the 'just like the majority of others' range, indicating that there is a level of variability present in sensory processing abilities. Despite an indication of typical functioning, in each of the four quadrants of the SSP-2; seeking (the degree to which a child obtains sensory input), avoiding (the degree to which a child is bothered by sensory input), sensitivity (the degree to which a child detects sensory input), and registration (the degree to which a child misses sensory input), the majority of participants (67%, 67%, 73%, and 73%, respectively) scored within the 'much more than others' range, demonstrating differences in how children with MYT1L-syndrome experience sensory input compared to typically developing children. Similar findings were reported in a study of children with ASD, where 271 children (age range 4y – 11y) were rated using the SSP-2, and differences were present across all four quadrants (67% scoring 'much more than others'), but particularly so in relation to avoiding and sensitivity (Simpson et al., 2019). The sensory

processing abilities of children with ASD are like that of children with FXS, where differences to sensory processing were significantly different than a control group of typically developing children, but not significantly different from each other (Rogers, Hepburn, & Wehner, 2003). Children with other syndromic ASDs, Phelan-McDermid Syndrome and SYNGAP1-related ID, were also found to exhibit atypical sensory profiles, where impairments were present in all quadrants of the SSP-2, but particularly high scores were observed in relation to avoiding and seeking (Lyons-Warren, McCormack, & Holder, 2022). The findings from FXS, Phelan-McDermid Syndrome, and SYNGAP1 all demonstrate the significant sensory processing differences in cohorts of children with syndromic ASDs. Given the SRS-2 scores found in the present study, strongly associated with a clinical diagnosis of ASD, it is important that future work further explores links between sensory processing differences and the prevalence of ASD in children with MYT1L-syndrome, as this insight is vital to guide the interventions delivered by healthcare professionals and education providers.

Attention-deficit hyperactivity disorder-related behaviours, as assessed by the Conners 3, identified that the domains of inattention, learning problems, and executive functioning were more impaired, with 86%, 100%, and 71% of individuals, respectively, scoring within the 'very elevated score' range. The other subscales, hyperactivity/impulsivity and peer relations, had more variable levels of impairment with 57% of participants scoring within the 'very elevated score' range on both. Hyperactivity, impulsivity, and inattention were all found to be present in more than half of participants (n = 40) studied with DS, and co-occurring ADHD has been observed in up to one-third of individuals diagnosed with DS

(Capone et al., 2006; Dykens et al., 2002). In WS, of 50 individuals, 20% were found to have co-occurring ADHD (Dodd & Porter, 2009). Whilst the Conners 3 is not a clinical diagnostic tool for ADHD, the findings of the present study indicate that some ADHD symptomatology may be more prevalent in MYT1L-syndrome than other genetic syndromes, such as DS and WS. Dodd & Porter (2009) also identified that whilst adults with WS appear to be at an increased risk of depressive disorders, co-occurring ADHD may be more common, or cause more notable impairment, in children. Further research is, therefore, warranted utilising a longitudinal methodological design to assess changes between the co-occurrence, or apparent functional impairment, of attention-deficit hyperactivity disorder-related behaviours in children and adults with MYT1L-syndrome.

Assessed using the SCAS-P, mean scores of all subscales and total score were not indicative of elevated anxiety. Most participants scored within the range of normal limits for all but one of the scales, panic attack and agoraphobia, where 4/7 individuals scored within elevated levels. Among healthy individuals, and individuals with ADHD, elevated sensory processing patterns were found to be linked to increased anxiety levels (Engel-Yeger & Dunn, 2011; Kamath et al., 2020). Given the presence of atypical sensory processing patterns and elevated attention-deficit hyperactivity disorder-related behaviours in the present cohort, it is, therefore, surprising that most participants in the present study scored within normal limits on the SCAS-P, assessing anxiety traits. In other populations, including individuals with ASD, higher cognitive ability has been associated with increased anxiety, as individuals possessing stronger cognitive abilities are considered to have greater awareness of their social and adaptive impairments, thus leading to elevated levels of

anxiety (Rieske, Matson, & Davis, 2013; Vasa & Mazurek, 2015). As the SCAS-P is only indicated for use in children 6.0-18.0, it may be that as children with MYT1L-syndrome develop more awareness of their condition and associated impairments, anxiety levels increase. Whilst data collected for individuals above the recommended age range for the measure suggests similar levels of elevated anxiety, a small sample size (n=7) means that concrete conclusions cannot be made about the presence of anxiety across the lifespan, and therefore additional research should further explore the presence of anxiety in adolescents and adults with MYT1L-syndrome.

The findings reported in this study indicate that multiple facets of cognition and behaviour are impacted in individuals with MYT1L-syndrome, as assessed by standardised quantitative assessments of adaptive behaviour, social responsiveness, ADHD-related behaviours, sensory processing, anxiety, and communication. Given 54% of individuals with MYT1L-syndrome scored within the threshold of scores strongly associated with a clinical diagnosis of ASD, it is important that routine screening is undertaken for ASD in children with MYT1L-syndrome. Further, studies utilising clinical examination tools, such as the Autism Disorder Observation Scale, would be valuable to explore the profile of traits associated with ASD. Children in the cohort also demonstrated poor adaptive behaviour outcomes, which emphasises the need for early and focused rehabilitation plans to alleviate the challenges associated with such issues. Impairments to pragmatic and structural language were also present, and the early assessment of pragmatic language and understanding the extent of any impairment, may provide an earlier marker for the detection of ASD and ADHD characteristics in affected individuals, both of which are

apparently prevalent in the cohort reported on in this study. It is important for education providers to be aware of the sensory profile impairments, principally to the domains of sensitivity and registration, and the ADHD-related behaviours that children with MYT1L-syndrome may present with, as this would enable the implementation of appropriate interventions in school.

Whilst the present study begins to define the cognitive and behavioural profile of MYT1L-syndrome, it is important that future work continues to investigate the phenotypes in the population. Quantitative research that adopts a longitudinal design would be advantageous to properly elucidate an understanding of how cognitive abilities are maintained or regress as an individual progresses into adulthood and would propel the identification of any syndrome-specific models of skill regression. Further, to address the small sample size utilised in the present research, future work with larger samples, of a diverse age range, would enable the investigation of adaptive behaviour changes across the lifespan. A limitation of the present study is that it was not pre-registered to a public repository in advance of undertaking the research. Future work should endeavour to specify the research plan and pre-register it to a public repository ahead of data collection, as this has been found to enhance research transparency, improve opportunities for collaboration, and support other researchers to advance existing research plans (Simmons, Nelson, & Simonsohn, 2020).

# Chapter 6: General discussion

This thesis aimed to investigate the cognitive and behavioural phenotype associated with MYT1L-syndrome, adopting a mixed-methods approach using both standardised measures of assessment and qualitative interviews to gain insights from a parental perspective. Although there is a growing body of work investigating the impact of MYT1L-syndrome, as discussed in Chapter 1, there is overall a paucity of published research that uses standardised outcome measures to objectively assess relative strengths and weaknesses in the population. Further, no evidence, to date, has utilised qualitative research methods to understand how MYT1L- syndrome impacts individuals, caregivers, and the wider family, from a parent perspective. In addition to providing a summary of the key findings reported in this thesis, this chapter will present the implications of the findings in the contexts of education, healthcare, and family therapy, and propose important directions for future research.

## 6.1. Summary of findings

### 6.1.1. The cognitive and behavioural phenotype of children with genetic disorders affecting chromatin remodelling: a systematic review

Chapter 2 presented the findings of a systematic review investigating the cognitive and behavioural phenotype associated with other genetic syndromes implicated in the same pathway as MYT1L-syndrome, chromatin remodelling. 26 papers were identified that explored domain(s) of cognition and/or behaviour using standardised empirical measures across five genetic conditions, CHARGE syndrome; CHD8 syndrome; Kabuki syndrome; KBG syndrome; and Kleefstra syndrome. The review highlighted that there are varying levels of

impairment to multiple facets of cognition and behaviour in individuals affected by one of the genetic disorders of interest. Areas of investigation in the studies focused on adaptive behaviour, ASD traits, intelligence, developmental delay/ID, problem behaviours, and speech, language, and communication. Whilst explored by fewer studies, domains including anxiety, memory, obsessions and compulsions, and sensory profiles were also discussed. Although a level of impairment, to some extent, was evident in most of the individuals reported on across the five syndromes, some domains appeared more consistently impacted in some of the syndromes compared to others – for instance, ASD symptoms were unanimously present in the CHD8 cohort, but significant variation was present in individuals diagnosed with CHARGE syndrome. This indicates that there is a level of heterogeneity present in affected individuals, both within single syndrome populations and between the genetic disorders of interest, where some individuals are more adversely impacted than others. Further, there are inconclusive reports of whether severity of impairment is associated with age as some studies exploring the same domain, in the same genetic disorder, report conflicting evidence. In addition to the lack of specificity provided by some of the papers regarding the measures used and the findings, one of the key limitations of all the studies identified is that findings are based on relatively small samples meaning the wider prevalence of such impairments have not been established, and the findings reported may not be generalisable to the wider population of affected individuals for the genetic disorders investigated. It is important to note, however, that the syndromes of interest are notably rare, and therefore any research exploring these populations is a significant and important advancement to our current understanding. Collectively, these studies will enable researchers to form a more in-depth understanding of the associated

phenotypes, and potentially lead to the development of syndrome-specific interventions – improving quality of life for individuals and their families. The systematic review also provided an understanding of the specific standardised measures used to explore domains relating to the cognitive and behavioural profile of individuals which could be applied to the quantitative chapter in this thesis, as discussed in Chapter 5.

### 6.1.2. The impact of MYT1L-syndrome on behaviour and cognition: a parent/caregiver perspective

Chapters 3 and 4 discussed the key findings of the qualitative interview study conducted with the parents and caregivers of children with MYT1L-syndrome. Following the principles of TA, discussed in Chapter 1, one analysis was conducted on the data, and two separate syntheses of the findings – the first investigating the impact of MYT1L-syndrome on cognition and behaviour from a parental perspective, and the second gaining insight into the impact on family life. The first analysis, exploring cognition and behaviour, included insights from 18 caregivers. Given the lack of published evidence in MYT1L-syndrome this was an important first step to begin to understand the most problematic areas of impairment in cognition and behaviour from a caregiver perspective. Qualitative research was an appropriate mechanism to gain this insight as it enables access to unique viewpoints given the hands-on delivery of care by parents, and such techniques have been used widely in other health conditions to understand domains of impairment. The analysis resulted in the identification of three key themes: 1) behaviour, 2) speech, language, and communication, and 3) cognitive ability and profile. The first theme, behaviour, gained insight into the sensory profile associated with affected individuals, the presentation of

problem behaviours, and other facets of behaviour such as social relationships, perceived autistic traits, and anxiety. The findings of theme 1 align with much of the previously reported literature, and an important avenue for future research was identified in that many caregivers reported challenges relating to food and diet – similar to challenges reported in PWS. The second theme provided insight into speech, language, and communication abilities and found that there is a high level of variability in impairment levels in the cohort ranging from individuals who are completely non-verbal and rely on assistive communication devices, to individuals who can effectively hold conversation with others. Finally, theme 3 sought to understand from caregivers the impact of the syndrome on cognition and it was found that, again, individuals appeared to present with a highly heterogeneous cognitive profile with severity of impairment ranging widely in affected individuals.

### 6.1.3. Life with MYT1L-syndrome: a parent/caregiver perspective

Following the completion of the first write-up regarding the impact on behaviour and cognition, an additional interview was conducted, transcribed and added to the analysis, meaning 19 caregivers were included in the synthesis relating to the family impact of MYT1L-syndrome. The analysis resulted in the identification of five themes. The first provided insight into the often-challenging journey that caregivers undertook to reach a diagnosis of the syndrome, including receiving incorrect diagnoses, not feeling trusted or respected by clinicians, and feeling like blame relating to syndrome onset was potentially attributed to them. Upon reaching the correct diagnosis, many caregivers felt relief although others felt that it was a challenge to adjust the expectations that they had initially

applied to aspects of development, such as reaching certain milestones. The diagnostic odyssey experienced by many in this thesis is a widely reported issue experienced by other families in countless other rare diseases which, following the advent and continual enhancement of modern genetic testing and the increased consideration of rare disease when clinically assessing symptoms, will hopefully decrease in the coming years. Theme 2 presented findings relating to the daily impact of the syndrome on caregivers, which included a perceived reduction in the ability to undertake tasks such as socialising with others, shopping, or eating meals out of the home. An impact was also present pertinent to the relationships between the primary caregiver and their spouse, which for many was a negative impact resulting in the breakdown of these relationships or marriages. Although, some reported that overcoming the challenges presented to them together resulted in the formation of a stronger unit. Again, these findings are present in the wider literature. Caregivers reported, as described in theme 3, that an increased involvement in care was required to adequately support their child, including a need to maintain communications with education providers to ensure that there is an appropriate care plan in place and needing to attend multiple healthcare appointments with clinicians from varying specialties – many of which were a considerable distance from the family home. The need to travel and pay for certain therapies, and other challenges relating to the syndrome, meant that caregivers needed to spend more money than they may do to support a typically developing child. This was explored in theme 4, as well as the restrictions that elevated care needs placed on job security and career progression. The final theme explored the impact on siblings and wider family members, in addition to external support sought by caregivers. Specifically in relation to siblings, challenges and positives aspects are

discussed which are largely consistent with the published literature in other health conditions.

### 6.1.3. The impact of MYT1L-syndrome on behaviour and cognition: a quantitative analysis

The findings of the systematic review discussed in Chapter 2, the insight provided by caregivers in Chapter 3, and a thorough search of the wider literature, resulted in the design of the quantitative study discussed in Chapter 5. Standardised measures were utilised to assess adaptive behaviour (Vineland-3), social responsiveness and ASD (SRS-2), sensory profiles (SSP-2), communication and language (CCC-2), ADHD behaviours (Conners 3), and anxiety (SCAS-P). Following an extensive data collection period, data was collected for 24 individuals, although this was lower for some of the measures in line with age limits and pre-requisite ability levels. In relation to adaptive behaviour skills, as measured by the VABS-3, most participants scores indicated at least borderline impairment, where impairment appears to be most profound in the communication domain. Additionally, there was the greatest variability in scores in the daily living skills domain where scores ranged from borderline impairment to profound impairment. This is largely consistent with the highly variable profile described by caregivers in Chapter 3. No relationship was identified between participant age and adaptive behaviour, although this may be related to the single point of data collection in the present study as opposed to a longitudinal study assessing developmental trajectory over time. The SRS-2 was also used to assess social responsiveness in 24 participants, where 63% of participants scored within the severe impairment range for restricted interests and repetitive behaviours – representing the most

severe level of impairment across all domains of the measure. Severe impairment was also present in the domains of social cognition, awareness, communication, and motivation but the scores were more variable between participants which potentially indicates a more heterogeneous profile in relation to impairments to social behaviours. There was also no relationship identified between impairment levels and age, however there was a significant difference present between restrictive interests and repetitive behaviours and social communication index scores, meaning that the more restrictive interests and repetitive behaviours present the lower the social communication score. Whilst this is not surprising given the social isolation findings reported by caregivers in Chapter 3 and consistent with the wider literature, it does highlight the importance of understanding more about the phenotype associated with the syndrome to appropriately support individuals with areas including social relationships. The sensory behaviours of individuals were found to consistently fall into the 'much more than others' range in all domains. Whilst only data for those within the recommended age range was formally analysed, data for those out of the age range was collected and suggests a similar sensory profile is present in older individuals, although the assessment of this using age-appropriate standardised measures would be advantageous for those out of the recommended age range within the present research. Findings relating to hyperactivity, as assessed by the Conners 3, are consistent with the challenges reported by caregivers in relation to education in Chapters 3 and 4, where 100% of individuals were found to have very elevated scores in relation to learning problems, and mostly very elevated scores in relation to inattention and executive function. Impairment, although varied across the cohort, was present in relation to hyperactivity, peer relations, and defiance. In relation to anxiety, children with MYT1L-syndrome were

found to mostly score within the normal limits across all subscales, other than panic attack. Whilst there were elevated levels of anxiety present in some individuals in all subscales, it was expected that more severe impairment would be identified in relation to anxiety given the caregiver reports in Chapter 3 – although, caregivers did report that anxiety seemed to become more problematic as individuals approached adolescence and adulthood, and the SCAS-P is only appropriate for use in children up to 14y 11m. Therefore, it may be that anxiety levels peak as individuals grow older, which is an important area for future research. The communication abilities of 8 individuals were assessed using the CCC-2, and mean scores fell 2SD or more below the standardised mean for typically developing individuals in the language structure subscales, pragmatic language subscales, and the autistic features subscales. Although the SRS-2 is a better indicator of ASD traits, the findings of the CCC-2 are consistent with the levels of impairment present in individuals with MYT1L-syndrome.

## 6.2. Research approaches

### 6.2.1. Qualitative research approach

The sample size of the qualitative interview study (n = 18-19) was consistent with those reported in the published literature in other qualitative explorations of caregiver experience (range = 15-21) (Weng et al., 2012; AlShatti et al., 2021; Ludlow, Brown, & Schulz, 2018). Additionally, the research sought insight from caregivers in various countries and who provided care for individuals with MYT1L-syndrome at different life stages, ranging from infancy to childhood, adolescence, and adulthood. This variation was critical to ensuring that the research pursued insights from caregivers at different stages of caregiving

across the lifespan, rather than from those with children at similar developmental stages, meaning that broader generalisations can be made to the wider syndrome population. The broadness of the interview schedule and the use of open questions also meant that caregivers were able to talk about areas they felt most appropriate and of the greatest importance to the study without feeling limited to topics decided by the interviewer. This meant that participants were provided a platform to speak openly about topics they felt important based on their lived experiences, resulting in insights regarding healthcare, family impact, education, finance, siblings, and intricacies relating to other areas of impact including diet, behaviour, and psychiatric symptoms including anxiety.

It is possible, however, that the findings of the qualitative study are biased towards the opinions of mothers given that only 4/19 participants were fathers. This is an important area for future research as a recent systematic review highlighted that parenting styles, and perceptions associated with caring for a child, differ between mothers and fathers where mothers are more accepting, more behaviour controlling and demanding than fathers (Yaffe, 2020). It may, therefore, be that reports of problem behaviour in the cohort are higher in comparison to that reported by fathers, although this was not immediately apparent in the accounts provided by fathers in the present study.

Another consideration in relation to the qualitative interview study is parent perceptions of the experiences of neurotypical siblings. Whilst participants did provide useful insight into sibling experience, it is important to acknowledge that parents have been found to overestimate the negative emotions experienced by unaffected siblings (Turnwald et al.,

2022) and therefore further research directly engaging with siblings would be useful to understand the true extent of impact. It is important to note, however, that within the present study caregivers did appear to provide a balanced overview of sibling experience, sharing some of the challenges faced alongside the positive impacts they saw. Whilst it could be proposed that the subjective nature of the qualitative study does not enable a cross-syndrome comparison of cognition and behaviour, the findings did inform the design of the subsequent quantitative study as standardised measures were chosen based on priorities highlighted by participants.

### 6.2.2. Quantitative research approach

The quantitative research study discussed in Chapter 5 used, to date, the largest sample to investigate the cognitive and behavioural phenotype associated with MYT1L-syndrome using standardised measures, which is a strength of the current research given the recency of identification and apparent rarity of the syndrome. However, small sample sizes are noted to lack generalisability to wider syndrome populations and therefore it is difficult to ascertain whether the findings of this study are applicable to others also affected by the syndrome. An additional consideration is that inclusion in this research relied on a confirmed genetic diagnosis of MYT1L-syndrome, and this is dependent on both the availability of such tests and often the motivation of families to pursue genetic testing. Although no screening was conducted prior to inclusion in this research, the current study is arguably a clinically representative sample that does not overestimate the challenges present within the wider population of individuals diagnosed with the syndrome, but it is

important to note that only individuals who have been identified and subsequently diagnosed are discussed.

Additionally, although the present study does provide insight into the cognitive and behavioural profile associated with MYT1L-syndrome the current study design, which collects data at only one time point, is likely not sensitive to changes in phenotypes associated with the syndrome across the lifespan of affected individuals as genetic mutations are thought to impact processes which have cascading effects on different domains as individuals develop over time (Farran & Karmiloff-Smith, 2011). Previous research investigating other genetic syndromes has identified differences across ages, where individuals with DS showed improvements as they progressed into adulthood, whereas those with FXS did not (Cornish, Scerif, & Karmiloff-Smith, 2007). It is important to understand how syndromes affect individuals across their lifespan as this enables the development of stage-specific interventions and identifies potential risk factors, for instance in DS where changes in emotional/behavioural functioning as individuals progressed into adulthood were linked to neurodegeneration and the increased onset of Alzheimer's disease (Grieco et al., 2015). It is appropriate to apply a longitudinal research design to understand changes across the lifespan. In WS, research adopting this design has identified both the persistence of clinically significant elevated anxiety levels in children and adolescents, and differences in the rates of verbal and non-verbal abilities, where vocabulary abilities progress at a higher rate than non-verbal domains (Woodruff-Borden et al., 2010; Jarrold et al., 2001).

Another methodological consideration is the parent-reported nature of the standardised measures. Whilst this is the most practical solution to collect data, particularly when conducting remote research, parents have been found to overestimate their child's ability in mathematical ability and overall intelligence (Zippert & Ramani, 2016; Chamorro-Premuzic et al., 2009). In relation to adaptive behaviour, the parents of children with Cerebral Palsy rated social functioning lower and emotional functioning higher than children themselves on the VABS-3, and whilst scores were generally comparable, indicates the importance of incorporating the opinions of the individual themselves where appropriate (Majnemer et al., 2008).

### 6.3. Practical implications

In line with previous research, the findings in Chapter 4 demonstrate that the impact on caregivers of individuals with MYT1L-syndrome are multi-faceted. For most participants the journey to a diagnosis was noted as a particularly problematic period, and suggest it is important that appropriate support is offered to the parents of children newly diagnosed with a rare disease to support them to begin to come to terms with the diagnosis and reframe their expectations in relation to developmental milestones and care needs. For clinicians, it is important that accessible and appropriate information is provided to the families of affected individuals to reduce the burden placed on caregivers to research the syndrome and educate themselves and others. In relation to information, particular focus should be put on educating neurotypical siblings about the syndrome as parents have been found to overestimate children's understanding of their sibling's diagnosis and therefore assumed that knowledge was at a higher level than in reality, impacting the ability of

siblings to process what is happening and develop appropriate coping strategies (Glasberg, 2000). Beyond the initial diagnosis, there is also a need to ensure that caregivers have access to appropriate support networks and therapy to manage the complex grieving process described by some participants. The findings from Chapter 4 also have important implications for family therapy, including the need to provide parents with strategies to ensure focus is given to maintaining a healthy relationship despite the stress and challenges associated with caring for a child with a rare disease. Additionally, a holistic approach should be adopted in family therapy given the wide-ranging impact on individuals, caregivers, siblings, and the wider family.

The findings from Chapters 3 and 5 demonstrate the diverse cognitive and behavioural profile associated with MYT1L-syndrome. First and foremost, the findings suggest that it is important for clinicians to routinely screen individuals diagnosed with MYT1L-syndrome for co-occurring NDCs such as ASD, ADHD, and ID, which would enable the implementation of appropriate interventions to best support individuals to manage problem domains identified in this research including hyperactivity, restricted interests and repetitive behaviours, and learning problems. An additional benefit of early and routine screening is increased access to services, as a diagnosis of ASD enables access to critical early intervention programmes which may inhibit the long-term impact of problem domains (Moore & Goodson, 2003). Many of the caregivers interviewed also felt that an ASD diagnosis was beneficial from a practical perspective and was useful for accessing support services that they were unable to access with a diagnosis MYT1L-syndrome alone. The caregivers of children with other rare diseases have also reported that secondary diagnoses beyond the

rare disease (such as ADHD or ASD) are helpful to access services given there are dedicated resources available for these diagnoses (Baumbusch et al., 2018).

Given the heterogeneity of impairment reported in the present sample, and the findings relating to challenges accessing education, it is important that specific consideration is given to how best support children with MYT1L-syndrome equitably access education - in line with their relative strengths and weaknesses. It is important that education providers take the time, where possible, to understand the cognitive and behavioural profile of the individual to appropriately advise caregivers on the most appropriate educational environment for their child. A recent qualitative interview study of 43 participants, including children and adolescents with a rare disease, family members, and school staff, identified that numerous variables dictated equity in education for children with rare diseases. These included a) physical adaptations, such as ramps and wider doors to enable wheelchair access, b) official recognition of the condition, as many caregivers reported the need to overcome bureaucracy to access services, c) curriculum adaptations, and d) the availability of additional staff resource to support with children's autonomy at school (Verger et al., 2020). In the classroom, additional support is also likely required for children diagnosed with the syndrome in relation to speech, and specifically the use of speech, syntax, and the use of context, and for some children it may be appropriate to introduce alternate means of communication, other than speech, such as PECS or simple sign language, both have which have been found the significantly improve functional communication for individuals diagnosed with a range of NDCs such as ASD and ID (Gilroy, Leader, & McCleery, 2018; Bracken & Rohrer, 2014). Finally, this thesis was intended to be

practically driven, acting as a tool for caregivers, healthcare professionals, and educators. It is hoped that the findings discussed will facilitate a knowledge exchange between the experiences of caregivers obtained through the lived experience of caring for an individual with MYT1L-syndrome to new parents, and other relevant stakeholders. In addition to information about the cognitive and behavioural profile associated with the syndrome, this research also provides practical guidance about interactions with healthcare professionals, identifying an appropriate educational environment, financial support, and how to navigate family life with MYT1L-syndrome.

### 6.4. Future research

In relation to the qualitative research presented in this thesis, it would be advantageous for future research to further explore the impact on neurotypical siblings – potentially through quantitative measures of quality of life or interviews. It may also be interesting for future research to collect, where possible, insights from both parents to assess any differences in parent perceptions of the syndrome and associated impact. Aspects of parental coping following the death of a child were explored in a qualitative interview study of 23 couples, and identified differences in coping mechanisms between parents, but also gained insight into how parents cope with grief separately, and together, which has important implications for family therapy and emotional support (Bergstraesser et al., 2015). Albeit a separate topic to the present research, this insight could be valuable to understand how to best support parents, together and separately, to cope with grief following the diagnosis of a child with a rare disease – as evident in Chapter 4. Whilst only caregivers were interviewed in the present research, it may be appropriate that interviews, with necessary adaptations,

are conducted with affected individuals themselves to ascertain how they perceive and understand the syndrome and any associated impact. This approach has been successfully adopted in other rare diseases, such as genetic kidney and neuromuscular diseases, to understand the information provision available to affected individuals and their caregivers, and how this differs to information needs (Litzkendorf et al., 2020).

Future research should also build on the progress made through the research presented in this thesis to continue to evolve our understanding of the cognitive and behavioural profile associated with MYT1L-syndrome. As genetic testing continues to advance, and more individuals are diagnosed with the syndrome, researchers should recruit larger and diverse samples to quantitative studies using standardised measures to identify the presence of a syndrome-specific profile. Additionally, a longitudinal research design would enable the exploration of changes to the phenotype across the lifespan. Although out of the scope of this thesis, it is important that other findings from the qualitative interview study are more fully explored such as the relationship between MYT1L-syndrome and diet and obesity, which warrants further research given the findings of this thesis and the genetic evidence of syndromic obesity.

Utilising other methodological approaches may also further our understanding of the syndrome, such as video observation studies to understand infant behaviours and EEG research to ascertain neuroanatomical differences in diagnosed individuals compared to those with other genetic disorders and typically developing individuals. Further, lab-based experiments could be conducted with affected individuals to validate the findings of the

quantitative study in this research and expand understanding of the relative strengths and weaknesses present in the syndrome population. Utilising a battery of cognitive tests in a lab environment has been useful in other conditions and led to the increased understanding of the visual-perception, visual-spatial and working memory abilities of children diagnosed with DS and FXS, enabling cross-syndrome comparisons (Kogan et al., 2009).

The focus of future research ideally will be formed by the priorities articulated by rare disease families, as it is important to acknowledge that the concerns of academics may differ to those of affected families. Further, the co-production of research with individuals from the population of interest has been found to challenge assumptions and democratise the research process (Lloyd & White, 2011). Arguably, it is most important that, irrespective of the topic, those conducting future research investigating this syndrome, or any other rare disease, make a conscious effort to appropriately format and disseminate the research findings in a way that is understandable, practically useful, and accessible to affected individuals, their caregivers, and those supporting diagnosed individuals.

It is also important that future research is pre-registered (documenting the study design, hypotheses, data collection methods, and analysis plan) before data collection begins to enhance research transparency, enable academic collaboration, and improve overall research quality. Ethics applications should also be authored to enable the sharing of research data in accordance with the FAIR Framework, which provides guidelines for making data more Findable, Accessible, Interoperable, and Reusable (Wilkinson et al.,

2016), which is particularly important in rare disease research. As there are a small number of individuals in the population affected by a rare disease, gathering sufficient data to achieve statistical power is challenging – however, data sharing would facilitate the pooling of data from multiple sources, potentially reducing the necessity for people to take part in multiple studies assessing similar domains and subsequently limiting participant fatigue. Further, data sharing enables collaboration between institutions, allowing researchers to share data, expertise, and resources to better understand rare diseases collectively (Rubinstein et al., 2020; Boycott et al., 2019).

### 6.5. General conclusion

In conclusion, the research presented in this thesis has advanced understanding of the cognitive and behavioural profile associated with MYT1L-syndrome and contributed to the body of literature assessing the impact rare diseases have on family life. The qualitative research presented is the only interview study, to date, that has been conducted with the caregivers of individuals with MYT1L-syndrome and provides a wealth of insight relating to the impact the syndrome has on multiple facets of life. Comparison of these insights to the published literature also shines a light on similar experiences within other rare disease families and provides a valuable contribution to our understanding of how support can be most appropriately delivered for those affected. The quantitative study built on this insight by quantitatively assessing the domains of adaptive behaviour, behaviours associated with ASD, ADHD, communication, anxiety, and sensory profiles, revealing highly varied levels of impairment between participants across all areas. It is clearly demonstrated by the studies presented in the thesis why research in rare disease populations is so critical, and why there

is a pressing need to build awareness of the syndrome with families, healthcare professionals, and educators. The findings reported in this thesis also contribute to the growing body of evidence relating to MYT1L-syndrome, which will enable the development of needed and specific interventions in line with the relative strengths and weaknesses of diagnosed individuals.

# Appendices

## Appendix 1: Qualitative interview study - Interview schedule

Interview Schedule (v2)

Introduction

**(Introductions)** Hello, my name is Louis and as you are aware I'm conducting this research as part of my PhD research into MYT1L-syndrome at The University of Sheffield. **(Check that the participant is comfortable/if conducting the interview online/telephone, check that they can hear/you can hear them and that they are in a comfortable/private environment).** What would you prefer that I called you throughout the interview?

**(Purpose)** Thank you for agreeing to participate in this research. This research, as you are aware, will investigate various aspects of what it means to live with MYT1L-syndrome. I will be asking you several questions that will explore your experience of being a parent/guardian of a child with [MYT1L-syndrome. Alongside these questions I may ask you some questions that gather demographic information. As the syndrome is relatively newly discovered, we hope that the information that you provide can be used to educate and inform decisions in numerous services including healthcare and education. You should have received some information from me that explains the research fully. **(Confirm that the participant has completed and emailed over the consent form)**.

**(Timing/Interview Housekeeping)** It is important to acknowledge that there may be some challenging questions that if you need a few moments to reflect on or if there are any questions that you are not comfortable answering or if you would like a break or would like to stop the interview at any stage let me know. The interview should take around 60 minutes, but this could be less or more depending on your response to each question. We can take as many breaks as you need throughout. As we are speaking [online **OR** on the phone] please let me know if there are any technical issues or if you need me to repeat any questions. If for whatever reason there are connectivity issues, leave and re-join the Google Meet and we will resume. Failing this, I will email you with further instructions. All of the information that you provide will remain confidential and the recording of this interview will be anonymised so that you cannot be identified.

Do you have any questions before we begin?

Main Interview Schedule

1) **Can you tell me about when [child's name] was diagnosed with MYT1L-syndrome?**

- *Prompts: ask about how they found out, symptoms, what support they had in place during this time*

2) **How has MYT1L-syndrome impacted [child's name]'s life?**

- *Prompts:*
    - *Sleep*
        - *What is their sleeping pattern, do they struggle to sleep, how many hours do they sleep, waking throughout the night, specific routines at bedtime etc.*
        - *What advice would you give to the parent of a child with MYT1L-syndrome to manage their sleep routine?*
    - *Eating*
        - *issues with eating, specific dietary requirements, ability to eat independently versus supported, choking etc.*
    - *School*
        - *additional support at school, ability to form and maintain friendships at school, relationships with teachers, parent/guardian interactions with the school, is school equipped to manage the additional needs their child may have, how educated is school about the syndrome*
    - *Health service*
        - *initial interactions with health services, professionals in contact with, regularity of contact, parental input into health management, overall utilisation of health service, ability of health service to educate you and others about the syndrome*
    - *What were the first signals that developmental milestones were not met?*
    - *Could you tell me about how things have changed over time?*
    - *Developmental strengths and weaknesses*

**3) What is the impact of the syndrome on family life?**

- *Prompts:*
    - *How did the family respond to the diagnosis?*
    - *Are you the main caregiver(s)? Do you share caregiving responsibilities?*
    - *Has there been any impact on family relationships?*
    - ***IF APPLICABLE*** – Can you tell me about [child's siblings name(s)] and their relationship with [child's name]?

**4) What difficulties have you experienced and how have you coped with them?**

- *Prompts:*
    - *Financial difficulties*
        - *additional costs due to the syndrome, costs of hospital visits, additional care and support costs, support received from the state to assist, impact on parental work and earning potential*
    - *Ups and downs of parenting a child with MYT1L syndrome?*
        - *Parental fatigue, positives and negatives, particular stressors or difficulties, expected versus unexpected difficulties, managing – support networks, links with other parents with children that have the syndrome etc.*
    - *COVID-19 and experience of lockdown*

        - *experience of homeschooling, relationships with other siblings, impact on support networks*
    - *In relation to overcoming difficulties, what do you think research into these syndromes should focus on?*
        - *Education of others, creation of resources, establishing interventions, giving parents and patients a voice*

5) **Is there anything else that I have not asked about today that you would like to tell me? Is there anything that you have not had the opportunity to speak about that you think is important for me to know?**

**<u>IF NECESSARY</u> - FOLLOW-UP DEMOGRAPHIC QUESTIONS**

What is your child's d.o.b?

How old was your child when they were diagnosed with MYT1L-syndrome?

Does your child have any other diagnosed illnesses or conditions?

Do you have any other children?

- How old are your other children?
- Do they have any diagnosed illnesses or conditions?

Do you live with your child/children?

**Appendix 2: Qualitative interview study – Researcher reflexive log**

| Event | Reflexive entry |
|---|---|
| Interview #1 | I felt incredibly nervous in lead up to the first interview and was worried that I would say the wrong thing or not ask enough follow-up questions to get the information needed to address the research question. Once the interview was underway the nerves that I had disappeared, and I was immersed in the conversation. Some of the topics we discussed were challenging because the participant became upset, and because the experiences they shared differed so much from my own. I made sure to check that the participant was happy to continue with the call, and afterwards tried to orient the participant to their surrounding by asking about the rest of their day and what the weather was like. |
| Interview #2 | The second interview was similar to the first, although I felt hesitant to probe more deeply about some elements that seemed to upset the participant. I think that I still gained insight into the impact MYT1L-syndrome has on the family. As the interview progressed, and we built rapport, it felt like the participant began to trust me more and so we were able to delve into topics in more detail. |
| Interview #3 - #5 | I have conducted three interviews this week, and they have all gone well. For one of the interviews, I had an issue with finding a room at the university so I didn't feel as prepared as I would have liked. I am already starting to see similarities, and differences, between the interviews. |
| Interview #6 | Now that I have conducted a handful of interviews, I am really starting to appreciate the process of speaking to participants and learning about their experiences. I am finding it much easier to develop rapport and ask follow-up questions that could potentially be more challenging. |
| Interview #7 | I found the interview today much more challenging because the participant was not as open about their experiences and descriptive as some the other interviews so far, so I had to ask a lot of follow-up questions. This meant that I was able to gain additional insight but at times felt like I was being intrusive and prying for more details which, at times, the participant did not seem willing to share. I am left thinking if I asked the questions in the right way or built the right level of rapport with the participant before I started asking questions. I think that I did, and it may simply be that this participant was not as open as some of the |

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| | other parents I have spoken to so far – which is to be expected. |
| Interview #8 | The interview today felt a bit more challenging than the others because the participant was distracted often and kept needing to leave the call and re-join. We were still able to have a conversation and discuss the topics in turn, but we weren't able to go into as much detail. Maybe if that happens in the future, I should ask the participant if they would like to reschedule instead. |
| Interview #9 | I felt very emotional following the call today because it was really evident from the conversation how challenging raising a child with a rare disease can be. I think that the participant was feeling a bit hopeless, and I instinctively felt like I wanted to help but of course that wouldn't have been appropriate. I have discussed the session with my supervisors and that was useful. |
| Interview #10 - #13 | I conducted three interviews in two days, and the topics of conversation, the length of the interviews, and the times (because not all participants are based in the UK) has led to me feeling very worn out. The interviews themselves were very insightful and I am always grateful with how much people are willing to share with me. For the rest of the interviews, I must try to space them out as much as possible. |
| Interview #14 | The interview went well, and the participant shared so much information with me. We had run out of time and hadn't even covered half of the interview schedule questions, but I think it was important to focus on what the participant felt was of value to talk about and so much detail was provided as a result. I asked the participant if they would like to continue or rearrange a second call, because the topics we discussed were quite heavy, and we are going to rearrange.<br><br>The follow-up call went just as well as the first, and I think it was best for both of us that we rearranged a second call as we were able to start on a fresh note and focus the session on the impact on the family in this session, so it didn't feel like we had interrupted a conversation that needed to continue by ending the first session. |
| Interview #15 & #16 | I conducted two interviews today because it was the only time that both participants were free, I made sure to go outside in between the interviews and have a break, and that helped. It is challenging now that I have conducted so many interviews to not bias participants responses by asking leading questions based on |

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| | what I have heard from others so far, and similarities that I see are present. I'm aware that although it's appropriate, at times, to deviate from the interview schedule I should continue to ask open questions in line with the research aims. |
| Interview #17 & #18 | The final two interviews went well, and now I am looking forward to coding the interviews. I think that I might find the process challenging, however, because there is so much information to synthesise and make sense of. I am going to meet with my supervisors to discuss the next steps. |
| Reflecting on coding | I have just finished transcribing the interviews and have begun to code the interviews so far, I am feeling incredibly overwhelmed by the amount of information contained in the transcripts. I'm not sure how to begin making sense of it, so I am going to take a break from the coding and focus on another element of the researcher. I am going to discuss with my supervisors how best to approach the interviews. |
| Reflecting on coding | I met with my supervisors to discuss the best approach to coding the interviews, and now that I am starting to code the interviews it seems easy. I think that before I was potentially coding at a too granular level meaning that the situations were inevitably going to be different between the participants – so it felt like I was ending up with far too many codes to make sense of. I'm still trying to ensure that the coding is specific and detailed, but I feel like it is easier to spot the similarities and differences between interviews now. |
| Interview #19 | Another participant expressed that they would like to take part in the interviews, which I was unsure about at first because I have started the analysis. I found that it was really refreshing and reminded me why I am undertaking the research. |
| Reflecting on coding | I feel like coding is becoming much more natural to me now, and I have really got the hang of it. Spotting the similarities with the other interviews is quite easy now because I feel so immersed in the data. I'm looking forward to synthesising the data and writing up the findings to properly articulate the similarities and differences in the cohort. |
| Reflecting on writing | I have started writing the qualitative work and I feel like I am not taking enough time to really immerse myself in the data and represent the overall codes and themes but also the idiosyncrasies expressed. I am going to re-read through some of the data and then revisit the codebook to help with the writing up process. I need to make sure that I give myself enough time to |

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| | think about the writing process |
| Reflecting on writing | I have taken much more time now to begin the write up and I am feeling more positive about it. I am going to continue working on the write up because I feel like I am finally more immersed in the data. Now that I have re-read the transcripts, I can visualise the participants and remember the context of the quotes I have extracted. |
| Reflecting on writing | Writing is still going well, but I have an overwhelming feeling that I want to do the participants proud and accurately reflect what they shared with me during the interviews. It is making me second guess everything that I am writing, and therefore is taking me much longer as I am getting bogged down in the minute details of specific sections. I spoke with Megan about the process of coding the interviews and then developing a coding framework, and subsequent codebook, and that has restored my confidence somewhat. I still feel like I have an enormous responsibility to appropriately represent the data. |
| Reflecting on writing | I have just finished the write up for both chapters of my thesis, and I am feeling content with what I have included and the quotes that I have chosen. I hope that I have portrayed the variability present in the cohort, but also the similarities observed. |

**Appendix 3: Qualitative interview study - Codebook used in the cognitive and behavioural analysis**

| Name | Description |
|---|---|
| Anxiety | The presentation of symptoms most commonly attributed to anxiety including feelings of fear |
| Regulation of emotions | The lack of ability to appropriately regulate emotions and the emotional response to stimulus |
| Literacy (reading & writing) | The inability to read and write to an age-appropriate level |
| Numeracy | The inability to carry out numeracy tasks to an age-appropriate level, difficulties adding, subtracting, multiplying and dividing for example |
| Money management | The inability to manage own money, count money or understand the value of money |
| Lack of formal qualifications | A lack of formal educational qualifications |
| Hyper-sensitivity to touch | An over sensitivity, or hyper-sensitivity, to touch |
| Hyper-sensitivity to sound | An over sensitivity, or hyper-sensitivity, to sounds |
| Inability to understand speech | The inability to understand what the child is saying |
| Speech is jumbled | Speech is jumbled or not in the correct order - words may be mixed up and spoken in the wrong order |
| Inability to stay on topic | The inability to stay on topic when conversing with others and wanting to talk about another topic |
| Speech delays | Delays in beginning to speak compared to a typically developing child |
| Word selection | Selecting the wrong word when speaking or not being able to remember and recall the correct word |
| Inability to remember sequences | Inability to remember and recall sequences |
| Poor comprehension | The inability to comprehend on a meaningful level what others are |

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| | saying during a conversation |
| Receptive Language | Relating to receptive language |
| Expressive Language | Relating to expressive language |
| Relative cognitive strength - ability to use technology | Compared to other abilities, the ability to use technology is a relative strength |
| Relative cognitive strength - long term memory | Relative cognitive strength in long-term memory and recall of information from LTM |
| Relative cognitive strength - communication and verbal | Ability to use sign language to communicate to compensate other communication delays, or a strength in another communication domain and a relative cognitive strength in comprehension of what others are saying compared to other communication domains, or a strength in another verbal domain |
| Hypo-sensitive response to pain | An unusual, or complete lack of, response to what would typically be considered a painful stimulus |
| Preference for routine | Driven by routine and challenges present when there are changes to routines |
| Global developmental delay | A global or overall delay in reaching milestones |
| Impulsivity | Inability to control urges and frequently making impulsive decisions |
| Lack of spatial awareness | Inability to recognise own body in relation to surrounding |
| Gives up easily | Lacks motivation and gives up easily |
| Repetitive speech and question-asking | Repeatedly asking questions and repetitively saying the same words or phrases |
| Developmental plateau | Development appears to be stunted or have stopped and cut-off at a specific age/developmental stage |
| Poor memory | Inability to retain information |
| Placid as a baby | Very placid as a baby, or not easily upset or excited, lack of crying and a lack of smiling for instance |
| Developmental or skills regression | The inability to retain skills previously developed, or the knowledge of how to do something |
| Early communicative | Relating to the development of early communicative behaviours |

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| behaviours | |

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| Self-injurious behaviour | Demonstrating behaviour that can cause harm or injure themselves |
| Screaming | Vocal outbursts of screaming or screeching |
| Behavioural coping strategies | Strategies implemented that enable coping with the behaviour exhibited |
| Improvements in behaviour over time | Behaviour has improved over time as the child has grown older |
| Declines or arising difficulties in behaviour | Circumstances when behaviour declines or behavioural difficulties are more likely to arise |
| Interactions with teachers | An insight into the child's relationships with teachers in educational institutions |
| Interactions with peers | An insight into the child's relationships with peers and those around them |
| Irritation due to lack of ability | The presence of irritation or anger due to the lack of ability to do something |
| Preference to socialise or play with adults over own age group | The preference to socialise with adults rather than peers of their own age |
| Unwillingness to share | Not willing to share with other children, including siblings |
| Stereotypic movements (stims) | The presence of stereotyped movements and stims |
| Preference for imaginative play | Preference for imaginative play rather than structured play or games |
| Jealous or attention-oriented | Becoming jealous when attention is not focused on them or seeking attention from others |
| Delays in toilet habits | Toileting habits picked up later than a typically developing child might have been expected to master this skill |
| Positive behaviours exhibited at school | Negative behaviours exhibited at home, whereas positive behaviours are exhibited at school with negative behaviours seldom present |
| Playing with faeces | Playing with own faeces |
| Not opening eyes as a | Seldom opening eyes as a baby |

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| baby | |
| Rigidity in movement | When moving there is rigidity or an inability to pivot from one point |
| Socially inappropriate loudness | Loudness that is not considered socially appropriate |
| Inability to compromise or change topic when playing | When playing with peers, an inability to change topic of play or to compromise what they would like to play |
| Seldom plays independently | A strong preference for playing with others compared to playing alone and independently |
| Falling and tripping | Frequent falls or trips |
| Difficulty with gross motor skills | For example - delayed walking, standing, and sitting |
| Behavioural outbursts | Behavioural outbursts including biting, the destruction of property and injurious behaviour |
| Autism or autistic features | Relating to the characteristics of autism or autistic features |
| Difficulties with fine motor skills | Relating to difficulties developing fine motor skills |
| Lack of independence | Lacking independence |
| Skills acquisition | Relating to the development, and gaining, of skills |

**Appendix 4: Qualitative interview study - Codebook used in the family impact analysis**

| Name | Description |
|---|---|
| Confusion regarding delayed milestones | Not understanding why child is not meeting developmental milestones in line with the expectations of typically development |
| Importance of diagnosis as adult | The diminished importance of the diagnosis as an adult |
| Incorrect diagnoses | Receiving one, or multiple, incorrect diagnoses from healthcare professionals before receiving the MYT1L-diagnosis |
| Involvement in diagnosis | Needing to be persistently involved with healthcare professionals to push for a diagnosis. Examples also include parent blood tests |
| Lack of drive regarding diagnosis | Feelings of despair, resulting in a lack of drive to continue pushing for a diagnosis |
| Lack of openness with family regarding diagnosis | Not sharing the full extent of the diagnosis with wider family members |
| Lack of preparedness for atypicality during pregnancy | Parent not feeling prepared for any atypicality following childbirth due to a typical pregnancy with no warning signs |
| Lack of understanding when diagnosis given | Not understanding the implications of the diagnosis, or what this means for the caregiver, child, or wider family |
| Length of time to reach a diagnosis | Varying time to receive the correct diagnosis |
| MYT1L-syndrome diagnosis made sense | Feeling that the descriptions of MYT1L-syndrome matched the profile their child exhibited |
| Parental intuition of idiosyncrasies of MYT1L-syndrome | Parent reporting that other diagnoses did not feel right, and that there was an underlying feeling that other factors were unaccounted for |
| Feeling alone or wrong in noticing something is not right | Feeling ignored by family and healthcare professionals when expressing concern about child |
| Relief due to de-novo nature of MYT1L diagnosis | Expressing relief due to the de-novo nature of the syndrome, no longer feeling that they may be to blame |

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| Relief when reaching MYT1L diagnosis | Feeling relieved once receiving the correct diagnosis |
| Source of parent information relating to the syndrome | For example – online internet searches, charity partners, other families affected by MYT1L-syndrome |
| Uncertainty regarding validity of co-occurring diagnoses | Parent feeling uncertain, or expressing concern, about co-occurring diagnoses given to their child – for example, not believing their child should have the diagnosis |
| Upset relating to diagnosis | Feelings of upset, sadness, or worry relating to the diagnosis |
| Additional costs relating to syndrome | Parents indicating that they need to spend money on additional resource that they may not need to when raising a typically developing child |
| Challenges accessing financial support | Feeling that there are barriers or challenges to access financial support parents believe they should be entitled to |
| Costs relating to replacing damaged items | Costs associated with replacing items that are damaged due to problem behaviours |
| Cost associated with therapy and healthcare | Potentially needing to spend additional money to access specialist, paid-for, services or due to the health system in their country |
| Financial support received | Parents indicating that they have received financial support |
| Negative impact on parental work | Reports that the care needs of the syndrome have a detrimental impact on work/career |
| Influence of parental career sector | Parent now works in a sector relating to care/rare disease, in part attributed to their child's diagnosis |
| Challenges balancing care and work | Feeling that it is challenging to keep up with the routine of work alongside balancing the care needs of their child |
| Challenges finding and maintaining caregiving | Difficulties identifying and maintain care from an external provider |
| Challenges of single parenting | Parents reporting challenges they feel specific to single parenting |
| Lack of external support in place | Not feeling that there is sufficient external support in place to cope with the demands/challenges |

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| Coping strategies for day-to-day | Parent reporting coping strategies that are in place |
| Empathy for child | Expressing how challenging they feel life is for their child, empathising for them |
| Feeling isolated | Not feeling that support is in place, resulting in feelings of isolation |
| Lack of understanding from general public | Expressing that there is a lack of awareness from the public, or sharing examples of stigma they have encountered |
| Impact on daily activities | Insight into how the care needs associated with the syndrome impact daily activities – for example shopping, eating out |
| Impact on sleep | Impact on parental sleep |
| Impact on social life | Impact on parental social life |
| Impact on wider family life | Insight into the impact on the wider family network |
| Impact of rare disease versus a well-known condition | Insight into perceptions that things are more challenging because MYT1L-syndrome is a rare disease, versus the experience they may have if it was a more well-known condition |
| Reflective on difficult journey | Looking back and reflecting on the challenges encountered |
| Need to educate others about the syndrome | Parent feeling that they are responsible and carry the burden of educating others about the syndrome |
| Daily involvement in care and management | Needing to be persistently involved in care and management of their child |
| Coming to terms with atypical development | Adjusting mindset to align expectations with atypical developmental milestones |
| Need to adjust expectations | Parent acknowledging the need to adjust their expectations |
| Openness with child about their condition | Being open with their child about the syndrome and the associated impact |
| Additional interventions required to manage behaviours | External support or additional interventions required to help manage problem behaviours |
| Challenging behaviours | For example, hitting, kicking, biting |

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| directed at parent | |
| Coping strategies for problem behaviours | Insight into coping strategies parents have implemented to cope with problem behaviours |
| Inability to cope with behaviours, feeling overwhelmed | Parent not feeling that they are able to cope with the behaviours exhibited by their child |
| Acknowledging variability in behaviours | Insight into the variability in behaviours – for example, depending on location or time |
| Challenges identifying appropriate educational environment | Challenges identifying an education environment that is in line with child's cognitive and behavioural profile |
| Increased communications with school | Needing to maintain increased communications with education provider |
| Challenges transitioning to adult services | Insight into challenges experienced when moving from paediatric to adult health services |
| Interactions with healthcare professionals | Positive or negative interactions with healthcare professionals regarding the management of their child |
| Medication concerns | Concerns with medication to alleviate challenges/symptoms |
| Documenting child's development | Needing to document and keep track of child's development |
| Need to travel to access to appropriate healthcare services | Needing to travel to access appropriate services as they are not available locally, or specialist services at other hospitals/centres are required |
| Negative impact on parental relationship | Feeling that there is a negative impact on the relationship with spouse/partner |
| Strengthening of parental relationship | Feeling that there is a positive impact on, or strengthening of, relationship with spouse/partner |
| Considering future pregnancies | Considerations about any future pregnancies in light of the MYT1L-syndrome diagnosis |
| Parental separation and divorce | Reports of divorce or separation |
| Challenging behaviours directed at siblings | For example – hitting, kicking, or biting |

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| Child requiring more attention than siblings | Feeling that child with MYT1L-syndrome requires/d more attention than neurotypical siblings |
| Impact on relationship with sibling | Parental observations of the impact on the relationship between the child with MYT1L-syndrome and neurotypical siblings |
| Negative impact on sibling | Parental noting negative aspects of impact on sibling |
| Need for sibling to adapt and mature to overcome challenges | Examples of sibling adapting to overcome challenges or support their sibling |
| Need to adapt parenting styles of child and sibling(s) | Feeling they different parenting approaches need to be taken to appropriately manage affected child and siblings |
| Protection of sibling from caregiving responsibility | Protection of sibling from needing to provide care for their brother/sister |
| Sibling highlighting atypical development | Younger or older neurotypical sibling highlighted to parent the atypical developmental trajectory of diagnosed child |
| Sibling imitating problem behaviours | For example – hitting, kicking, biting |
| Impact on wider family relationships | Insights into how wider family relationships have been impacted |
| Lack of understanding from wider family members | Members of the wider family demonstrating a lack of understanding about the syndrome and associated impact |
| Need to protect family from behaviours | Parent feeling that they need to protect family from challenging behaviours |
| Stress on family relationships | Feeling that there is additional pressure or stress on relationships with those in the wider family |
| Wider family treating child differently | Observations of when members of the wider family have treated diagnosed child differently to neurotypical children in the family |
| Wider family understanding once diagnosis is received | Wider family demonstrating a greater understanding of the syndrome, or willingness to acknowledge why challenges may be present |
| Reluctance to engage with support networks | Parent expressing reluctance to engage with support networks for families of children diagnosed with MYT1L-syndrome |

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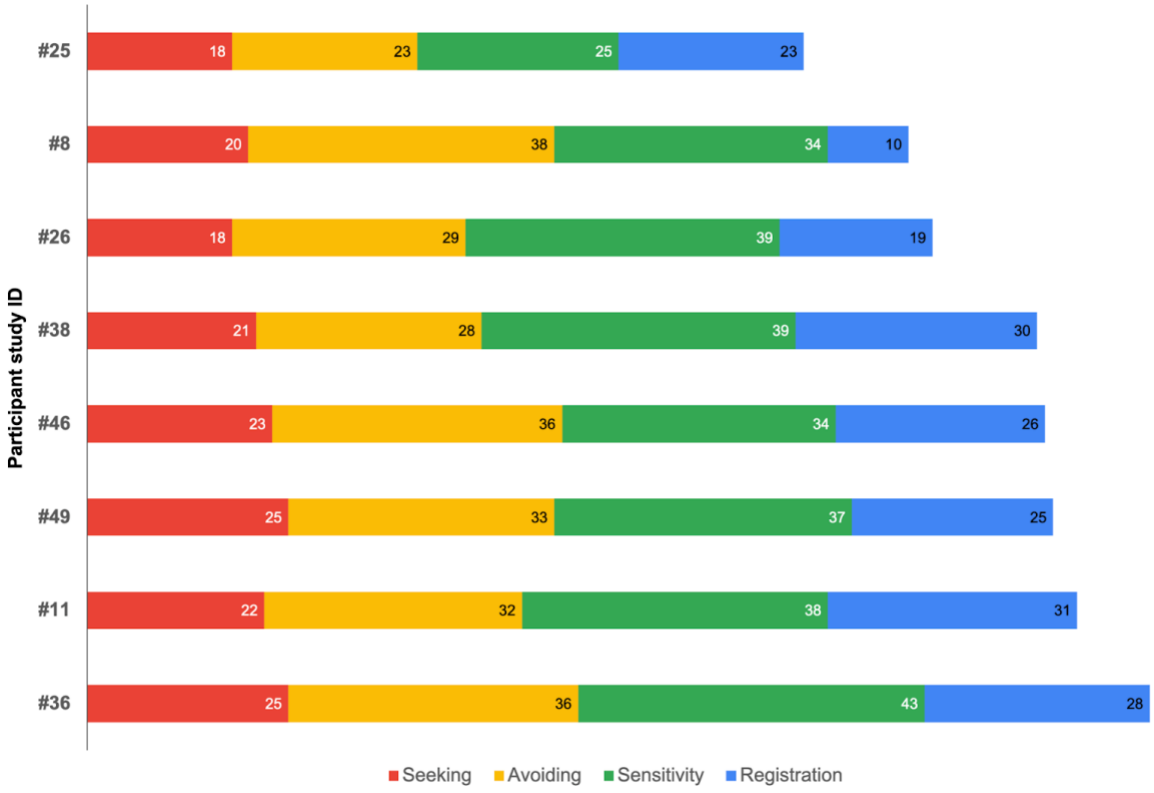
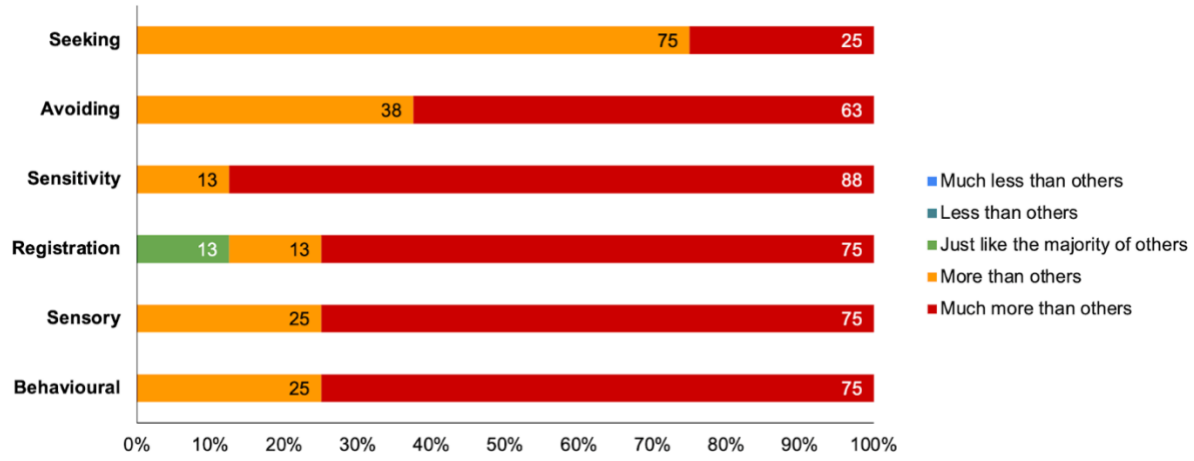
| Reliance on family for care and support | Feeling that there is a reliance on the wider family to provide care and support |
| Support from external organisations | Insight into support received from external organisations, such as charities of advocacy groups |
| Support from other families | Parents sharing experiences of accessing MYT1L-syndrome family support groups |
| Reliance on respite | Reliance on respite for a break from persistent care needs |

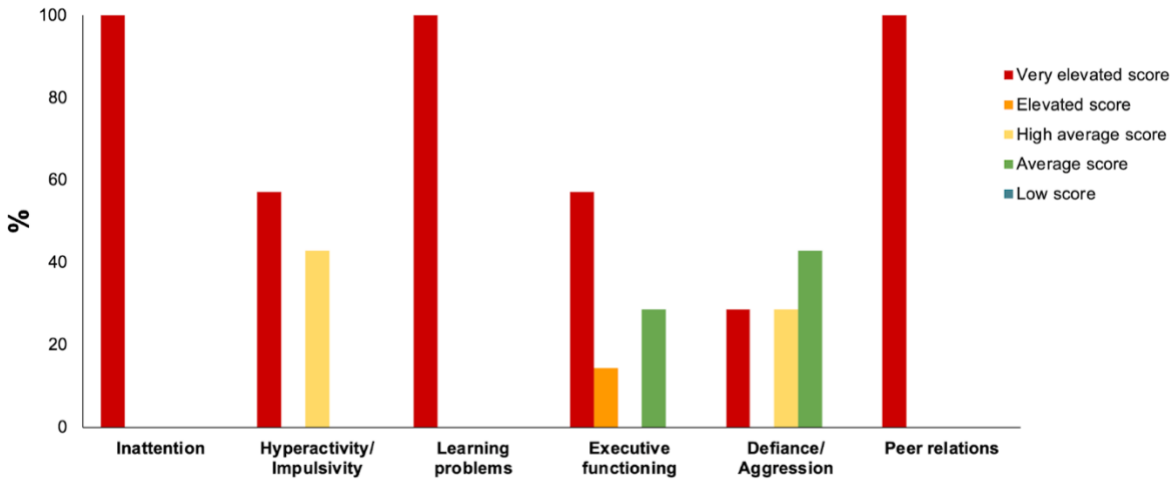
**Appendix 5: Quantitative study - Figures for participants out of the recommended age range of the standardised measures**




**Appendix 5a.** Raw SSP-2 domain scores for individuals outside of the recommended age range (n=8). Ordered from lowest to highest total score.



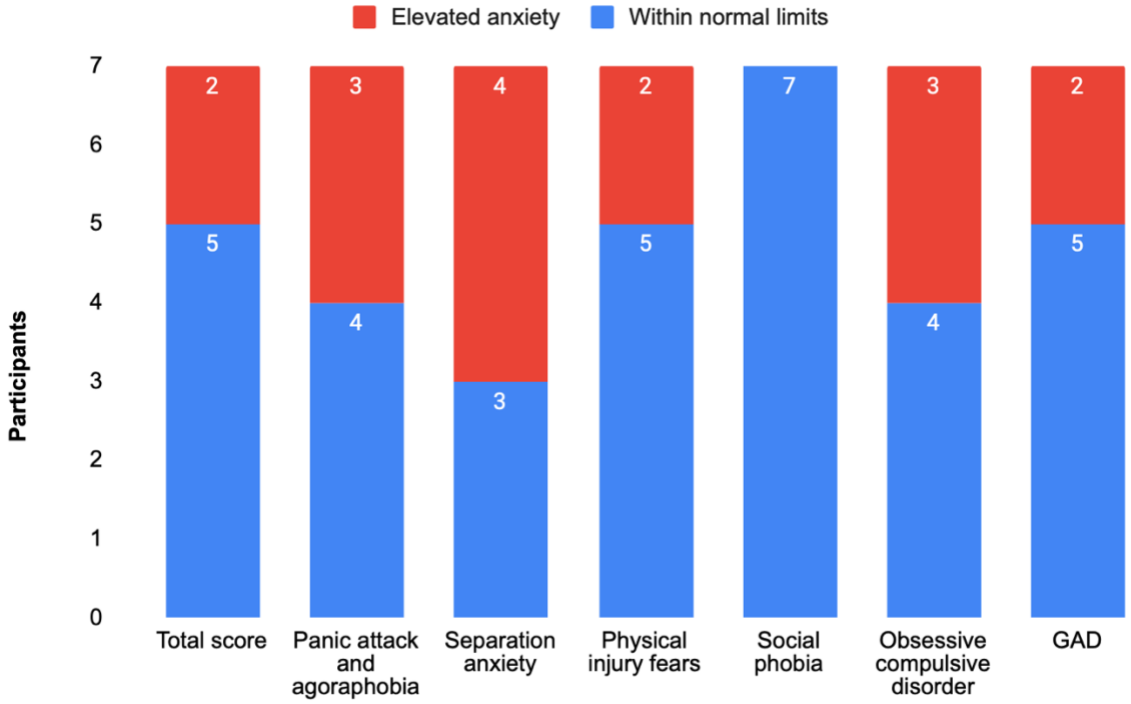

**Appendix 5b.** Sensory profile of MYT1L-syndrome for individuals out of the recommended age range (%; n=8)




**Appendix 5c.** Conners 3 subscale scores for participants out of the recommended age range (%; n=7).

| SCAS-P | N | Mean (SD) | Range |
|---|---|---|---|
| *SCAS-P total score* | 7 | 55.86 (5.27 | 48-62 |
| *Panic attack and agoraphobia* | 7 | 58.43 (5.32) | 50-64 |
| *Separation anxiety* | 7 | 61.14 (8.86) | 47-70 |
| *Physical injury fears* | 7 | 52.71 (8.92) | 40-65 |
| *Social phobia* | 7 | 49.00 (8.23) | 40-60 |
| *Obsessive compulsive disorder* | 7 | 57.29 (8.23) | 50-64 |
| *Generalised anxiety disorder/overanxious disorder* | 7 | 56.43 (3.82) | 52-61 |

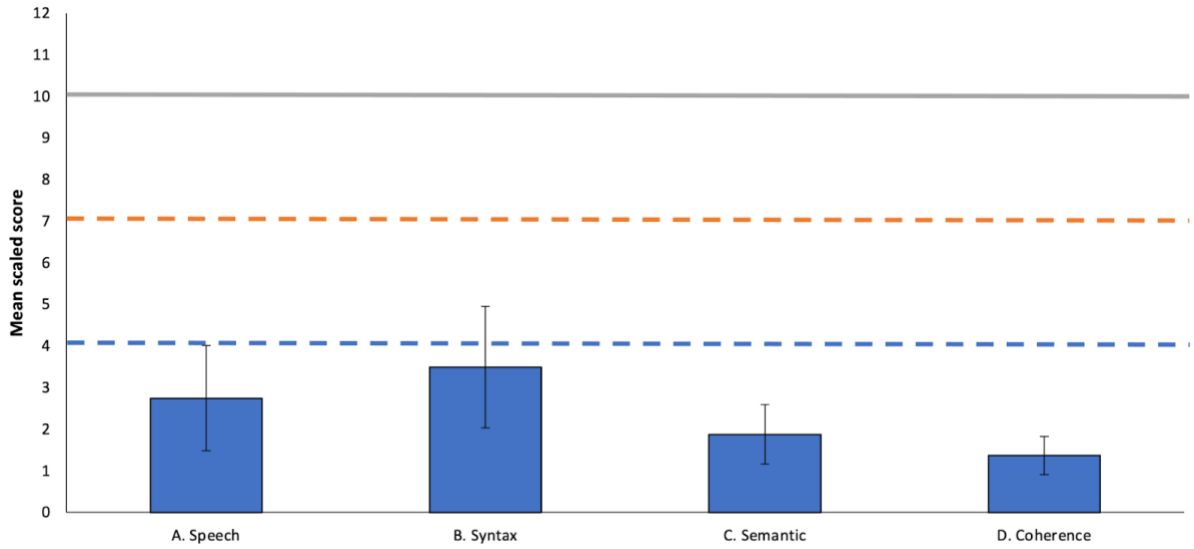
**Appendix 5d.** Summary of SCAS-P standardised t-scores for individuals with MYT1L-syndrome out of the recommended age range (n=7).



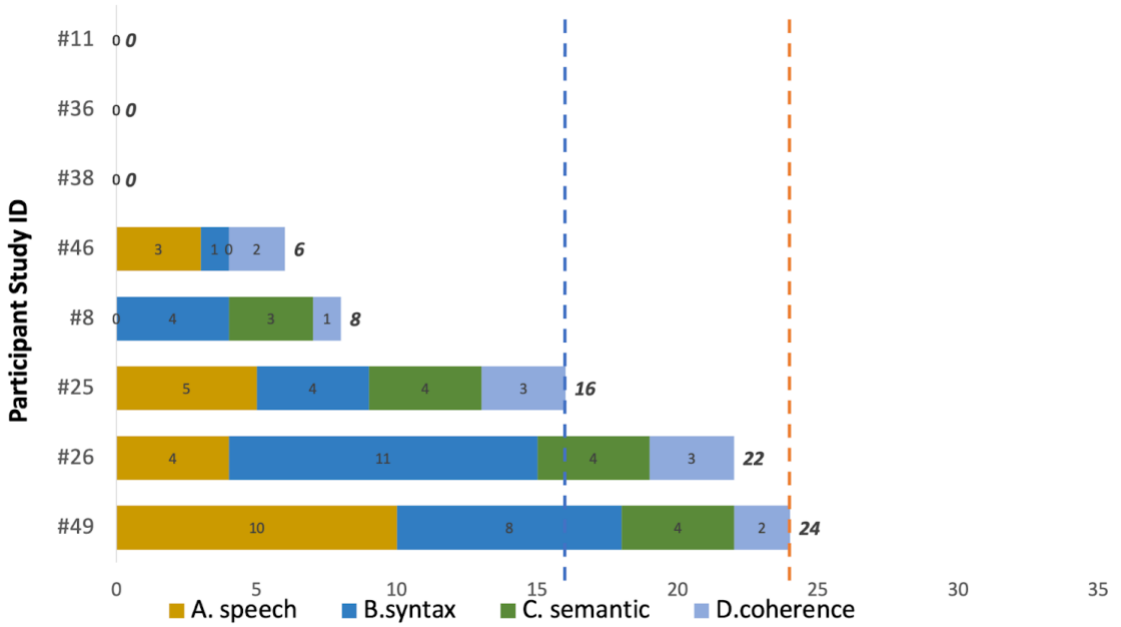

**Appendix 5e.** SCAS-P total t-score and subscale t-scores for participants out of the recommended age range (n=7).

| *Summary of CCC-2 scaled scores for MYT1L-syndrome* | | | |
|---|---|---|---|
| **CCC-2** | **N** | **Mean (SD)** | **Range** |
| ***General Communication Composite (GCC)*** | 8 | 21.75 (19.70) | 0-50 |
| ***Language structure*** | 8 | 9.50 (9.96) | 0-24 |
| *Speech* | 8 | 2.75 (3.58) | 0-10 |
| *Syntax* | 8 | 3.50 (4.14) | 0-11 |
| *Semantics* | 8 | 1.88 (2.03) | 0-4 |
| *Coherence* | 8 | 1.38 (1.30) | 0-3 |
| ***Pragmatic language*** | 8 | 4.50 (3.96) | 0-10 |
| *Inappropriate initiation* | 8 | 0.75 (1.39) | 0-4 |
| *Stereotyped language* | 8 | 2.13 (2.47) | 0-4 |
| *Use of context* | 8 | 0.00 (0.00) | 0 |
| *Non-verbal communication* | 8 | 1.63 (1.30) | 0-4 |
| *Social Relations* | 8 | 1.38 (1.51) | 0-4 |
| *Interests* | 8 | 1.88 (0.99) | 0-3 |

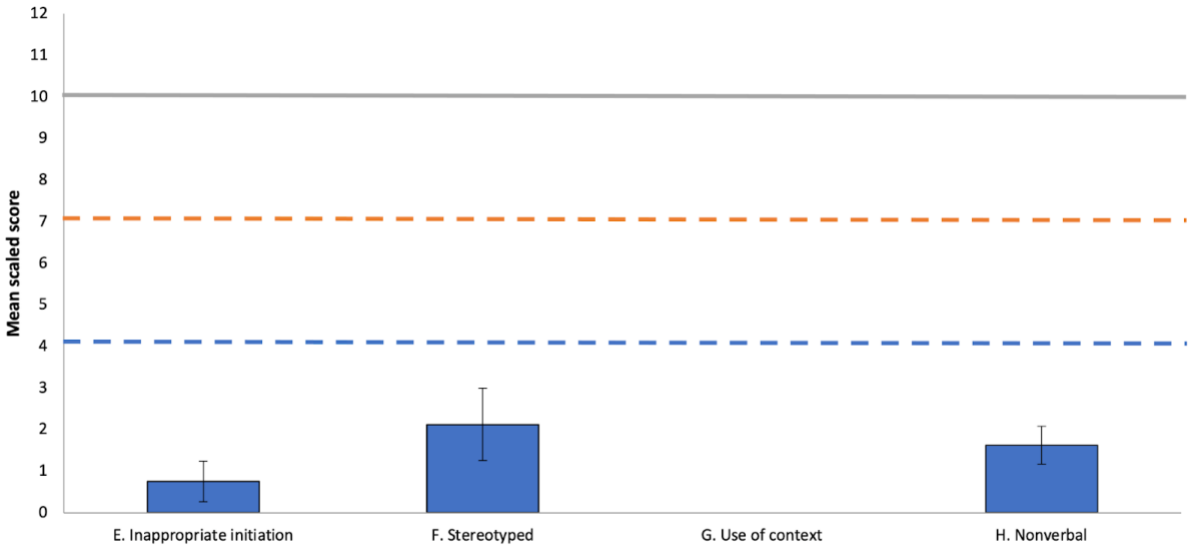
**Appendix 5f.** Summary of CCC-2 scaled scores for individuals with MYT1L-syndrome out of the recommended age range (n=8)



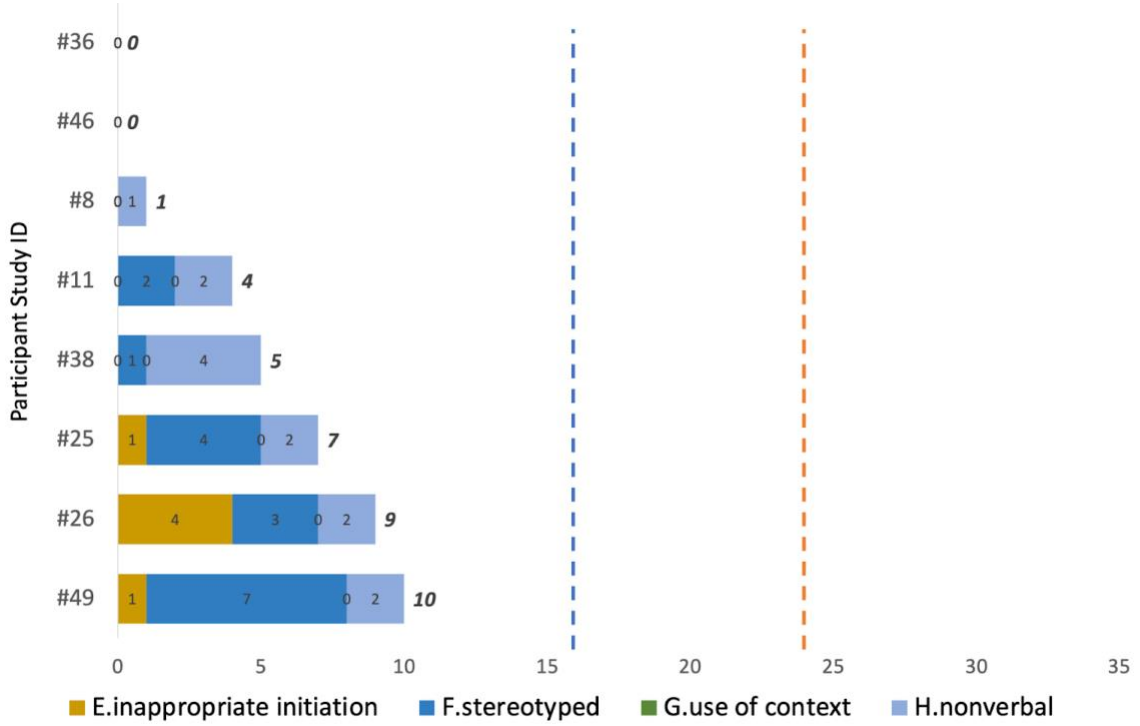

**Appendix 5g.** The means and standard error of the scaled language structure subscales (speech; syntax; semantic; coherence) for participants out of the recommended age range (n=8). The mean score for each subscale for TD standardised norms = 10, SD=3, and the grey line indicates the standardised mean for the norms of individuals who are TD, the orange dotted line highlights 1 SD below the mean of TD norms, and the blue dotted line highlights 2SD below.



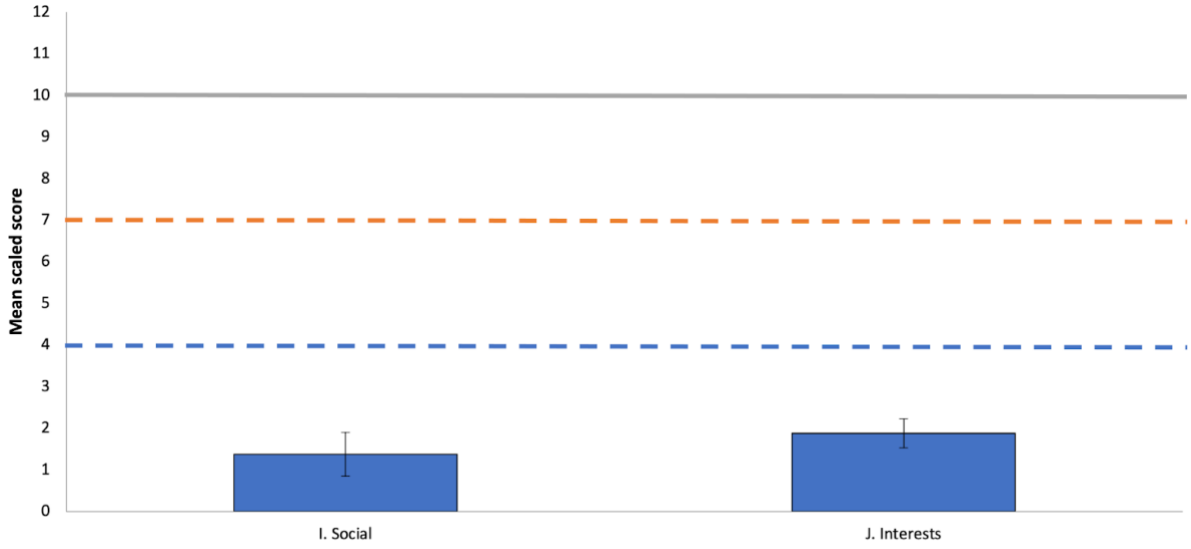

**Appendix 5h.** Coloured bars represent each of the language structure subscales (speech; syntax; semantic; coherence) for participants out of the recommended age range (n=8). The language structure composite score is visible in bold italics to the right of each coloured bar. Scores >24 represent 'typical functioning' (represented by the orange dashed vertical line), scores 17-24 represent 'borderline functioning' and scores <17 represent 'impaired functioning' (represented by the blue dashed vertical line). In order of lowest to highest total score.



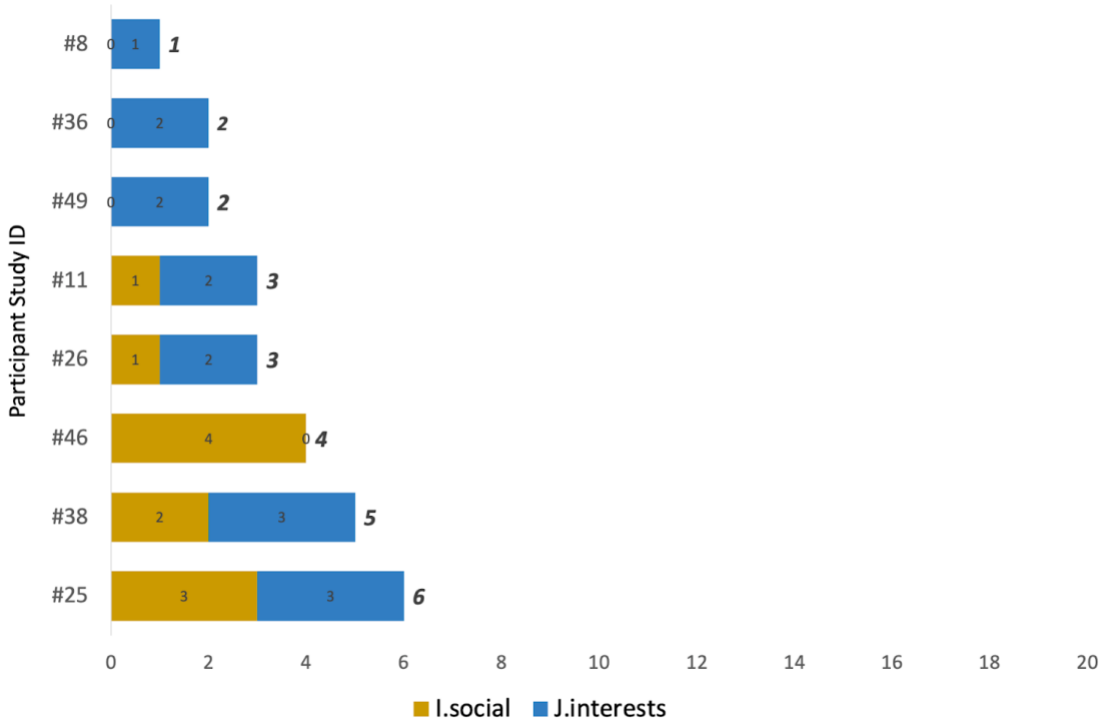

**Appendix 5i.** The means and standard error of the scaled pragmatic language subscales (inappropriate initiation; stereotyped speech; use of context; nonverbal communication) for participants out of the recommended age range (n=8). The mean score for each subscale for TD standardised norms = 10, SD=3, and the grey line indicates the standardised mean for the norms of individuals who are TD, the orange dotted line highlights 1 SD below the mean of TD norms, and the blue dotted line highlights 2SD below.




**Appendix 5j.** Coloured bars represent each of the pragmatic language subscales (inappropriate initiation; stereotyped speech; use of context; nonverbal communication) for participants out of the age range (n=8). The pragmatic language composite score is visible in bold italics to the right of each coloured bar. Scores >24 represent 'typical functioning' (represented by the orange dashed vertical line), scores 17-24 represent 'borderline functioning' and scores <17 represent 'impaired functioning' (represented by the blue dashed vertical line). In order of lowest to highest total score.




**Appendix 5k.** The means and standard error of the scaled autistic features subscales (social relations and interests) for participants not within the recommended age range (n=8). The mean score for each subscale for TD standardised norms = 10, SD=3, and the grey line indicates the standardised mean for the norms of individuals who are TD, the orange dotted line highlights 1 SD below the mean of TD norms, and the blue dotted line highlights 2SD below.




**Appendix 5l.** Coloured bars represent each of the autistic features subscales (social relations and interests) for participants out of the age range (n=8). In order of lowest to highest total score.

## Appendix 6: Conference poster presented at the Neurodevelopmental Disorders Annual Seminar 2022 (NDAS22)

# The impact of MYT1L-syndrome on behaviour and cognition: a parent/caregiver perspective

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### Background

MYT1L-syndrome is a novel genetic cause of impaired neurogenesis, a process in which the brain's neurons do not form properly, leading to a variety of clinical problems including intellectual disability, autism spectrum disorder (ASD) and epilepsy (Harada et al., 2016).

As MYT1L-syndrome was only recently identified there is a paucity of published research outlining the impact on the individual, including the impact on cognition and behaviour. This research hoped to learn from the lived experience of parent/caregivers to understand important avenues for future research.

### Method

Parents and caregivers of children with MYT1L-syndrome, or a 2p25.3 deletion, were invited to participate in a semi-structured online interview. 18 respondents participated, with interviews lasting between 45 and 140 minutes. Participants were based worldwide, including participants from the United Kingdom, United States of America, Canada, Brazil, and France.

The principles of thematic analysis were applied to analyse the transcripts, and the resultant codes identified were developed into themes.

### Aim

To understand, from parents and caregivers, the impact of MYT1L-syndrome on the behaviour and cognition of affected individuals.

### Themes and subthemes

The following three themes, and subthemes, were identified:
**Theme 1:** Behaviour (Sensory responses; Challenging and unusual behaviour; Anxiety; Executive functioning and emotion regulation; Perceived autistic traits; Social relationships; Motor)
**Theme 2:** Speech, language and communication
**Theme 3:** Cognitive ability and profile (Intellectual disability; Memory and encoding; Numeracy; Literacy)

### Theme 1: Behaviour

"I couldn't even take him to the store… the sound of the cart bothered him" [10]

"They broke their leg… without complaining too much" [23]

"He didn't move much… he was just kind of there" [22]

"She is very anxious… she will just wake up and have tantrums in the middle of the night" [15]

"She has to have routines and they have to be a certain way" [15]

"She's not interested as much in her peers as she is adults" [17]

"She's quite aggressive with her brother and she's constantly hitting him, pinching him" [14]

### Theme 2: Speech, language and communication

"His language, everything was super delayed" [10]

"I suspected that something was not quite right, and he was not really smiling… that was the first sign" [23]

"She still has a hard time accessing her words… when she is emotional or frustrated" [14]

"He does, like twisted… he will like talk backwards – not backwards but he'll say something and get mixed up" [10]

"She's been a conundrum for teachers because when she presents to them she speaks very well, she uses words appropriately, but she doesn't always know what they mean… her receptive language is very behind" [17]

"She will peter off halfway through her sentences and can't sing songs – she just can't remember the sequence of the words" [14]

"she's always very loud and you… have to constantly tell her to keep her voice down" [25]

### Theme 3: Cognitive ability and profile

"Delays in everything… the milestones have been achieved quite late so far. It seems that as she's got older it takes longer for the next milestone to come… it seems to follow a pattern… she's always about half her age developmentally" [15]

"she has no concept of money" [8]

"Fine motor skills are more delayed still… she's 11 but it's probably the writing of a 5-year-old" [21]

"it's her memory, she just doesn't imprint, you could do the same task with her every day and on Friday it would feel like a new task" [12]

"he always needs me all of the time" [37]

### Conclusions

- **Heterogeneity.** The analysis identified both how heterogeneous the impact of MYT1L-syndrome is, and also how profound and extensive the impact can be for affected individuals.
- **Activities of daily living.** Shopping or eating in public, for example, were often challenging due to a hypersensitivity to sound, light and noise, and challenging behaviours were reported to impact various elements of daily life.
- **ASD.** Many caregivers reported traits that they perceived to be ASD, including a strict adherence to routine, an inability to maintain eye contact and impairments to social functioning. It is important to note that some participants did not think this was true for their child.
- **Future research.** Research should explore quantitative impairment levels and identify appropriate interventions and better education.

### Clinical Implications

- **Using support tools.** Many parents reported that they have overcome difficulties with communication, for instance, through the use of sign language and PECS or digital communication tools such as text-to-speech.
- **Diet and eating.** Many individuals were reported to be overweight, and behavioural problems stemmed from individuals wanting to access food, as participants reported the inability for many children to feel satiated. Research in other rare genetic conditions has led to understanding the underlying mechanisms and tailored dietary management plans.
- **Anxiety.** Education and healthcare appointments were commonly reported stressors for individuals with MYT1L-syndrome.

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