Volume I

RESEARCH COMPONENT

EXPLORING SENSORY MODULATION ACROSS RARE GENETIC SYNDROMES AND EXPLORING THE BEHAVIOURAL PHENOTYPE OF PALLISTER-KILLIAN SYNDROME

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Thesis Overview

This thesis is presented in two volumes: the research (Volume One) and clinical (Volume Two) components. Volume One presents three research papers. The first paper is a systematic review exploring sensory modulation difficulties in rare genetic syndromes associated with Intellectual Disability (ID) and Autism Spectrum Disorder (ASD). The second is an empirical paper examining the behavioural phenotype in Pallister-Killian Syndrome (PKS). The third is a public dissemination report written to inform carers/parents of individuals with genetic syndromes with the results of the two papers.

Volume two consists of five clinical practice reports (CPRs). CPR One presents two formulations (using behavioural and psychodynamic models) of a girl with anxiety and a specific phobia of vomiting in a Child and Adolescent Mental Health Service (CAMHS). CPR Two is a service evaluation determining if a neurodevelopmental pathway assessing ASD in young people met the standards of NICE guideline. CPR Three is an experimental functional analysis of a girl with Tuberculous Complex (TSC) who was displaying aggressive behaviour. CPR Four is the case study, including assessment, formulation and intervention of a woman with schizoaffective disorder who required a relapse prevention plan. The abstract of CPR 5 (an oral case presentation) is the assessment of a man with Mild Cognitive Impairment (MCI), low mood and Leukaemia.

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CHAPTER 1

Sensory Symptoms in Rare Genetic Syndromes: A Systematic Review

Abstract

Introduction: Sensory modulation difficulties are now part of the Autism Spectrum Disorder (ASD) diagnostic criteria in the DSM-5. There is a high number of ASD symptomology in rare genetic syndromes, each with unique behavioural phenotypes and different profiles of ASD. Therefore, the diagnostic criteria changes will potentially have different assessment implications for assessing ASD in individuals with genetic syndromes.

Method: A literature search was completed using twenty-two different syndromes and sensory modulation search terms. Sixteen papers examining seven syndromes; Angelman syndrome (AS), Down syndrome (DS), Fragile X syndrome (FXS), Phelan-Mc Dermid syndrome (PHMDS), Smith-Lemli-Opitz syndrome (SLOS), Smith Magensis syndrome (SMS) and Williams syndrome (WS), were included in the review. A quality assessment framework was developed and used to determine the validity and reliability of the research conclusions.

Discussion: All of the syndrome groups displayed a range of sensory modulation difficulties, although the precise profile of the sensory symptoms was only reliably defined for FXS, WS (hyper-sensitivity) and AS (hypo-sensitivity). There was a lack of reliable research evidence to draw conclusions about the sensory profiles of the other syndromes. Hypotheses are discussed about the potential implications of the change in DSM-5 criteria in genetic syndromes. The limitations of the evidence base are described, including a lack of comparison groups, the use of single assessments methods with questionable validity and few longitudinal studies.

Introduction

Autism Spectrum Disorder (ASD) is a behaviourally diagnosed neurodevelopmental disorder (WHO, 1992) estimated to occur in approximately 1% of the general population (Centres for Disease Control and Prevention, 2014). It has traditionally been defined by impairments in three domains: social interaction, communication and imagination (Wing and Gould, 1979)[1]. However, recently there has been a change in the most influential diagnostic criteria (and thus, arguably, the definition) of ASD. The Diagnostic and Statistical manual fifth edition (DSM-5; APA, 2013) has combined the five previous subcategory diagnoses[2] into one ASD diagnosis. In addition, the criteria now fall into two rather than three categories. These are: A: difficulties in social communication and interactions, and B: restricted and repetitive behaviours and interests (RRBI) (Appendix 1). For a diagnosis to be given, individuals need to display three symptoms from criterion A and two symptoms from criterion B in a child's early development.

There have been debates in the research literature about whether the DSM-5 has increased the reliability and specificity of ASD diagnoses. The Kulage, Smaldone and Cohen (2014) meta-analysis of the consequences of the DSM-5 criteria changes indicated a 31% reduction in ASD diagnoses. Grapel, Cicchetti and Volkmar (2015) and Volkmar, Klin, Siegel, Szatmari, Lord and Campbell (1994) suggest the DSM-5 now

[1] Individuals with ASD may be described as 'aloof', lack affective expression and have a decreased interest in reciprocal social interactions. A lack of flexibility and difficulty adapting to changes in routines also characterises the diagnosis (Gerdts and Bernier, 2011). In addition, many people diagnosed with ASD display repetitive sensory and motor behaviours (Szatmari et al., 2006) and up to 70% of individuals with ASD also have an intellectual disability (ID) (Fombonne, 2003).

[2] Asperger's disorder, Kanner's syndrome (classic Autism disorder), pervasive developmental disorder-not otherwise specified, Rett's syndrome and childhood disintegrative disorder.

has less discriminant validity. Conversely Mandy, Chairman and Skuse (2012) argue that the changes have increased the validity of diagnosis, as confirmatory factor analysis revealed that the two-factor model gave a better fit than the three-factor model to the presentation of individuals with ASD.

One potentially important change in the DSM-5 ASD criteria is in the recognition of "sensory" symptoms, such as tactile, olfactory and taste over-responsivity (Reynolds and Lane, 2008). Sensory symptoms were previously viewed as comprising a peripheral or co-morbid phenomenon in ASD, and thus were not formerly considered to be part of the diagnostic criteria for ASD in the DSM-IV (APA, 2000; Volkmar, Reichow and McPartland, 2012). However, in the DSM-5, they form part of the diagnostic criteria under the category of RRBI (the B set of criteria). Therefore, it is timely to consider sensory symptoms (Schaaf and Lane, 2015) and their role in ASD diagnoses.

Baranek, Little, Perham, Ausderau, Sabatos-De-Vito (2014) and Schaaf and Lane (2015) have described how the different terminology used to describe sensory symptoms has led to a lack of clarity in the literature and suggest that future research should focus on the sensory modulation terms described in the DSM-5. Sensory modulation is defined as abnormal responses to sensory stimuli, which causes functional impairments and comprises three different categories: sensory over-responsivity, under-responsivity and sensory-seeking. Sensory over-responsivity (hyper-sensitivity/low threshold) is demonstrated when individuals experience more intense sensory experiences and display distress, avoidance or hypervigilance in

response to sensory stimuli. Sensory under-responsivity (hypo-sensitivity/high threshold) is demonstrated when an individual is unaware of, or is slower to respond to sensory stimuli, which, normally provokes a response in other individuals. Sensory-seeking is demonstrated when an individual displays an unusual interest, preoccupation or need to experience certain sensory stimuli (Miller, Anzalone, Lane, Cermak and Osten, 2007).

Dunn (1997; 2001) proposed a model of sensory modulation, which considers individuals' neurological responses/thresholds and their behavioural responses/coping strategies. While some individuals may respond in accordance with their thresholds, others respond by attempting to adapt to their thresholds. Therefore, individuals can be described as residing in one of four quadrants that are based on two continuous dimensions. Firstly, individuals who have high thresholds for noticing sensory stimuli show a slow or lack of responsiveness (under-responsivity) and are passive in their coping style, are termed 'low registration', whereas those who are active in their coping strategies try to enhance their sensory experience, are termed 'sensory seeking'. Individuals who have a low threshold, show a quicker and exaggerated responsiveness to sensory stimuli (over-responsivity) and are passive in their coping strategies (often making them appear lethargic), are termed 'sensory sensitivity'. Those who are active in their coping strategies by trying to avoid or limit their sensory experience are termed 'sensory avoiding' (Figure 1.1).

Figure 1.1: **Dunn's (1999) Model of Sensory Processing**

Thresholds/ Reactivity		Responding/ Self-Regulation Strategies	
		Passive	Active
	High/low reactivity	Low Registration	Sensory Seeking
	Low/high reactivity	Sensory Sensitivity	Sensory Avoiding

This model is supported by different types of physiological responses to sensory stimuli for sensation seekers and avoiders (Brown, Tollefson, Dunn, Cromwell and Filion, 2001; Zuckerman, 1994). Individuals with high thresholds/reactivity display a reduced heart rate and an orienting response to sensory stimuli, which, as a result, means they are more able to receive and process sensory information, if the sensation is detected. Individuals with low thresholds/reactivity, on the other hand, display an increasing heart rate and fear.

A large percentage (45-96%) of individuals with ASD have sensory difficulties (Baker, Lane, Angley and Young, 2008; Ben-Sasson et al., 2008; Klintwall et al., 2011; Leekam, Nieto, Libby, Wing and Gould, 2007; Tomchek and Dunn, 2007), across all sensory modalities (Baranek, David, Poe, Stone, and Watson, 2006; Lane, Dennis and Geraghty, 2011). Arguably, the severity of ASD symptoms relate to the severity of sensory symptoms in children, although not for adolescents or adults (Kern et al., 2007).

These sensory difficulties have not only been reported by the parents of individuals with ASD but by the individuals themselves (O'Neil and Jones, 1997; Williams, 1994). Furthermore, it has been suggested that the high levels of carer strain in parents/ carers of children with ASD are related to hyposensitivity and hypersensitivity specifically (Kirby, White and Baranek, 2016).

Some studies have reported auditory over-responsivity (Gillberg and Coleman, 1996), perhaps influenced by enhanced frequency discrimination (Jones et al., 2009), whereas, other research has shown auditory under-responsivity and atypical auditory attention and processing skills (Baranek, 1999; O'Connor, 2012; Magness, de Gelder, van England and Kemner, 2011). Tomchek and Dunn (2007) found that 77.6% of children with ASD had auditory sensitivities.

Visual difficulties are reported in the literature, with numerous explanations and descriptions of processing difficulties. Specifically, reports describe perceptual alterations in face processing (Bachmann, Thomas and Humphreys, 2006), differences in eye gaze patterns (Deconinck, Soncarrieu and Dan, 2013) and a reliance on peripheral vision (Lord, Rutter and Le Couteur, 1994).

There have been consistent findings of tactile over-responsivity, which is described as the most common sensory symptom, with individuals having difficulty with touch, clothes materials, grooming and personal hygiene tasks (Reynolds and Lane, 2008; Rogers, Hepburn and Wehner, 2003; Tomchek and Dunn, 2007), perhaps due to difficulties processing tactile information at the cortical level (Marco, Hinkley,

Hill and Nagarajan, 2011). Schaaf and Lane (2015) concluded individuals with ASD have a similar lower level somatosensory (e.g. pain and temperature) sensitivity threshold to typically developing (TD) individuals.

Some individuals with ASD have high vestibular thresholds, whilst others have low. This is attributed to their vestibular processing difficulties and integration of sensory information (Kern et al., 2007), potentially contributing to observed motor-control difficulties, including poor balance, unusual posture, sway, spin and difficulty moving on uneven ground (Vernazza-Martin et al., 2005).

Taste and smell over-responsivity has been reported and accounts for a restricted food intake, as individuals with AD specifically avoid food with certain textures, tastes, temperatures and smells (Cermak, Curtin and Bandini, 2013; Twachtman-Reilly, Amaral and Zebrowski, 2008). Whilst there have been no differences found for olfactory discrimination (Tavassoli and Baron-Cohen, 2012), individuals with ASD are able to detect smells further away in comparison to TD individuals and the over-responsivity is associated with greater ASD symptomology (Ashwin et al., 2014).

Whilst the majority of sensory modulation research in ASD has focused on sensory over-responsivity (Baranek, David, Poe, Stone and Watson, 2006; Ben-Sasson et al., 2007; Tomchek and Dunn, 2007) the Ben-Sasson et al., (2009) review found that sensory under-responsivity difficulties had the highest prevalence. Overall, there is the suggestion that individuals with ASD present with a combination of under and over-responsivity (Hazen, Stornelli, O'Rourke, Koesterer and McDougall, 2014).

Factor analysis of the Sensory Profile (SP; Dunn, 1999) has revealed that children with ASD have four distinct sensory subtypes, which suggests there may be specific sensory phenotypes (Lane, Young, Baker and Angley, 2010; Lane, Dennis and Geraghty, 2011; Lane, Molloy and Bishop, 2014). Specifically, there is a subset of children (25-40%; Ausderau et al., 2014) who do not experience significant difficulties and are thus, sensory adaptive. Secondly, others experience significant taste and smell sensitivities, hypo-reactivity, and sensory–seeking and auditory filtering difficulties. Whilst another cluster of children experience significant difficulties with low energy/weak features, with hypo-reactivity, sensory-seeking and auditory filtering difficulties. The final cluster of children experience generalised sensory difficulties in all sensory domains, although this is perhaps dependent on the time of assessment.

There have been mixed results investigating sensory symptoms changes with age. Some authors report sensory symptoms have no relationship with age (Baranek, David, Poe, Stone and Watson, 2006). Therefore, suggesting sensory symptoms remain stable over time, except for slight differences based on developmental stage, for example, very young children (birth to six-months) are very responsive to tactile and oral stimuli (Dunn, 2001). However, retrospective research has reported that sensory symptoms in early development, including poor visual orientation, excessive mouthing and hypersensitivity to touch and hyposensitivity to auditory stimuli are able to predict a later diagnosis of ASD (Baranek, 1999; Goldsmith, Van Hulle, Arneson, Schreiber and Gernsbacher, 2006; Lane and Heathcock, 2014).

A meta-analysis reported that sensory symptoms increase until they reach a peak in children aged six to nine-years-old, and then subsequently decrease (Ben-Sasson et al., 2008). However, it has not been determined if this peak is due to environmental changes and stress (e.g. entering a school environment) and decreased as children develop coping strategies (Kern et al., 2006) due to a maturation process (Kern et al., 2007) or a selection bias in research focusing only on school-age children, thus reporting higher incidence of difficulties in this age range (Baranek, Little, Perham, Ausderau and Sabatos-De-Vito, 2014). However, sensory modulation symptoms have been reported to continue into adulthood (Billstedt, Gillberg and Gillberg, 2007; Crane, Goddard and Pring, 2009).

Individuals with ASD have higher rates of sensory symptoms compared to age and IQ matched individuals with developmental delay (DD) (Leekam, Nieto, Libby, Wing and Gould, 2007), although, having a lower IQ and more severe ASD symptomology are risk factors for developing sensory impairments (Liss, Saulnier, Fein and Kinsbourne, 2006; Lane, Young, Baker and Angley, 2010; Ben-Sasson et al., 2009; Leekam, Nieto, Libby, Wing and Gould, 2007). It is also hypothesised that executive functioning processes influence sensory modulation (Gazzaley and D'Esposito, 2007) via attentional control and flexibility to adapt behavioural responses to varying stimuli (Gillbert and Burgess, 2008)[3].

[3] Specifically, it has been suggested that sensory over-responsivity is due to over-focusing attention (Liss, Sauhier, Fein, Kinsbourbourne, 2006) and that under-responsivity is due to difficulties in allocating attention in a sensory environment (Schoen, Miller, Brett-Green and Nielsen, 2009). It is noteworthy that, one third of children with ASD would also meet diagnostic criteria in the DSM-IV for a diagnosis of ADHD (Simonoff, Pickles, Charman, Candler, Loucas and Baird, 2008).

In addition, RRBI are part of the diagnostic criteria for the DSM-5, and includes hand flapping, body rocking, covering eyes and ears, arranging things in certain orders and insisting on sameness (Bodfish, Symons, Parker and Lewis, 2000). Research has frequently demonstrated a strong relationship between increased severity of sensory symptoms and increased severity of RRBI, in particular, tactile, auditory and visual hyper-sensitivity (Chen and Rogers, 2009). Furthermore, self-injurious behaviour can be perhaps considered as a more severe form of stereotypic behaviour (Matson et al., 1997) and sensory symptoms are reported to be the strongest predictor of self-injurious behaviour (Duerden, Tannock and Duckstader, 2012).

Factor analysis has revealed five distinctive categories within the RRB constructs; repetitive sensory-motor/stereotypic behaviours, ritualistic/insistence on sameness behaviours, compulsive behaviours, restricted/circumscribed interests, self-injurious behaviours (Bishop et al., 2013), and that sensory symptoms are specifically related to the first factor of repetitive sensory-motor/stereotypic behaviours (Esbensen, Seltzer, Lam, Bodfish, 2009; Mirenda et al., 2010). This factor is considered independent from the other factors, as it is more severe in younger children and improves with age, whereas, the other factors are not associated with age-related changes (Bishop, Richler and Lord 2006). Moreover, factor analysis of the Autism Diagnostic Interview (ADI), revealed that sensory symptoms and repetitive behaviours were on two distinct factors, which had a low inter-correlation between them (Tadevosyan-Leyfer et al., 2003).

However, the direction of the relationship between RRB and all three sensory modulation symptoms (hyper-sensitivity, hypo-sensitivity and sensory-seeking) is unknown, due to the lack of experimental evidence (Boyd et al., 2010). It is possible that repetitive sensory-motor/stereotypic behaviours could be a functional coping strategy to help regulate and manage sensory symptoms (Cunningham and Schreibman, 2008; Leakam, Prior and Uljarevic, 2011; Liss et al., 2006). Therefore, suggesting RRB may have an underlying sensory origin (Rogers and Ozonoff, 2005). However, there are concerns regarding the criterion validity of assessments, as some assessments label items as assessing RRB on one scale, whereas, the same items are labelled as assessing sensory symptoms in another assessment measure (Gabriel et al., 2008).

In addition, sensory symptoms in individuals with ASD are related to lower adaptive functioning and problem behaviours (Jasmin et al., 2009; O'Donnell, Dietz, Kartin, Nalty and Dawson, 2012). In particular, sensory hypersensitivity is a risk marker for problem behaviours (Lundqvist, 2013). Furthermore, relationships have been reported between sensory symptoms and social communication and engagement (Hilton et al., 2010; Hochhauser and Engel-Yeger, 2010). Watson et al., (2011) found that more severe hypo-responsivity and sensory-seeking symptoms were associated with more severe social communication difficulties and language delays in both children with ASD and children with developmental delays.

Research has also focused on the relationship between sensory symptoms and anxiety, not only due to the high comorbidity of anxiety in ASD (11-84%; White, Oswald, Ollendick, Scahill, 2009), but also due to the similarity between the two

constructs. Whilst anxiety and sensory symptoms (specifically over-responsivity) have independent clinical definitions, they can manifest behaviourally in similar ways, for example, individuals displaying avoidance and dysregulation. This is challenging for the observer to interpret the behaviour and to differentiate the two (Ben-Sasson, Carter, and Briggs-Gowan, 2009).

The majority of research supports the notion that anxiety is the result of a behaviourally conditioned response to distress from sensory stimuli (over-responsivity) (Ben-Sasson et al., 2008). For example, in a longitudinal study of toddlers with ASD, sensory over-responsivity predicted anxiety a year later, although anxiety was not predictive of sensory over-responsivity (Green, Ben-Sasson and Soto, 2012).

Children and adolescents with ASD and more severe sensory difficulties were also reported to have a lower mood, more withdrawal and separation anxiety (Ben-Sasson et al., 2008; Brock et al., 2012). Specifically, adults with sensory defensiveness showed significant anxiety and depression (Kinnealey and Fuiek, 1999).

Genetic Neurodevelopmental Syndromes

As sensory modulation difficulties are not unique to ASD but are reported in ID populations with ASD symptomology (Engel-Yeger, Hardal-Nasser and Gal, 2011) and due to the high genetic heritability of individuals with a broader ASD phenotype (up to

90%; Geschwind, 2009)[4], assessing the literature about sensory modulation in genetic neurodevelopmental syndromes may prove useful.

As even similar ASD phenotypes do not involve the same genetic markers and not every individual with the predicted predisposing genotype developed ASD (Woodbury-Smith et al., 2015). There is also evidence that different gene defects may sometimes feed into similar molecular pathways in the development of ASD (Voineagu et al., 2011). Therefore, it is suggested that underlying genetic contributions are complex and interact with the foetal environmental and biological components, which develop more specific ASD phenotypes and increase the ASD prevalence in genetic syndromes (Marshall et al., 2008; May and Nadler, 2008). Abrahams and Geschwind (2008) suggested that genetic syndromes account for 10-20% of all individuals with ASD. Zafeiriou, Ververi, Dafoulis, Kalyva and Vargiami (2013) completed a systematic search and were able to identify reported rates of ASD symptomology in individuals with different genetic syndromes (Appendix 2). Recently, Richards, Jones, Groves, Moss and Oliver's (2015) meta-analysis provided estimates of ASD phenomenology in twelve genetic syndromes, which ranged from 11% for individuals with 22q11.2 to 61% for individuals with Rett syndrome (Appendix 2)[5].

[4] Despite a lack of precise neuropathological markers (Freitag, 2007; Santangelo and Tsatsanis, 2005; Voineagu, 2012), over 1000 genetic markers have been suggested (Alarcon et al., 2008; Ch'ng, Kwok, Rogic and Pavlidis, 2015; De Rubis et al., 2014; Santangelo and Tsatsanis, 2005), although, there is a lack of consistent results (Betancur, 2011; De Rubeis et al., 2014).
[5] There are numerous limitations to the research investigating ASD prevalence in genetic syndromes. Consequently, the reported prevalence of ASD diagnosis should only be regarded as an estimate of the presence of ASD symptoms (Charman and Gothman, 2013; Richards, Jones, Groves, Moss and Oliver, 2015).

Moreover, these specific ASD phenotypes are reported more consistently across genetic neurodevelopmental syndromes, each with a relatively specific genetic "cause". Despite Kulage et al., (2014) suggesting research should focus on investigating the level of ID accounting for variation in diagnosis between the DSM versions. Moss, Howlin, Magiati and Oliver (2012) found that differences in ASD symptomology between individuals with ASD and Cornelia de Lange Syndrome (CdLS), were not a consequence of ID or language skills. They reported that individuals with CdLS displayed less repetitive behaviour, sensory interests, stereotyped speech and more eye contact and anxiety in comparison to individuals with idiopathic ASD. Highlighting that ASD associated with certain genetic neurodevelopmental syndromes differs from idiopathic ASD (Moss, Howlin and Oliver, 2011) raises the possibility that the effect of changes to the DSM-5 may be different for idiopathic ASD compared to different neurodevelopmental syndrome groups (Wheeler et al., 2015).

Rationale and Aim

The literature presented highlights why it is timely to examine the role sensory modulation has in ASD diagnosis due to the recent changes to the diagnostic criteria for ASD in the DSM-5 (Schaaf and Lane, 2015). Whilst some research has investigated the impact of the sensory modulation criteria in the DSM-5 for individuals with idiopathic ASD (Kulage, Smaldone and Cohen, 2014), there is a lack of research which has investigated the impact for individuals with genetic syndromes. The only study to report the implications for the DSM-5 changes was Wheeler et al., (2015) who found that significantly fewer individuals with Fragile X Syndrome (FXS) met criteria for DSM-5

(27.8%) compared to DSM-IV (38.7%). This reduction was predominantly due to fewer individuals meeting the communication/interaction criterion (A), since high percentages met the RRBI criterion (B).

Therefore, the changes in the DSM-5 have implications for assessing ASD in individuals with genetic syndromes given that the manifestation of symptoms compatible with an ASD diagnosis in syndrome groups may differ from idiopathic ASD, it is possible that the implications of diagnostic changes differ for syndrome groups. Investigating sensory modulation in a range of syndromes with different ASD symptomology and behavioural phenotypes allows a unique exploration of the relationship between sensory modulation and other behavioural symptoms.

In addition, exploring sensory modulation in genetic syndromes is fundamental to the clinical implications that sensory difficulties can have, including a reduced quality of life, a restriction on meaningful activity (Bundy, Shia, Qi and Miller, 2007; Engel-Yeger, 2008) and significant strain on carers (Kirby, White and Baranek, 2016). Moreover, there is a critical need for systematic studies of sensory modulation in different genetic syndromes to further understand sensory modulation phenotypic characterisation (Hildenbrand and Smith, 2011). Understanding of sensory symptoms in genetic syndromes associated with ASD will lead to a better understanding of causal pathways to behaviour, with implications for early interventions (Waite et al., 2014).

The present systematic review aims to summarise and evaluate the research examining sensory modulation in individuals with rare genetic syndromes associated

with ID and ASD symptomology. The review will then evaluate if the addition of sensory modulation difficulties to the ASD criteria in the DSM-5 has implications for the potential diagnosis of ASD in genetic syndromes.

Method

Search Strategy

In order to focus the systematic search on sensory symptoms and ASD, only genetic syndromes associated with ID were selected for which there have been recent reports of the raised prevalence of ASD phenomenology. Accordingly, the list of syndromes searched was developed from a recent review (Zafeiriou, Ververi, Dafoulis, Kalyva and Vargiami, 2013) and meta-analysis (Richards, Jones, Groves, Moss and Oliver, 2015) of ASD phenomenology in genetic syndromes. This resulted in twenty-four syndromes being included in the search. The Online Mendelian Inheritance in Man (OMIM, accessed 06.04.2016) database was used to ensure alternative syndrome names were included in the search.

Schaaf and Lane (2015) have described how the different terminology used to described sensory symptoms has led to inaccuracy in the literature and suggest that future research focuses on the sensory modulation terms described in the DSM. However, other sensory processing terms were also used to ensure research articles were not missed. The sensory symptoms search terms included: sensory* modulation,

sensory* sensitivity, sensory* profile, sensory* information, sensory* processing, hypersensitivity* and hyposensitivity*[6].

Literature searches were conducted in Ovid PsycINFO (inclusion dates: 1967 to April Week 1 2016), Ovid MEDLINE (inclusion dates: 1946 to March Week 5 2016) and Ovid Embase (inclusion dates: 1974 to 2016 April 12) on 13.04.2016. A list of the syndrome group search terms are displayed in Table 1.1. Searches were conducted by combining all variations of the syndrome search terms with any sensory symptom search terms.

[6] Preliminary additional search terms were used to describe each specific modality e.g. visual, auditory and olfactory. However, these terms resulted in a vast amount of cognitive processing related articles; therefore, the terms were excluded in the final search to increase the specificity of the search.

Table 1.1: ***The Search Process.***

Syndrome	Syndrome Search Terms	Records identified through database search	Duplications removed	Non-English language journals removed	Non empirical peer reviewed journals removed	Articles not related to each syndrome removed	Articles not related to sensory modulation	Animal studies removed	Articles with no behavioural data removed	Full text articles assessed for eligibility	Excluded after full text read due to a lack of sensory data	Articles included in review
Angelman Syndrome	Angelman* syndrome; Happy puppet syndrome; Isodicentric 15; Interstitial duplications syndrome; Maternal deletion 15q11 2-q13; UBE3A gene mutation	16	6	0	3	0	2	2	1	2	0	2
CHARGE Syndrome	CHARGE syndrome; Hall-Hittner syndrome; HHS; Choanal atresia, retardation, genital and ear abnormalities; CHD7 gene mutation; 8q12 2 chromosome; SEMA3E gene mutation; 7q21 11 chromosome	16	4	0	4	8	0	0	0	0	0	0
Chromosome 22q11.2 Deletion Syndrome	Chromosome 22q11 2 deletion syndrome; Distal chromosome 22q11 2 deletion syndrome	0	0	0	0	0	0	0	0	0	0	0
Chromosome 2q37 Deletion Syndrome	Chromosome 2q37 deletion syndrome; Albright hereditary osteodystrophy-like syndrome; Bachydactyly-mental retardation syndrome; BDMR; Chromosome 2q37.2 deletion	0	0	0	0	0	0	0	0	0	0	0
Cohen's Syndrome	Cohen* syndrome; Obesity-hypotonia syndrome; Pepper* syndrome; Prominent-incisors syndrome; COH1; CHS1; 8q22 2 chromosome	2	0	0	0	2	0	0	0	0	0	0
Cornelia de Lange Syndrome	Cornelia de Lange* syndrome; CDLS; CDL; CDLS1; De Lange* syndrome; Branchmann-De Lange* syndrome; BDLS; Brachmann* syndrome; typus degenerativus Amstelodamensis; NIPBL gene mutation; 5p13 2 chromosome	6	2	0	0	1	2	0	0	1	1	0
DiGeorge syndrome	DiGeorge* syndrome; CATCH22; 22q11 deletion syndrome; Hypoplasia of thymus and parathyrois; DGS; Chromosome 22q11.2 deletion syndrome; Chromosome	40	5	2	9	12	12	0	0	0	0	0

Syndrome	Syndrome Search Terms	Records identified through database search	Duplications removed	Non-English language journals removed	Non empirical peer reviewed journals removed	Articles not related to each syndrome removed	Articles not related to sensory modulation	Animal studies removed	Articles with no behavioural data removed	Full text articles assessed for eligibility	Excluded after full text read due to a lack of sensory data	Articles included in review
	22q11.21 deletion; TBX1 gene mutation											
Down Syndrome	Down*; Down syndrome; Trisomy 21; DSCR; Transient myeloproliferative disorder; megakaryoblastic of Down syndrome; 21q22 3 chromosome; GATA1 gene mutation	173	53	14	35	32	31	1	1	5	2	3
Fragile X Syndrome	Fragile X mental retardation syndrome; Fragile X syndrome; FXS; Martin-Bell* syndrome; Marker X syndrome; X-linked mental retardation; marXq28 X-linked mental retardation; Macroorchidism; xq27 3 chromosome; FMR1 gene mutation	132	57	1	16	3	24	16	10	5	1	4
Klineflter Syndrome	Klinefelter* syndrome; Klinefelter's syndrome; KS; 47XXY syndrome; XXY syndrome	12	4	0	1	3	4	0	0	0	0	0
Neurofibromatisis Type 1	Neurofibromatosis*; Neurofibromatosis type 1; Neurofibromatosis 1; NF1; NF-1 gene; Peripheral Neurofibromatosis; Neurofibromin; Recklinghausen disease;	114	25	1	32	19	21	2	1	1	1	0
Noonan's Syndrome	Noonan* syndrome; Female pseudo-Turner syndrome; Male Turner* syndrome; Turner phenotype with normal karyotype; pterygium colli syndrome; 12q24 13 chromosome; PTPN11 gene mutation	19	4	0	9	1	5	0	0	0	0	0
Phelan-McDermid Syndrome	Phelan-McDermid* Syndrome; PHMDS; Chromosome 22q13.3 deletion syndrome; Telomeric 22q13 monosomy syndrome; SHANK3 gene mutation	6	0	0	0	0	3	2	0	1	0	1
Potocki-Lupski Syndrome	Potocki-Lupski* syndrome; PTLS; Chromosome 17p11 2 deletion syndrome	3	0	0	2	1	0	0	0	0	0	0
Prader Willi Syndrome	Prader-Willi* syndrome; PWS; Prader-Labhart-Willi syndrome; Prader-Willi chromosome region; PCR; Prader-	19	5	0	6	2	4	2	0	0	0	0

Syndrome	Syndrome Search Terms	Records identified through database search	Duplications removed	Non-English language journals removed	Non empirical peer reviewed journals removed	Articles not related to each syndrome removed	Articles not related to sensory modulation	Animal studies removed	Articles with no behavioural data removed	Full text articles assessed for eligibility	Excluded after full text read due to a lack of sensory data	Articles included in review
	Willi-like syndrome associated with chromosome 6; Isodicentric 15; Interstitial duplications syndrome; Paternal 15q112 chromosome; imprinted NDN gene; imprinted SNRPN gene											
Rett Syndrome	Rett* syndrome; Rett disorder; RTS; RTT; Autism-dementia; Ataxia; Loss of purposeful hand use syndrome; xq28 chromosome; MECP2 gene mutation	115	36	1	28	46	2	1	1	0	0	0
Smith-Lemli-Opitz Syndrome	Smith-Lemli-Opitz* syndrome; SLOS; SLO syndrome; RSH syndrome; Rutledge lethal multiple congenital anomaly syndrome; Lethal acrodysgenital syndrome; 11q13 chromosome; DHCR7 gene mutation	46	5	1	5	27	5	1	0	1	0	1
Smith-Magenis Syndrome	Smith-Magenis* syndrome; SMS; Chromosome 17p11 2 deletion syndrome; Smith-magenis chromosome region; SMCR; RAI1 gene mutation	32	10	2	2	13	3	0	0	2	0	2
Soto Syndrome	Soto* syndrome; STOT1; Sotos syndrome; Cerebral gigantism; Chromosome 5q35 deletion syndrome; chromosome 5q35 3 deletion; NDS1 gene mutation	1	0	0	1	0	0	0	0	0	0	0
Timothy Syndrome	Timothy* syndrome; Long QT syndrome with syndactyly; Long QT syndrome; LQT8; 12p13 33 chromosome; CACNA1C gene mutation	0	0	0	0	0	0	0	0	0	0	0
Tuberous Sclerosis Complex	Tuberous sclerosis* syndrome; Tuberous sclerosis complex; TSC; TS; TSC1 gene mutation; Harmartin; 9q34 chromosome	58	10	8	20	11	10	0	0	0	0	0
Turner Syndrome	Turner* syndrome; Ullrich-Turner syndrome; Gonadal dysgenesis; 45X syndrome; X chromosome deletion	22	7	0	4	9	2	0	0	0	0	0

Syndrome	Syndrome Search Terms	Records identified through database search	Duplications removed	Non-English language journals removed	Non empirical peer reviewed journals removed	Articles not related to each syndrome removed	Articles not related to sensory modulation	Animal studies removed	Articles with no behavioural data removed	Full text articles assessed for eligibility	Excluded after full text read due to a lack of sensory data	Articles included in review
Velocardiofacial syndrome	VCF; VCFS; Velocardiofacial* syndrome; Velo-cardio-facial syndrome; Takao VCF syndrome; Shprintzen VCF syndrome; Chromosome 22q11 2 deletion syndrome; TBX1 gene mutation	8	0	0	2	3	2	0	1	0	0	0
William's Syndrome	William* syndrome; Beuren* syndrome; Williams-Beuren* syndrome; WBS; Chromosome 7q11 23 deletion syndrome	64	25	3	16	4	12	0	1	4	1	3

Inclusion and Exclusion Criteria

Research was included if it was available in English and published in a peer-reviewed journal. Furthermore, research was included if it involved the specific syndrome being searched and included human participants. Articles which assessed sensory modulation and included behavioural data were included, due to recommendations made by previous research to focus on the terminology used in the DSM-5 and explore functional impairment and behavioural responses to sensory stimuli (Schaaf and Lane, 2015). Thus, articles were excluded which assessed early sensory processing at the neuroanatomical level, including assessment of higher cognitive operations such as visual and auditory memory and attentional processes at the primary and secondary cortices (Light, Swerdlow and Braff, 2007). Finally, some ASD assessment measures contain some items regarding sensory symptoms, including the Autism Diagnostic Observation Scale (ADOS; Lord et al., 2000) and the Childhood Autism Rating Scale (CARS; Schopler and Van Bourgondien, 2010). However, research articles that contained these ASD assessments were reviewed to determine if there was an adequate amount of specific sensory data was displayed, if not research containing only these measures was excluded, as the focus of the research was not related to sensory modulation. Therefore, only research that included comprehensive measures of sensory symptoms were included (Rogers and Ozonoff, 2005; Table 1.2).

Table 1.2: ***Inclusion and Exclusion Criteria.***

Inclusion Criteria	Exclusion Criteria
Articles published or available in English	Articles published in a language other than English
Empirical peer-reviewed papers	Conference proceedings, magazines, dissertations, review articles and books
Related to the specific syndrome	Articles related to any other difficulties or stimuli
Related to sensory modulation	Articles related to any other difficulty or stimuli
Human participants only	Animal studies
Contains behavioural data	Contains gene, brain imaging or biological data only
Adequate amount of sensory data	Insufficient amount of sensory data to draw meaningful conclusions

Selection Strategy

A total of 904 papers were identified by the searches. The titles and abstracts were screened for suitability using the inclusion and exclusion criteria. Twenty-two full texts were read to determine suitability and six were excluded, due to insufficient sensory modulation results to aid discussion.

Results

Participants

The articles in the review included individuals with seven genetic syndromes (Table 1.3). Two studies included individuals with Angelman Syndrome (AS), three studies included individuals with Down Syndrome (DS), four studies included individuals with FXS, one study included inviduals with Phelan-Mc Dermid Syndrome (PHMDS), one study included inviduals with Smith-Lemli-Opitz Syndrome (SLOS), two studies included individuals with Smith-Magensis Syndrome (SMS), and three studies individuals with Williams Syndrome (WS). Each genetic syndrome is defined by a unique behavioural phenotype with different ASD symptomology (Table 1.3).

Specifically, AS, is defined by sensory-seeking behaviours and an excessive happy demeanour, with 34% of individuals displaying ASD symptomology (Oliver, Horsler, Berg, Bellamy, Dick and Griffiths, 2007; Richards et al., 2015). Individuals with DS display motor difficulties and fewer behavioural difficulties and the least frequency of ASD symptomology (16%; Chapman and Hesketh, 2000; Richards et al., 2015). The behavioural phenotype of FXS includes, hyperactivity and social anxiety, with 22% of individuals displaying ASD symptomology (Hagerman and Hagerman, 2002; Richards et al., 2015). The SMS behavioural phenotype includes aggressive and repetitive behaviours and nighttime arousal, with a large number of individals displaying ASD symptomology (68.4%; Arron, Oliver, Berg, Moss and Burbidge, 2011; Zafeirous et al., 2013). Individuals with WS have an over-social personality and fewer displays of ASD symptomology (12%; Jarvinen-Pasley et al., 2008; Richards et al.,

2015). The age of participants ranged from three months- thirty-two-years old, although the age range was not reported by Horvat, Croce and Zagrodnik (2010).

Table 1.3: ***Descriptions of Genetic Syndromes.***

Syndrome	Number of Articles investigating the Syndrome	Genetic Mechanisms	Estimated Prevalence	Behavioural Phenotype	Prevalence of ASD symptomology	Description of ASD Symptomology
Angelman Syndrome (AS)	2	Loss of functioning in the UBE3A gene on the maternally driven chromosome 15, predominantly due to deletions or imprinting errors (Kishino, Lalande and Wagstaff, 1997).	One in 10,000-20, 000 live births (Williams, 2005)	Severe ID, speech and language delays, epilepsy, sleep difficulties, ataxic gait, sensory-seeking behaviours and an excessive happy demeanour and laughing (Oliver, Horsler, Berg, Bellamy, Dick and Griffiths 2007; Williams et al., 2006).	34% (Richards et al., 2015) 50-61% (Zafeirous et al., 2013).	Peters, Beaudet, Madduri and Bacino (2004) found that individuals with AS, despite displaying excessive laughing, can still lack social engagement and interaction skills. However, other research has reported that individuals with AS show appropriate social reciprocity, and emotional contact (Clayton-Smith and Lann, 2003; Thompson and Bolton, 2003) and less stereotyped and repetitive behaviours compared to individuals with idiopathic ASD. Trillingsgaard and Ostergaad (2004) argue that ASD in AS is over-diagnosed due to individuals' ID and developmental delay.
Down Syndrome (DS)	3[7]	An additional copy of chromosome 21 (trisomy 21), which includes genes DYRK1A, RCAN1, SIM2 and GIRK2.	18.2 in 10,000 still births, live births and terminated pregnancies (Cocchi et al., 2010)	Mild to severe ID, difficulties with motor function, language delays and fewer behavioural difficulties, compared to other genetic syndromes (Chapman and Hesketh, 2000).	16% (Richards et al., 2015) 16-19% (Zafeirous et al., 2013)	Research has reported that individuals with DS and ASD have a similar symptomology to individuals with idiopathic ASD, aside from individuals with DS being slightly more engaged in their environment. (Moss, Richards, Nelson and Oliver, 2012). It has also been found that the more severe the ID and seizures the more likely individuals with DS would have a co-morbid diagnosis of ASD (Capone, Grados, Kaufmann, Bernard-Ripoll and Jewel, 2005; Molloy et al., 2009).
Fragile X Syndrome	4	The silencing of the FMR1 gene at	One in 5,160 male births	Hyperactivity, impulsivity, attention difficulties,	22% (Richards et al., 2015) and 15-	The ASD symptomatology in FXS is different from idiopathic ASD (Kerby and Dawson,

[7] Rogers, Hepburn and Wehner, 2006, also included individuals with DS, although there were no individual data for this syndrome group.

Syndrome	Number of Articles investigating the Syndrome	Genetic Mechanisms	Estimated Prevalence	Behavioural Phenotype	Prevalence of ASD symptomology	Description of ASD Symptomology
(FXS)		chromosome Xq27.3, leading to production of the Fragile X mental retardation protein (FMRP), which is associated with ID (Kaufmann and Reiss, 1999)[8]	(more severely affected) (Coffee et al., 2009) and one in 8000 female births (Sherman, 2002).	anxiety, shyness, aggression, moderate ID, SIB, hand-flapping and hypersensitivity (Hagerman and Hagerman, 2002).	52% (Zafeirous et al., 2013)	1994). As a group, people with FXS are more able to recognise emotional expression (Turk and Cornish, 1998) and display better theory of mind skills (Mazzocco, Pennington and Hagerman, 1994).
Phelan-Mc Dermid Syndrome (PHMDS)	1	A deletion or mutation of chromosome 22q13, which includes the SHANK3 gene that contains protein-building properties necessary for glutamatergic synapses (Durand et al., 2007).	Unknown (Soorya et al., 2013).	There is a lack of details about the behavioural phenotype, although, it does include ID, motor skill difficulties and delayed or absent speech (Soorya et al., 2013).	50% (Zafeirous et al., 2013).	Preliminary research has suggested that the ASD symptomology is somewhat unique in that individuals with PHMDS display greater difficulties in social interaction and communication, but less difficulties with repetitive behaviour and restricted interests (Philippe et al., 2008; Phelan and McDermid, 2012). It has been suggested that the level of developmental delay significantly contributes to a co-morbid ASD diagnosis and that smaller deletions in PHMDS are not associated with greater impairments in social communication deficits (Oberman, Boccuto, Cascio, Sarasua, and Kaufmann, 2015).
Smith-Lemli-Opitz	1	An inborn error of cholesterol	One in 20,000-	ID, hyperactivity, repetitive behaviour and	53-57% (Zafeirous et al.,	Sikora, Pettit-Kekel, Penfield, Merkens and Steiner (2006) reported that individuals with

[8] The gene normally contains 5-50 repetitions of cytosine-guanine-guanine (CGG). Some individuals' genes may contain 50-200 CGG sequences, and these people are known as premutation carriers and may have no symptoms. Individuals with FXS have the full mutation and have more than 200 CGG sequences.

Syndrome	Number of Articles investigating the Syndrome	Genetic Mechanisms	Estimated Prevalence	Behavioural Phenotype	Prevalence of ASD symptomology	Description of ASD Symptomology
Syndrome (SLOS)		metabolism, due to mutations in gene DHCR7 on chromosome 11912-13, which consequently causes abnormalities in embryonic and fetal somatic development (Tierney, Nwokoro and Kelley, 2000).	80,000 live births (Kelley and Hennekam, 2006).	self-injurious behaviour (Ryan et al., 1998; Porter, 2008).	2013)	SLOS and ASD have specific impairments in communication, relative to their social interaction skills. However, it has not been established if this is a true reflection of the ASD symptomology in this syndrome or an artefact of a small sample.
Smith Magensis Syndrome (SMS)	2	A deletion or mutation of chromosome 17p11.2 9, which includes the RA1 gene (Elsea and Girirajan, 2008; Vlangos, Wilson, Blancato, Smith and Elsea, 2005)	One in 25,000 live births (Juyal et al., 1996)	Severe to moderate ID (Udwin, Webber and Horn, 2001), aggression, self-injurious behaviours, repetitive behaviours (Arron, Oliver, Berg, Moss and Burbidge, 2011) and sleeping difficulties, specifically daytime sleepiness and nighttime arousal (Gropman, Elsea, Duncan and Smith, 2007).	68.4% (Zafeirous et al., 2013)	Research suggests that severity of ASD symptoms in individuals with SMS are in the mild (Martin, Wolters and Smith, 2006) to moderate range (Wolters et al., 2009). It has also been suggested that the ASD symptomology in SMS is defined by considerable repetitive behaviours, yet only mildly affected social communication skills (Fidler, Philofsky and Hepburn, 2006; Udwin, 2002).
Williams Syndrome (WS)	3	A deletion on chromosome 7q11.23 containing 21 genes, which	One in 7,500 live births (Stromme, Bjornstad and	Mild ID, an 'over-social' personality with exaggerated tendency to approach others (Jarvinen-Pasley et al., 2008). It is	12% (Richards et al., 2015) to 50% (Zaferious et al., 2013)	Authors have suggested that actually WS and ASD are 'opposite' disorders (Peterson and Panksepp, 2004). Individuals with WS have more typical face-processing (Lincoln et al., 2007) and greater social engagement skills,

Syndrome	Number of Articles investigating the Syndrome	Genetic Mechanisms	Estimated Prevalence	Behavioural Phenotype	Prevalence of ASD symptomology	Description of ASD Symptomology
		includes the ELN gene (Osborne, 2006).	Ramstad, 2002).	noteworthy that in WS auditory hypersensitivity and a strong interest in music (Levitin, Cole, Chiles, Lai, Lincoln and Bellugi, 2004; Levitin, 2005) is recognised as part of the behavioural phenotype.		but display the same vocabulary strengths and difficulties with language pragmatics seen in individuals with ASD (Asada and Itakura, 2012).

Articles

The review includes sixteen articles published between 1999-2016 (Table 1.4).

Table 1.4: ***Descriptions of the Articles Included in the Review.***

Authors (Year)	Participants	Sensory Assessment	Additional Assessments	Procedure	Results/Conclusion
Baranek, Chin, Greiss, Hess, Yankee, Hatton and Hooper (2002)	n=15 males with FXS (mean age=53 months)	1. Sensory Profile (SP) 2. Tactile Defensiveness and Discrimination Test Revised (TDDT-R), has subscales for internally and externally controlled tactile experiences. 3. Sensory Approach-Avoidance Rating (SAAR; observational method developed by the authors)	1. Brief IQ 2. Vinelands Adaptive Behavioural Scale (VABS)- only daily living skills subscale. 3. School Function Assessment (SFA)	Teacher completed SFA, parent completed SP and self-help skills on VABS. Researchers completed observation methods. SAAR- children presented with nine multisensory toys and their level of approach or avoidance rated (used as sensory observation). The amount of time the child engaged with toys (used as a functional play assessment)	1. BriefIQ in the 'mild' range (mean=60), although considerable variability n=7 3-4 SD below mean, n=3 2-3 SD below mean, n=1 normal range, 1 unable to test. 2. SP not related to TDDT-R or SAAR. 3. SP- overall total 'definite' differences. 'Typical' performance n=2, 'probable' difference n=2. 4. No normative data for TDDT-R and SAAR, although authors suggest these would be at floor level (0). 5. TDDT-R- near floor n=2, few concerns n=3, others varying levels, high levels of aversion/ avoidance n=4. 6. VABS- mean=56.4, all except 1 fell more than 2SD below mean. 7. SFA- All low, except full participation n=3 (100), (93) n=1. 8. Relationship between TDDT-R and VABS- higher aversive- avoidance reactions to tactile stimuli related to less independence in ADL. 9. Relationship between SAAR and SFA- higher aversive- avoidance behaviours lower school function (less engagement). 10. Relationship between SAAR with play duration- Higher aversion- avoidant less time engaging with toys.
Baranek, Roberts,	n=13 children with	1. The Sensory Processing	1. Mullen Scales of Early Learning	Initially assessed at nine-twelve-	1. Children displayed increasing SP difficulties over time in SEQ, SPA and

Authors (Year)	Participants	Sensory Assessment	Additional Assessments	Procedure	Results/Conclusion
David, Sideris, Mirrett, Hatton and Bailey (2008)	FXS. Mean chronological ages across assessments= nine, twelve, eighteen, twenty-four, thirty-six and fifty-four-months.	Assessment for young children (SPA) 2. Sensory Experience Questionnaire (SEQ) 3. Test of Sensory Function in Infants (TSFI) 4. Baseline heart activity whilst playing before assessments 5. Inter-beat-interval (IBI; measure of arousal) and vagal tone (measure of neural regulation of heart activity associated with parasympathetic influences)	(MSEL) 2. FMRP DNA analysis (n=10)	months old and needed at least one more assessment between eighteen to sixty-five-months-old Total forty-five assessments (two-six per child). Parents completed questionnaires, researcher completed observation methods.	TSFI. 2. >90% in TSFI and 70-80% in SPA obtained scores indicating high risk or deficient performance at nine, twelve and eighteen-months old. 3. None displayed deficient scores at nine-months, at fifty-four months >40% did. 4. Only the SPA hyper-responsiveness scale increased with chronological age. 5. The SEQ hypo-responsiveness scale decreased with increased cognition. 6. The TSFI hypo-responsiveness scale decreased with increased age and cognition. 7. At nine-months, children with low cognition showed more hypo-responsiveness on TSFI compared to children with high cognition. By eighteen-months differences were no longer significant. 8. SEQ hypo-subscale decreased at a greater rate initially for children with lower gross-motor abilities. 9. TSFI hypo-responsivity decreased from children aged at nine-month. Children with lower gross motor skills had fewer hypo-symptoms than children with higher gross motor abilities, but by eighteen-months, scores converged.
Bruni, Cameron, Dua and Noy (2010)	n=75 children with Down Syndrome (53% response rate),	1. Short Sensory profile (SSP) 2. Parental Questionnaire (PQ)	N/A	Questionnaires posted to parents to complete. Used constant comparative	1. SP- 49% 'definite' differences in comparison to normative sample. 2. Largest differences in low energy/weak (69%), under-responsive/ seeks sensation (48%) and auditory filtering

Authors (Year)	Participants	Sensory Assessment	Additional Assessments	Procedure	Results/Conclusion
	n=37 male. Inclusion criteria three to ten-years, mean age missing.			method to identify themes in open-ended questions in PQ.	(43%) 3. 'Typical' performance in taste/smell sensitivity (68%) and movement sensitivity (64%). 4. PQ- 55% parents spent time trying to increase child interests in play and participation. 5. 16% SP significant impact on family life, 37% moderate impact on daily life. 6. Five strategies identified to manage sensory difficulties: Seek sensory modulation, intolerance to touch during ADL, avoidance of environment triggers (19%), routines and transitions, developmental phrases 'growing out of difficulties'.
Hildenbrand and Smith (2011)	n=41 children with Smith-Magenis Syndrome, n=7 excluded due to not returning forms. n=34 children (mean age=6.85 years). Divided into two age groups (younger: three-five years, older:	1. Sensory profile (SP) and SP supplement	N/A	Parents completed the questionnaire and nine participants in the younger group were followed up (two-three years later) and parents completed the questionnaire again, compared to normative data.	1. Significant 'definite' differences in all sensory profile quadrants and modulation areas compared to normative data. 2. 'Probable' differences in oral, visual and auditory processing. 3. 'Definite' differences in multisensory, touch and vestibular processing. 4. Stereotypic behaviours' difficulties observed in less than 50%. 5. More than 50% had weak muscle tone due to lethargy. 6. Three-five year olds closer to norms. 7. In the longitudinal data, there was a trend to more sensory difficulties as children grew older, although only

Authors (Year)	Participants	Sensory Assessment	Additional Assessments	Procedure	Results/Conclusion
	six-fourteen years)				significant for sensation-seeking. 8. Interaction effect of age and gender in modulation of sensory input affecting emotional responses. Older females had the most difficulties.
Horvat, Croce and Zagrodnik (2010)	n=8 children with mild intellectual disability (ID, mean age= 16.5 years), n=8 with Down Syndrome (DS, mean age=17.5 years) (identified on school education plans) and n=8 without intellectual disability (TD mean age=17.7 years), n=4 Males in each group (age range not reported)	1. Computerised dynamic posturography performed on NeuroComEqitestSystem using Sensory Organisation Test (SOT) protocol.	N/A	SOT tested under six sensory conditions, each three times for twenty seconds. Conditions differed depending on manipulation of somatosensory, visual and/ or vestibular environments and resulting movements measured.	1. No significant difference between groups when no sensory information was compromised. 2. No significant difference in gender 3. TD significantly higher than ID and DS and MID higher than DS on condition with inaccurate somatosensory information and only accurate vestibular information. 4. TD significantly higher than DS, but not ID in three conditions: 1. Inaccurate vision, accurate vestibular and somatosensory information. 2. Inaccurate somatosensory information but accurate vestibular and vision information. 3. Inaccurate vision and somatosensory and vision information, but accurate vestibular information. 5. No significant difference between groups in somatosensory scores. 6. TD and ID higher than DS for visual sensitivity. 7. TD higher than ID and DS, and ID higher than DS for vestibular sensitivity. 8. Conclusion- ID and DS worse movement abilities when visual, vestibular and somatosensory

Authors (Year)	Participants	Sensory Assessment	Additional Assessments	Procedure	Results/Conclusion
					information is disrupted.
Janes, Riby and Rogers (2014)	n=21 children with Williams syndrome (72% consent rate). n=12 male, six-fifteen-years, mean age=9.3 years.	1. Short Sensory Profile (SSP) 2. The Assessment of Sensory Processing, Repetitive behaviour, Anxiety, Fear in Williams Syndrome-Semi Structured Interview (SRAF-SSI)	1. Wechsler Intelligence Scale for Children (WISC)	SP posted to parents, researcher completed WISC and interview with parents.	1. FSIQ= 52.6 2. SP mean= 'definite' differences range. 3. Results of thematic analysis of SRAF-SSI: • Vestibular hypersensitivity- n=11 oversensitive to body movements, n=13 improvement over time, n=6 impacts on family life 'often' or 'always'. • Proprioceptive hypersensitivity- n=14 difficulties, n=11 improvements over time, n=8 impacts on family life 'often' or 'always'. • Auditory hypersensitivity- n=14 reported over- sensitive to auditory stimuli often or always, n=9 improvements over time, n=10 impacts on family life 'often' or 'always'. • Gustatory hypersensitivity- n=16 difficulties, n=5 improvements over time, n=12 impacts on family life 'often' or 'always'. • Repetitive behaviours- n=18 difficulties, n=11 worsened over time. • Unusual interests- n=14 difficulties, n=12 stable over time.

Authors (Year)	Participants	Sensory Assessment	Additional Assessments	Procedure	Results/Conclusion
					• Special hobbies- n=17 difficulties, n=12 stable over time. • Majority indicated anxiety was a trigger for RB, and explained relationship between SP and RB. • No hyposensitivity reported. • No difficulties with tactile, visual and olfactory sensitivity.
John and Mervis (2010)	n=78 children with Williams Syndrome (mean age= 6.53 years, age range= 4.0-10.95 years)	1. Short Sensory Profile (SP)	1. Short Sensory Profile (SP) 2. Kaufman Brief Intelligence Test (KBIT-2) 3. Peabody Picture Vocabulary Test (PPVT) 4. Behaviour Rating Inventory of Executive Functioning (BRIEF) 5. Children's Behaviour Questionnaire (CBQ) 6. Scales of Independent Behaviour-Revised (SIB-R) 7. Conners Parent Rating Scale Revised (CPRS)	Parents completed questionnaires and researchers administered KBIT-2 and PPVT on children.	1. SP results: 9.9% 'typical', 56.3% 'definitely problems', (auditory filtering, low weak/energy, under-responsive/ seeks sensations), 33.8% 'probably problems'. 2. Two clusters identified- high sensory impairments and low sensory impairments (classified 98.6% of cases) on significant difference on age, KBIT-2 or PPVT. 3. High sensory impairments clusters worse scores on BRIEF (executive function), CBQ (temperament), SIB-R (independence) and CPRS-R (Oppositional, anxious, social problems, restless-impulsive and inattentive). 4. Executive functioning had strongest relation to sensory modulation impairments (46% variance), then temperament (31% variance), then adaptive functioning (25% variance) and problem behaviour (25% variance).
Mieses et	n=24 children	1. Short Sensory	1. Mullen Scales of	Researchers	1. 95% of children with PHMDS met

Authors (Year)	Participants	Sensory Assessment	Additional Assessments	Procedure	Results/Conclusion
al., (2016)	with PHMDS (63% male, mean age=5.4 years, range=two-six-years). 61 children with ASD (82% male, mean age=4.6 years, age range=two-ten-years).	Profile (SSP)	Early Learning (MSEL)	completed the MSEL to determine intellectual functioning. Parents completed SSP.	criteria for ASD. 2. Children with ASD and PHMDS had a nonverbal developmental quotient (NVDQ) score of <70. 3. 80% of children with PHMDS and 81% of children with ASD had 'probable' or 'definite' differences in sensory modulation. 4. Children with PHMDS had 'typical' performance in visual/auditory sensitivity, 'probable' differences in taste/smell sensitivity, auditory filtering, and movement sensitivity. 'Definite' differences in under-responsivity and low-energy/weak. 5. Children with PHMDS had significantly fewer difficulties with taste/ smell sensitivity, visual/ auditory sensitivity, auditory filtering and tactile sensitivity compared to children with ASD. However, children with ASD had significantly greater difficulties in low-energy/weak symptoms compared to children with PHMDS. 6. There were no significant differences between children with PHMDS in movement sensitivity and under-responsivity.
Miller, McIntosh, McGrath, Shyu, Lampe, Taylor,	Group A: n=25 Fragile X Mutation (FXM) n=15 male (full mutation-full	1. Sensory Challenge Protocol (SCP)-Laboratory paradigm. 2. Skin	1. FMRP DNA analysis and FMRP immunocytochemistry to determine percentage of lymphocytes expressing FMRP.	The researcher presented different sensory stimulation while EDR was being recorded. All had	1. Strong relation among all responses across sensory domains, pattern in one domain predicted pattern of EDR in other domains- so data was averaged. 2. More lymphocyte FMRP (FXM) expression related to more normal EDR,

Authors (Year)	Participants	Sensory Assessment	Additional Assessments	Procedure	Results/Conclusion
Tassone, Neitzel, Stackhouse and Hagerman (1999)	methylation n=11, mean age= 21 years; full mutation-partial methyl n=3, mean age=22 years; mosaic, n=3, mean age=22 years; permutation, n=2 mean age= 10 years) n=6 female, all full mutation, mean age=12 years) Group B: (selection from group A, Participants with FXM and not FXS) all male. (Full mutation-full methylation n=11, mean age= 21 years; full mutation-partial methyl n=2, mean age=29 years; mosaic, n=2,	conductance by examining electrodermal readings (EDR)		five contiguous trials in each of five sensory systems-olfactory (wintergreen oil), auditory (fire engine noise), visual (strobe light), tactile (cloth finger puppet with feather on) and vestibular (tipping child 30%). EDR baseline data collected.	3. FXS had a great magnitude of EDR, more EDR per stimulation, EDR on a greater proportion of trials compared to controls. 4. Controls decreased responding after repeated stimulation (habituated), whereas, FXS did not cease responding to stimuli repetition.

Authors (Year)	Participants	Sensory Assessment	Additional Assessments	Procedure	Results/Conclusion
	mean age=27 years. Control participants were age matched. (age range=4-49 years)				
Peters, Horowitz, Barbieri-Welge, Taylor and Hundley (2012)	n=42 individuals with Angelman Syndrome , n=17 larger class 1 deletion, n=25 smaller class 2 deletion. (n=24 male, mean age at baseline=five-years, five-months, range= two-twenty-five-years)	1. Behaviour and Sensory Interests Questionnaire (BSI)- Unusual sensory interests/ Aversions subscale	1. Bayley Scales of Infant Development- Third Edition (BSID-III) 2. Autism Diagnostic Observation Schedule (ADOS) 3. Autism Diagnostic Interview Revised (ADI-R) (although, not reported) 4. Aberrant Behaviour Checklist- excluded inappropriate speech category	Assessments completed at baseline and three-year follow-up.	1. No difference in cognitive ability between deletion classes both improved over time. 2. No difference in adaptive functioning between deletion classes both improved in age-equivalent scores over time. 3. Class 1-deletion higher levels of social impairment, no difference over time in both groups. 4. Class 1 deletions more repetitive behaviour, no significant difference over time in both groups. 5. Class 1 deletions more likely to exceed Autism cut-offs at baseline and 12 months 6. No difference in sensory behaviours between deletions classes, no significant differences over time. Trend to increase in sensory seeking. 7. No difference between deletion classes in maladaptive behaviours and no significant change over time
Riby, Janes and Rogers (2013)	Same as Janes, Riby and Rogers (2014)	1. Short Sensory Profile (SSP)	1. Repetitive Behaviour Questionnaire (RBQ) 2. Wechsler Intelligence Scale for Children (WISC)	Questionnaire posted to parents and researcher completed WISC.	1. FSIQ= 52.6 2. No significant relationship between FSIQ and SP, FSIQ and RBQ. 3. Higher RBQ associated with more SP difficulties.

Authors (Year)	Participants	Sensory Assessment	Additional Assessments	Procedure	Results/Conclusion
					4. Significant relationship between RBQ repetitive movement and 3 subscales of SP (tactile, taste/ smell and under-responsive/seeks sensation). 5. Significant relationship between RBQ repetitive language and under-responsive/seeks sensation subscales of SP. 6. Significant relationship between RBQ sameness of behaviour and taste/smell sensitivity subscale on SP.
Rogers, Hepburn and Wehner (2003)	n=102 children Autism n=26, Fragile X n=20, some with and without autism, developmental delay n=32 (n=15 Down Syndrome), (mean= 31 months, range= 21-50 months) typically developing n=24 (mean age=19 months)	1. Short Sensory Profile (SSP)	1. Autism Diagnostic Interview- Revised (ADI-R) 2. Autism Diagnostic Observation Scale (ADOS) 3. Mullen Scales of Early Learning (MSEL) 4. Vinelands Adaptive Behavioural Scale (VABS)	TD group matched on mental age using MSEL. Mothers completed SSP, and children were administered other tests by researcher.	1. 'Definite' sensory impairments in ASD and FXS, but not DS, TD or DD. 2. Participants with FXS had more difficulties in low weak energy/weak muscles compared to all other participants and participants with ASD had more difficulties with taste/smell sensitivity compared to all other participants. 3. ASD more repetitive behaviours than FXS- more likely to identify between groups, rather than SP. 4. Difficulties in SP were associated with a clinical diagnosis of ASD or FXS, rather than IQ or developmental delay, except for FXS. 5. No significant relationship between social-communication scores and sensory scores in ASD, DD and TD, except for FXS. Results indicate those with co-morbid ASD and FXS had more SP difficulties. 6. Relationship between more SP

Authors (Year)	Participants	Sensory Assessment	Additional Assessments	Procedure	Results/Conclusion
					difficulties and lower adaptive functioning, stronger relationship, than ASD severity, although only 4%. 7. Substantial correlation between SP, ADOS repetitive and restrictive scores, provides independent validation of parent questionnaire data.
Smith, Hildenbrand and Smith, (2009)	Thirty-seven-month-old female twins, one with Smith-Magenis syndrome, one typically developing.	1. Sensory Profile (SP)	1. Sensory Profile (SP) 2. Brief Assessment of Motor Function (BAMF) 3. Peabody Developmental Motor Scales, second edition (PDMS-2) 4. Paediatric Evaluation of Disability Inventory (PEDI)	Occupational therapist administered SP, BAMF (fine motor scale) and PDMS-2 (fine motor scale) and physical therapist administered BAMF (lower extremity gross motor scale) and PDMS-2 (gross motor subset) and PEDI.	1. Twin with SMS- 'typical' sensory processing in visual processing, touch processing, behavioural outcomes of sensory processing and items indicating thresholds for responses. 2. Twin with SMS- 'probable' difference in auditory and vestibular processing. 3. Twin with SMS- 'definite' differences in multisensory and oral processing. More difficulty with high threshold items. 4. Twin with SMS- 'probable' to definite' differences in all items of modulation and 'typical' emotional/ social responses. 5. TD twin- 'typical' sensory processing. 6. SMS twin- more difficulties in fine and gross motor tasks. 7. SMS twin- more difficulty in visual-motor integration. 8. SMS twin- more difficulties in self-care, mobility and social function.
Tierney, Nwokoro, Porter, Freund, Ghuman,	n=56 individuals with Smith-Lemli-Opitz Symdrome	1. Sensory Profile (SP)	1. Questions to parents about their concerns and cholesterol supplementation. 2. Screen for Social	Parents completed questionnaires and researchers completed	1. SSI (n=13), compared to aged matched TD, Autism and DD, SLOS less difficulties than Autism group and same level as DD group. 2. Nisonger CBRF (n=31), 3%

Authors (Year)	Participants	Sensory Assessment	Additional Assessments	Procedure	Results/Conclusion
and Kelley (2001)	(SLOS), n=31 male, (age range= three-months to 32.4 years, mean age= 7.8 years) Data used from previous research studies for individuals with Autism, Aspergers, ADHD, FXS, DD and TD.		Interaction (SSI) 3. Nisonger Child Behaviour Rating Form-parent version (Nisonger-CBRF) 4. Infant Toddler Symptom Checklist (ITSC) 5. Temperament and Atypical Behaviour Scale (TABS) 6. MacArthur Communicative Developmental Inventory (MacArthur CDI) 7. Autism Diagnostic Interview-Revised (ADI-R) 8. Parenting Global Rating Form- question asking if the child's behaviour had improved since receiving cholesterol supplementation.	interviews and assessments. Comparison data from other research studies.	hyperactive (>85th percentile) and 19% self injury/stereotypic. 3. ITSC- (n=8) No children under twenty-two-months had impairment, but all older did show regulatory disorder. 4. TABS- (n=11) Compared to TD, Autism and DD and FSX. SLOS more dysfunction of temperament and self-regulation than TD, DD but less than Autism and FXS. SLOS more dysfunction of sleep and self-soothe than TD, Autism, FXS and DD. Total score- 36% SLOS higher than FXS and 18% higher than Autism. 5. SP (n=35) Comparison to normative data, Autism, Aspergers, ADHD and DD. Auditory, oral, tactile and visual processing difficulties greater than 2SD from TD. Visual processing- n=30 SLOS greater than TD, ADHD, Asperger, Autism and DD. 6. McArthur CDI, (n=49), 78% expressive language age 30 months or less and 79% receptive language ages 16 months or below. 7. ADI-R (n=17), 53% met criteria for Autism 8. Parent Global Rating Scale- (n=38), 75% believed cholesterol supplementation had a very positive effect on average.
Walz and Baranek (2006)	n=340 individuals with	1. Sensory Experience Questionnaire	1. Parent report of genetic subtype	Parents completed the questionnaire.	1. 75% abnormalities in sensory processing, mostly in hypo-responsiveness to tactile and vestibular

Authors (Year)	Participants	Sensory Assessment	Additional Assessments	Procedure	Results/Conclusion
	Angelman Syndrome (mean age= 10.98 years, range= three-twenty-two-years).Including Maternal deletion of 15q11.2-q13 n=203, Paternal uniparental disomy n=25.	(SEQ)			input- 'sensory seeking'. 2. Most hyper-responsive behaviours-mixed sensory response styles within same individual. 3. More difficulties compared to normative data. 4. Hyper-responsiveness behaviours highly inter-correlated. 5. Hypo-responsiveness behaviours highly inter-correlated. 6. Hypo-behaviours slight decrease with age. 7. Hyper-behaviours not related to age and persist into adolescence. 8. No relationship between seizures, gender and genetic subtype (maternal deletion and paternal uniparental disomy) and sensory experience.
Wuang, and Su (2011)	n=246 children met criteria n=206 agreed to participate (average age=eight-years, one-month) Down Syndrome. Divided into three age groups: 1. Young (six-eight- years),	1. Sensory profile (SP)	1. Demographic Questionnaire 2. Hooper Visual Organisation Test (HVOT) 3. Wechsler Intelligence Scale for Children (WISC) 4. Vineland Adaptive Behaviour Scale (VABS) 5. School function assessment (Chinese version)	Parents and teachers completed questionnaires and children were administered the HVOT and WISC by researchers.	1. Poorer visual organisation ability in DS compared to normative data on HVOT, although was age related improvement. There were significant correlations between HVOT and VABS and SFA, showing relationship between visual ability and activity performance. 2. Difficulties in sensory processing and modulation (low energy/ weak, under-responsive/ seek sensation, auditory processing and tactile sensitivity), compared to normative data, although age-related improvements. 3. Sensory processing related to hypotonia. 4. Sensory processing difficulties related

Authors (Year)	Participants	Sensory Assessment	Additional Assessments	Procedure	Results/Conclusion
	2. Middle (nine-ten-years), 3. Old (eleven-thirteen-years).				to lower participation in school activities and poorer adaptive behaviours, due to less responsivity to sensations. 5. IQ related to sensory processing (small effect). 6. No effect of age or sex on SP.

Assessment Methods

The research articles used a number of different methods to assess sensory modulation (Table 1.5). The most frequent assessment method was the Sensory Profile (SP; Dunn, 1999) and the Short Sensory Profile (SSP; Dunn, 1999). These assessments are parent/carer questionnaires, which assess their childs sensory responses to everyday functioning. The questionnaire has normative data for both individuals with ASD and TD individual's aged three-years to fourtten-years-old, has good discriminative validity (McIntosh, Miller and Shyu, 1999) and internal consistency (Dunn, 2006). The Sensory Experience Questionnaire (SEQ; Baranek, 1999c) is similiary a parent/carer questionnaire, which was used by two research articles. The questionnaire assessess children's sensory behaviours across a range of modalities and response patterns, which also has good psychometric properties (Baranek, David, Poe, Stone and Watson, 2006). Additional parent questionnaires/interviews included the Behaviour and Sensory Intrests Questionnaire (BSI; Hason et al., 2016), Parental Questionnaire (PQ; Bruni, Cameron, Dua and Noy, 2010) and the Assessment of Sensory Processing, Repetitive Behaviour, Anxiety, and Fear in Williams Syndrome-Semi Structuted Interview (SRAF-SSI; Janes, Riby and Rogers, 2014).

Other studies used observational methods including the Sensory Processing Assessment for Young Children (SPA; Baranek, 1999b), Test of Sensory Function in Infants (DeGangi and Greenspan, 1989), Tactile Defensiveness and Discrimination Test-Revised (TDDT-R; Baranek, 1997), and Sensory-Approach-Avoidance Rating (SAAR; Baranek et al., 2002). These assessments coded childrens behaviour including their play and engagement with their sensory environments.

Three articles used physiological response methods, including measurement of body movements, skin readings, balance and heart activity, which are reported to have questionable validity (Hessl et al., 2002). Furthermore, other studies used experimental methods including the Sensory Organisation Test (SOT; Guskiewicz, 2001) and the Sensory Challenge Protocol (SCP; Miller et al., 1999).

Overall, the quality of the assessments used varied considerably with some established assessments demonstrating high validity and reliability, whilst others were specifically designed for the research article and, therefore were exploratory and lacked psychometric properties (Table 1.5).

Table 1.5: ***Descriptions of the Assessment Methods used by the Research Articles.***

Assessment	Authors (Year)	Number of Studies in the Review Using the Assessment	Description	Normative Data	Validity	Reliability
Behaviour and Sensory Interests Questionnaire (BSI)	Hason, Sideridis, Jackson, Porche, Campe and Huntington (2016)	1	A 174-item semi-structured interview designed to assess type, frequency, intensity, age of onset and duration of unusual behaviours and sensory interests in children >18months old with DD and ASD. It contains two factors including repetitive and sensorimotor behaviours and insistence on sameness. It contains seven subsections including stereotyped behaviours, unusual sensory interests/aversions, compulsive and ritualistic behaviours, rigidity, aggression/self-injurious behaviour, language perseverations and perseverative interests. It includes codes for 'current' and 'ever' and asks age of onset of behaviours to detect change over time. Other items asked parents/carers to report if behaviours are present and are coded zero 'behaviour of that type not currently present' – three 'marked mannerisms of type specified associated with social impairment and/or distress when interrupted. There are also additional codes when these codes are not applicable. Training is necessary before the interview can be administered and scored.	Normative data for individuals two to twenty-four-years-old with ASD, DD and TD.	Discriminant validity good between individuals with ASD and TD (sensitivity= 72-80%, specificity= 44-77%).	Internal consistency for repetitive and sensorimotor behaviours= .83 and for insistence on sameness= .73. Test-retest reliability= .95, inter-rater reliability=.95 (Hason et al., 2016).
Computerised Dynamic Posturography performed on NeuroComEqite	Guskiewicz (2001) NeuroCom International , 2001).	1	The system is a form of posturography and measures the body's movement and balance in response to different sensory manipulations including; somatosensory, visual and/or vestibular conditions. The	Condition 1 used as baseline data, no normative data.	Guskiewicz, Riemann, Perrin and Nasher (2001) and Shumway-Cook and	Wrisley et al (2007) used healthy adult participants and reported a

Assessment	Authors (Year)	Number of Studies in the Review Using the Assessment	Description	Normative Data	Validity	Reliability
system using the Sensory Organisation Test (SOT)			system was designed for use on adult's eighteen to sixty-five-years-old. The SOT contains six different conditions each lasting twenty-seconds. It determines the participant's ability to rely on other senses to compensate sensory misconceptions/errors. Condition one provides accurate vestibular, visual and somatosensory information. Condition two provides accurate vestibular and somatosensory information and compromised visual sensory information. Condition three provides accurate vestibular and somatosensory information and compromised visual information. Condition four provides accurate vestibular and visual information but compromised somatosensory information. Condition five provides accurate vestibular information and compromised somatosensory information. Condition six provides accurate vestibular information and compromised visual and somatosensory information. The score is the weighted average of postural stability scores in each condition.		Woollacott (2006) report the NeuroCom device is a valid instrument for assessing balance in healthy adults. Whitney, Marchetti and Schade (2006) reported composite scores <38 can identify repeat fallers (sensitivity=53%, specificity=87%) and that scores were significantly related with reported falls history. Cohen and Kimball (2008) reported sensitivity= 85% and specificity= 77% for adult participants with vestibular conditions.	standard error of measurement= 2.81, composite score reliability= .67 and individual equilibrium scores =.35—0.79. Ford-Smith, Wyman, Elswick, Fernandez and Newton (1995 reported test-retest reliability=.66)
Heart Activity-Inter-beat Interval	-	1	Inter-beat-interval (IBI) used to measure arousal and vagal tone (measure of neural regulation of heart activity associated with	Baseline heart activity prior to assessment is	Lack of correlation between IBI and vagal tone with	-

Assessment	Authors (Year)	Number of Studies in the Review Using the Assessment	Description	Normative Data	Validity	Reliability
(arousal), Vagal Tone (neural activity)			parasympathetic influences. The heart activity was collected, edited and analysed following validated procedures (Roberts, Boccia, Bailey, Hatton and Skinner, 2001).	used as comparison data.	SPA TSFI (Baranek et al., 2008). Arousal may be related to anxiety (Hessl et al., 2002).	
Parental Questionnaire (PQ)	Bruni, Cameron, Dua and Noy (2010)	1	A thirty-three-item parent/carer completed questionnaire designed to supplement the SP with additional information. Questions ask parents to state the frequency of sensory behaviours and presence of medical difficulties. There are additional open-ended questions regarding the impact of sensory symptoms on occupational performance in daily life and related strategies parents use to manage the child's sensory behaviours. Also parents have to rate to what degree of impact sensory symptoms have on daily life, from 'not at all' to 'significantly'. It contains nine themes including; seeks sensor stimulation, intolerance to touch during activities of daily living, avoidance of environmental triggers, routines and transitions, developmental phases, attention and engagement, independence and inclusion, communication and time, and activity level. The last 4 themes do not relate to sensory processing.	-	-	-
Sensory Challenge Protocol (SCP)	Miller et al (1999)	1	A laboratory experiment, in which experimenters present a range of different sensory stimuli in a pretend 'space ship', whilst recording skin conductance-electrodermal readings (EDR). It includes ten contiguous trials of five sensory	Own recording of EDR at baseline level used as comparison. No normative data.	Individuals with anxiety also show abnormal EDR activity, including failure to habituate to stimuli	-

Assessment	Authors (Year)	Number of Studies in the Review Using the Assessment	Description	Normative Data	Validity	Reliability
			domains; olfactory, auditory, visual, tactile and vestibular. Each sensory stimulus is presented for three seconds and with a recorded set of instructions. The olfactory stimulus was wintergreen oil placed 2.5cm from the participant's nose. The auditory stimuli were recorded fire engine sirens placed at ninety decibels. The visual stimuli were a twenty watt-strobe light with ten flashes per second. The tactile stimulus was a cloth finger puppet with a feather placed on the participant's ears and chin. The vestibular stimulus involved the experimenter tipping the participant back at a thirty-degree angle. EDR recordings are quick phasic changes imposed on shifts in tonic level in conductivity (Fowles, 1986). They are recorded at baseline (before sensory stimuli), during exposure and afterwards (habituation). Hypo-responsiveness indicated by decreased amplitude of EDR.		(Boucsein, 1992)	
Sensory Experience Questionnaire (SEQ)	Baranek (1999c)	2	A 105-item parent report questionnaire to assess sensory symptoms in children aged two to twelve- years. It assesses frequency of sensory behaviours across sensory response patterns, modalities and social and non-social contexts. The first ninty-seven items assess frequency of sensory behaviours on a five-point Likert scale ranging from 'almost never' to 'almost	ASD normative data being developed (Ausderau, Sideris, Little and Baranek, in preparation). Well validated in TD children, ASD	Good discriminative validity as can identify the unique sensory pattern for ASD from TD children or DD (Baranek, David, Poe, Stone and	High internal consistency for each modality, Cronbach's alpha for hyper-responsivity= .73, hypo-responsivity= .75, sensory-

Assessment	Authors (Year)	Number of Studies in the Review Using the Assessment	Description	Normative Data	Validity	Reliability
			always'. The final eight questions are not scored, but give qualitative contextual information. A total score is given, plus sub-scores for four types of sensory patterns including; hyper-responsivity, hypo-responsivity, sensory-seeking and enhanced perception, and scores for each of the five modalities including; auditory, visual, tactile, gustatory and vestibular, and a score for social and non-social contexts. A higher score indicates more severe sensory symptoms.	and DD (Baranek, David, Poe, Stone and Watson, 2006).	Watson, 2006). The SEQ in combination with other sensory assessments has been used to validate sensory patterns and assess their unique association with repetitive behaviours (Boyd et al., 2010) and social communication difficulties (Wason et al., 2011). The factor structure implies a distinct construct that significantly correlated (r=.19-.77; Ausderau, Sideris, Little and Baranek, in preparation).	seeking= 80, social= .69 and non-social= .78.
Sensory Profile (SP)	Dunn (1999)	5	125-item parent/proxy questionnaire, which assesses children's responses to sensory stimuli and their impact on everyday functioning. On a five-point Likert scale assessing the frequency of behaviours from 'always' to 'never'. The questionnaire contains fourteen categories, although, Dunn	TD and ASD, 3-14 years old	Good convergent validity with the School Function Assessment (Dunn, 1999)	Cronbach's alpha internal consistency = .47-.91 and the standard error of measurement= .8-.9 (Dunn,

Assessment	Authors (Year)	Number of Studies in the Review Using the Assessment	Description	Normative Data	Validity	Reliability
			(2006) recommends use of the four quadrant scores, which coincide with the model. A lower score indicates greater difficulties. It provides published cut-off scores;< 1SD below the mean= 'typical', ≥1SD below the mean= 'probable difference', ≥2SD below the mean= 'definite difference			2006).
Sensory-Approach-Avoidance Rating (SAAR)	Baranek et al (2002)	1	An observational measure in a naturalistic context, which assesses level of engagement with sensory toys. Items were selected based on Dunn's (1997) model. The child is presented with nine novel multisensory toys, selected by the authors. The toys had a minimum of three interactive sensory properties and included primary features of three tactile, three auditory, one visual and two vestibular. The child's level of approach and avoidance was observed and rated on a three-point scale from 'engages-approaches' to 'avoids engagement-aversion' for each toy.	-	Inter-observed agreement reported to .98 (Baranek et al., 2002).	The authors reported the SAAR significantly correlated with the TDDT-R internal-control score (r=.62), however, not with external-control score (r=-.11) or the SSP (r=.09).
Short Sensory Profile (SSP)	Dunn (1999)	6	Thirty-eight- item parent/proxy questionnaire, taken from the SP. Questions organised into seven categories; tactile sensitivity, taste/smell sensitivity, movement sensitivity, under responsive/seeks sensation, auditory filtering, low energy/weak and visual/auditor sensitivity.	TD and ASD three to ten-years-old	Strong discriminate validity, as it is able to distinguish > 95% of children with and without sensory symptoms (McIntosh, Miller and Shyu, 1999).	Strong inter-rater reliability (Dunn, 2005). Cronbach's alpha for the total score ranges from .90-.95 for the normative sample (Dunn, 1999).

Assessment	Authors (Year)	Number of Studies in the Review Using the Assessment	Description	Normative Data	Validity	Reliability
Tactile Defensiveness and Discrimination Test-Revised (TDDT-R)	Baranek (1997)	1	Standardised, structured, behavioural observation assessing tactile sensitivity, which contains two subscales. The externally controlled subscale involves the examiner touching the child with stickers or a finger puppet and assessing their response. The internally controlled subscale assesses child's responses to their own initiated exploration of tactile toys. The child's responses are measured on a four-point scale e.g. hyper-responsive behaviours (avoidance, negative affective reactions), seeking-behaviours (excessive engagement, strong positive affective reactions). Overall scores calculated by averaging scores according to the manual. Higher scores indicate greater tactile sensory difficulties. The assessment needs to be administered by trained professionals, video-recorded and inter-observer reliability checked.	No TD normative data, although validated in children with DD and ASD, ages two to fourteen-years (Baranek and Berkson, 1994; Watson et al., 2011)	Good inter-observer reliability reported=0.951 (Sensory defensiveness) and 0.904 (seeking-behaviour) (Foss-Feig, Heacock and Cascio, 2012). Total inter-observer reliability ≥ .90 (Baranek et al., 2002).	-
Test of Sensory Function in Infants (TSFI)	DeGangi and Greenspan, (1989)	1	A twenty-four-item observational assessment of sensory symptoms. Assesses five sensory functions including reactivity to tactile deep pressure, visual-tactile integration, adaptive motor responses, ocular-motor control and reactivity to vestibular stimulation. Designed for children four-months to eighteen-months-old with regulatory disorders. Scores classify children as 'normal', 'at risk' or 'deficient' in each of the five sections. A lower score indicates greater severity of sensory symptoms,	Norms for TD children with regulatory disorders.	The authors suggest the assessment is most valid for children >7 months old and can used for children >10 months old if they had a DD.	Test-retest reliability for TD children, Pearson correlation coefficient for the total r=.81 and for the 5 subtests r=.26-.96 (DaGangi and Greenspan, 1989).

Assessment	Authors (Year)	Number of Studies in the Review Using the Assessment	Description	Normative Data	Validity	Reliability
			although, reversed scoring used by Baranek et al., (2008).			Lower test-retest reliability reported in the 'borderline' range for children with DD, Pearson correlation for the total r=.78 and for the 5 subtests r=.54-.74 (Jirikowic, Engel and Dietz, 1997).
The Assessment of Sensory Processing Repetitive Behaviour, Anxiety, and Fear in Williams Syndrome-Semi Structured Interview (SRAF-SSI)	Janes, Riby and Rogers (2014)	1	A twenty-nine-item semi-structured interview delivered to parents. It was developed after considering other resources including the ADI (Lord, Rutter and Le Couteur, 1994) and the sensory modulation literature. The sensory section covers seven different features including; tactile hypersensitivity and hyposensitivity, proprioception, visual hypersensitivity and hyposensitivity; auditory hypersensitivity and hyposensitivity, gustatory features and olfactory features. Each question includes a description of the target behaviour and parents are asked if the behaviours displayed by their child and described in what way. Also asked to indicate on a five-point Likert scale the frequency and intensity of the behaviour and if it has changed over time.	-	-	-

Assessment	Authors (Year)	Number of Studies in the Review Using the Assessment	Description	Normative Data	Validity	Reliability
The Sensory Processing Assessment for Young Children (SPA)	Baranek (1999b)	1	A semi-structured, play-based observational assessment of sensory symptoms in young children. Observers have to code children's responses based on four scales including; play with novel toys (rates hyper-responsivity and sensory-seeking behaviours), habituation (responses to repeated sensory stimuli), orienting (hypo-responsivity) and stereotyped behaviours (marked as observed or not). Designed for children with ASD or DD aged nine-months to six-years-old.	Used on children with DD and ASD (Boyd et al., 2010).	-	-

Quality Review

A quality framework was developed to guide evaluation of each research article to consider the value of the conclusions made across studies. A pre-existing broad quality framework was not used due to the need for the assessment to focus on specific features considered important to research in rare genetic syndromes. Richards et al., (2015) developed a quality framework used in the meta-analysis of ASD in rare genetic syndromes, which considered the sample identification of participants, the confirmation of the syndrome and the assessment method used. These quality criteria were used and adapted for the purposes of this review. The additional quality criteria were developed by reviewing the literature on critical appraisals (Young and Solomon, 2009), sensory modulation (e.g. Ben-Sasson et al., 2009; Schaaf and Lane, 2015), standardised quality frameworks for intervention studies (Downs and Black, 1998) and observational studies (CASP, 2014; Von Elm, Altman, Egger, Pocock, Gotzsche and Vandenbroucke, 2007) (see Appendix 3 for the explanation and description of additional items).

Additional criteria included evaluation of the comparison group/data, confounding variables and developmental changes. In line with Richard et al., (2015), criteria were colour-coded (red (0)= poor, yellow (1)= adequate, amber (2)= good, green (3)= excellent). Total and mean calculations and mean colour codes are reported for each research article and each criterion to help visually summarise the overall quality of the research. However, it is noteworthy each criterion is arguably not equally important to the validty of the research. Furthermore, the evaluation checked that p values were reported (Downs and Black, 1998, question ten) (Table 1.6).

Table 1.6: ***The Quality Assessment Framework.***

Table 3	0 Poor	1 Adequate	2 Good	3 Excellent
Sample Identification	Not specified/ reported Not confirmed/ reported	Single restricted or non-random sample e.g. a specialist clinic or previous research study. Single regional sample e.g., a regional parent support groups.	Multiple restricted or non-random samples e.g., multi-region specialist clinics. National non-random sampling e.g., national parent support groups.	Random or total population sample.
Confirmation of Syndrome	Clinical diagnosis only suspected	Clinical diagnosis by 'generalist' e.g. General Practitioner or Paediatrician.	Clinical diagnosis by 'expert' e.g., Clinical Geneticist or Specialist Paediatrician.	Molecular/Cytogentic/ Metabolic confirmation of diagnosis.
Sensory Assessment	Not specified/ reported Clinician judgement only	Assessment methodologies, which have not been validated in previous research e.g. methods specifically designed for the research paper. Validated or previously used assessments, which have not been used on individuals with ID or ASD or are being used out of the normative age range.	Validated assessment measures, which have been validated or previously used on individuals with ID or ASD and are being used on participants in the normative age range, includes physiological data.	Consensus from multiple assessments and that *at least one* of these assessments would have obtained a score of 2 in isolation.
Comparison Group	No comparsion group or data	Published normative data only or published data in other research articles.	Use of one or more comparison group, TD, ID, or another syndrome group recruited by the paper	Age, ID or different syndrome / difficulty matched comparison group recruited by the paper.
Confounding Variables	Not reported	At least one known confounding variable assessed, e.g. age, ID, repetitive behaviours, social communication, but only used to describe participant sample.	At least one known confounding variable assessed and the relationship between constructs were considered e.g. correlational analysis between sensory modulation and repetitive behaviour assessment or age, functional ability. However,	At least one known confounding variables assessed and controlled for in analysis or used in direct analysis (non-correlational) to determine the interaction between different domain

			confounding variables were not controlled for in sensory analysis.	and sensory modulation.
Developmental Changes	Not reported	Retrospective developmental data. or correlational data analysed between age and sensory modulation.	Comparison across specific age ranges with the same syndrome.	Longitudinal data collected from multiple assessments from same participants.

The results of the quality review are displayed (Table 1.7). One research article did not report the sample identification, whilst ten recruited from a single regional sample and five recruited from multiple or national samples. Therefore, the overall quality of the sample identification was considered 'adequate' (mean score=1.38). Four research articles did not report how confirmation of the genetic syndrome was established and one study established the syndrome by the view of a general practitioner. However, genetic testing was used in eleven studies, thus overall syndrome confirmation across the studies were considered to be 'good' (mean score=2.13). Five research articles used assessments that were not validated or that had been validated but used out of the normative sample, nine used a valid sensory assessment in the age range of the normative data. Yet, only two studies used multiple established methodologies. The results of the evaluation criteria found the sensory assessmens to be 'good' (mean total=1.94). Nine research articles compared sensory assessment data to normative samples, whilst seven had the advantage of using matched comparison groups, Thus sudies were rated as 'good' (mean score=2.06). Furthermore, five research articles described possible confounding constructs to describe participants, three studies considered the relationship between these constructs and eight controlled for confounding constructs in the sensory analysis. The assessment of confounding variables across studies was also considered 'good' (mean score=2.13). The majority of studies (n=10) neglected to report developmental changes, three studies displayed retrospective data, one study made comparisons across age groups and three used a longitudinal method. Therefore, the overall assessment of developmental changes were considered to be 'poor' (mean score=0.63). Finally, three studies failed to provide precise p values.

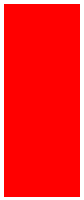
Table 1.7: ***Results of the Evaluation Criteria Applied to the Research Articles.***

Authors (Year)	Sample Identification	Confirmation of Syndrome	Sensory Assessment	Comparison Group/ Data	Confounding Variables	Developmental Changes	P Value reported[9]	Total Score	Mean Total Score	Mean Total Colour	Comment
Baranek, Chin, Greiss, Hess, Yankee, Hatton and Hooper (2002)							No	12	2		Many significant findings are dependent on the SAAR assessment, which is the invalidated observational assessment. TDDTR and SAAR= 90-98% agreement.
Baranek, Roberts, David, Sideris, Mirrett, Hatton and Baily (2008)							Yes	15	2.5		SEQ used out of age range. SPA and TSFI subscales= 87-95% and 82-96% agreement.
Bruni, Cameron, Dua and Noy (2010)							N/A	6	1		Descriptive analysis only. PQ used qualitative constant comparative analysis to identify themes. No inter-rater reliability checked. No information about syndrome confirmation
Hildenbrand and Smith (2011)							Yes	6	1		Lack of information recruitment, just that participants were part of an on-going SMS study.
Horvat, Croce and Zagrodnik (2010)							Yes	6	1		Syndrome identified using school education plans. Assessment not validated on individuals with ID and no ID normative data.

[9] Have the actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is <0.001 (Down and Black, 1998; question 10).

Authors (Year)	Sample Identification	Confirmation of Syndrome	Sensory Assessment	Comparison Group/ Data	Confounding Variables	Developmental Changes	P Value reported[9]	Total Score	Mean Total Score	Mean Total Colour	Comment
Janes, Riby and Rogers (2014)							N/A	11	1.83		Descriptive analysis only. Thematic analysis and frequency counting used to analyse the SRAF-SSI. The relationship between confounding variables and developmental changes were based on the SRAF-SSI only and is the invalidated interview assessment.
John and Mervis (2010)							Yes	10	1.67		Lack of information about recruitment, just that participants were part of an on-going study in WS.
Mieses et al., (2016)							Yes	12	2.00		Comparison groups differed on sex and marginal difference in age. SP used out of age range
Miller, McIntosh, McGrath, Shyu, Lampe, Taylor, Tassone, Neitzel, Stackhouse and Hagerman (1999)							No	10	1.67		For twelve participants, KIDCal was unable to locate baseline, thus, analysis set the baseline at which most responses bottomed out over the entire data collection period. Also, for three participants, the analysis adjusted the baseline due to artefact. Cronbach's alpha for magnitude and number of peaks= .94 and .92.
Peters, Horowitz, Barbieri-Welge, Taylor and Hundley (2012)							Yes	15	2.50		Sensory-seeking behaviours corrected for skewing, although sensory aversions could not be due to considerable skewing.

Authors (Year)	Sample Identification	Confirmation of Syndrome	Sensory Assessment	Comparison Group/ Data	Confounding Variables	Developmental Changes	P Value reported[9]	Total Score	Mean Total Score	Mean Total Colour	Comment
Riby, Janes and Rogers (2013)							Yes	11	1.83		SP and RBQ Cronbach alpha >.8= good reliability.
Rogers, Hepburn and Wehner (2003)							Yes	10	1.67		Lack of details about recruitment, but part of a larger trial. SSP used out of age range. ADOS and ADI-R= 80-85% agreement. Preliminary analysis revealed no significant differences in mental functioning or sensory modulation between DS and DD, thus, groups collapsed into one group. Corrections made for non-normality of SSP.
Smith, Hildenbrand and Smith, (2009)							N/A	6	1.00		Descriptive analysis only. SP used out of age range. No information about syndrome confirmation
Tierney, Nwokoro, Porter, Freund, Ghuman, and Kelley (2001)							N/A	7	1.17		SP used out of age range Comparison to published data for individuals with TD, Autism, Asperger's, DD and ADHD Descriptive analysis only
Walz and Baranek (2006)							No	9	1.5		No information about confirmation of the syndrome, but recruited through AS support group and parents reported genetic subgroup. SEQ used out of normative age range. Correlational analysis between age and sensory modulation. No separate demographic data given for each genetic subtype. Comparison between maternal deletion and parental-uniparental disomy.

Authors (Year)	Sample Identification	Confirmation of Syndrome	Sensory Assessment	Comparison Group/ Data	Confounding Variables	Developmental Changes	P Value reported[9]	Total Score	Mean Total Score	Mean Total Colour	Comment
Wuang and Su (2011)							Yes	8	1.33		Lack of information about where participants were recruited from, although the authors did explain that they used a purposeful sampling method.
Total Score	22	34	31	33	34	10					
Mean Score	1.38	2.13	1.94	2.06	2.13	0.63					
Mean Total Colour											

Discussion

Angelman Syndrome

Two studies examined sensory modulation in individuals with AS (Peters et al., 2012; Walz and Baranek, 2006). Both articles used assessments, which have been validated in individuals with ID and both studies made use of good genetic subtype comparison groups. Peters et al., (2012) completed a longitudinal comprehensive assessment of a range of confounding variables including cognitive ability, adaptive functioning, ASD phenomenology and maladaptive behaviours. The research was considered to be 'excellent' by the quality review framework, thus the Peters et al., (2012) paper should be considered more methodologically sound and results should be considered more valid.

Walz and Baranek (2006) reported 75% of individuals with AS had sensory modulation difficulties in comparison to TD normative data, especially hypo-responsivity to tactile and vestibular input. Difficulties in sensory modulation were also found by Peters et al., (2012), although the BSI does not provide specific scores in each modality. Peters et al. (2012) reported no differences between class 1 and class 2 genetic subtypes[10] in cognitive and adaptive functioning, and both genetic subgroups improved with age. However, individuals with class 1 deletions had greater social impairment, were more likely to exceed ASD cut-off scores and display more repetitive behaviours than class 2 deletions, which did not change over time. Despite this, there were no differences in sensory modulation over time or between deletion classes,

[10] Deletion breakdown was established by microarray-based genomic hybridization using chromosome 15 specific bacterial artificial chromosome. Class 1 deletions are larger and extend from BP1 to PB3. Class 2 deletions are smaller and extend from BP2 to PB3. Larger deletions extending from BP4 to PB5 were excluded.

however, there was a trend towards increased sensory-seeking with age. Similarly, Walz and Baranek (2006) found no differences between maternal deletion and parental-uniparental disomy deletion classes in sensory modulation. However, in contrast, they reported hypo-responsivity decreased with age, where hyper-responsivity was not related to age. Overall, both papers report individuals with AS have sensory modulation difficulties, specifically, sensory-seeking/hypo-responsivity with no differences between genetic subtypes, although they do not report consistent findings regarding age-related changes.

Sensory modulation difficulties are reported in mice with AS (Yashiro et al., 2009) and children with AS have been reported to have fascinations with tactile and oral stimulation (Williams, 2005; Williams et al., 2006). Thus, previous research supports Peters et al., (2012) and Waltz and Baranek (2006) findings of sensory-seeking/hypo-responsivity difficulties. However, research has reported low RRB in the AS phenotype (Thompson and Bolton, 2003), suggesting individuals are not using their own body movements to seek sensory sensations, which might have been expected due to the relationship between RRB and sensory modulation. It is possible their sensory-seeking is directed at specific tactile stimuli, such as a fascination with water (Clarke and Marston, 2000). Furthermore, it could be hypothesised that due to the high frequency of sensory symptoms, a higher proportion of individuals with AS may meet criterion B in the DSM-5 since the addition of sensory symptoms due to the lower frequency of RRBI.

Fragile X Syndrome

Four studies (Baranek et al., 2002; Baranek et al., 2008; Miller e al., 1999; Rogers, Hepburn and Wehner, 2003) investigated sensory modulation in FXS. Baranek et al., (2002) and Baranek et al., (2008) research is evaluated to be methodologically sound due to a more valid assessment of sensory modulation and consideration of more confounding variables. Baranek et al (2008) was the only study to assess developmental changes using a longitudinal design. However, Miller e al., (1999) and Rogers, Hepburn and Wehner (2003) were the only studies to use well-matched comparison groups. The quality review considered all studies to be 'good', except Branek et al., (2008), which was considered as 'excellent'.

Baranek et al., (2002) reported 'definite' differences in sensory modulation, although, did not provide differences for specific modalities. Furthermore, the authors reported varying levels of sensory difficulty assessed by the TDDT-R and SAAR. Higher levels of aversion/avoidance were related to less independence, less engagement at school and with play. Rogers, Hepburn and Wehner (2003) also reported 'definite' differences in sensory modulation, which, overall were more severe compared to sensory modulation difficulties in participants with ASD, DD, DS and TD. Participants with FXS had more difficulties in low weak energy/weak muscles compared to all other participants and participants with ASD had more difficulties with taste/smell sensitivity compared to all other participants. Sensory difficulties were related to a lower IQ, delayed development, lower adaptive functioning and more social-communication difficulties only for FXS participants. Furthermore, the authors reported that

participants with ASD had significantly more RRB compared to participants with FXS, which was more likely to identify the different syndrome groups.

Miller et al., (1999) concluded physiological responses indicated hypersensitivity difficulties across all modalities, as participants with FXS did not habituate to the repeated presentation of sensory stimuli. Furthermore, they concluded that participants with FXS had more sensory difficulties compared to those participants with FXM. These physiological findings in FXS have been supported by other research (Castren, Paakkonen, Tarkka, Ryynanen and Partanen, 2003; Rojas, Benkers, Rogers, Teale, Reite and Hagerman, 2001), although Baranek et al., (2008) found a lack of relationship between physiological measures and their other sensory modulation assessments, which, perhaps is explained by the difference in age between participants across groups. Baranek et al., (2008) also reported individuals with FXS have sensory modulation difficulties, which worsen from nine to eighteen-months-old. Specifically, hyposensitivity decreased or remained stable with age, whilst, hypersensitivity increased with age.

Baranek et al., (2008) concluded age, lower cognitive ability and motor skill difficulties impact on sensory modulation difficulties in different ways at different developmental stages. However, it is possible sensory difficulties in young children restrict their learning and engagement; therefore, as sensory difficulties improve, children may be more responsive to learning.

Overall, the research reviewed here and additional sensory processing literature (Cohen, 1995; Hagerman, 2002), suggests individuals with FXS specifically demonstrate hypersensitivity difficulties. This conclusion also supports the ASD symptomology research, which suggests individuals with FXS are less able to engage in social communication due to hypersensitivities (Roberts, Weisenfeld, Hatton, Heath and Kaufmann, 2007). However, Rogers, Hepburn and Wehner (2003) reported fewer RRBs, whereas, Wheeler et al., (2015) described frequent RRB in individuals with FXS, highlighting the consistencies across research. Furthermore, Wheeler et al., (2015) suggested fewer individuals with FXS meet criterion A of the DSM-5, yet more individuals meet criterion B; a suggestion which is supported by this review due to the high frequency of sensory modulation difficulties.

Williams Syndrome

Three studies (Janes, Riby and Rodgers, 2014; John and Mervis, 2010; Riby, Janes and Rodgers, 2013) investigated sensory modulation in WS. All studies used the SSP to assess sensory modulation. Two studies analysed the relationship between sensory modulation and confounding variables (Riby, Janes and Rogers, 2013; John and Mervis, 2010). Neither John and Mervis (2010) or Riby, Janes and Rogers (2013) assessed developmental changes, whilst Janes, Riby and Rogers (2014) used the SRAF-SSI to retrospectively consider age-related changes. All three studies were considered to be ‘good’ by the quality review.

Both Janes, Riby and Rogers (2014) and Riby, Janes and Rogers (2013) reported ‘definite’ differences in the total SSP in comparison to normative data, although they

did not report the precise results for each modality. Nevertheless, Riby, Janes and Rogers (2013) found that IQ was not related to sensory difficulties; yet, found more RRB were related to more sensory difficulties. Specifically; repetitive movement was related to tactile, taste/smell and under-responsive/seeks sensation, repetitive language was related to responsive/seeks sensation and sameness of behaviour was related to taste/smell sensitivity. Janes, Riby and Rogers (2014) also reported individuals had hyper-responsivity difficulties with vestibular, proprioceptive, auditory and gustatory stimuli, which impacted on daily life, although, improved over time. They reported typical sensitivity with tactile, visual and olfactory modalities. They also reported frequent RRB, which were often triggered by anxiety. Similarly, John and Mervis (2010) found over 90% had 'probable' to 'definite' differences in sensory modulation and specifically in auditory filtering, although they also reported specific difficulties in low/weak energy and under-responsive/seeks sensation. Furthermore, those individuals with more severe sensory modulation difficulties had more executive functioning, temperament, oppositional and functioning difficulties.

Despite, Riby, Janes and Rogers (2013) reporting no relationship between IQ and sensory modulation, John and Mervis (2010) concluded that sensory difficulties might be due to executive functioning deficits. This hypothesis has also been suggested in the literature (Gazzaley and D'Esposito, 2007; Gillbert and Burgess, 2008). The findings of auditory sensory modulation difficulties in WS are supported by the auditory processing research literature (Leyfer, Woodruff-Borden, Klein-Tasman, Fricke and Mervis, 2006; Marler, Elfenbein, Ryals, Urban and Netzloff, 2005), specifically,

auditory hypersensitivity to loud noises and auditory aversions (Levitin, Cole, Lincoln and Bellugi, 2005).

Riby, Janes and Rogers (2013) concluded that RRB occurs as a consequence of tactile under-responsivity and sensory-seeking, in an attempt to regulate their hypo-arousal. This relationship has also been suggested for individuals with ASD, whereby RRB are potentially used as a coping strategy to manage hypo-responsivity (Baker, Lane, Angley and Young, 2008; Chen, Rogers and McConachie, 2009; Leekam, Prior and Uljarevic, 2011). However, this relationship may also be accounted for due to the lack of construct validity and theoretical clarity between RRB and sensory modulation. Furthermore, Janes, Riby and Rodgers (2014) reported no tactile hyposensitivity difficulties. The review suggests that due to the sociability of the behavioural phenotype and the high frequency of sensory symptoms and RRBs, individuals with William Syndrome are more likely to meet criterion B and not meet criterion of A of the DSM-5.

Down Syndrome

Three studies (Bruni, Cameron, Dua and Noy, 2010; Horvat, Croce and Zagrodnik, 2010; Wuang and Su, 2011) investigated sensory modulation in DS. None of the research used multiple validated sensory assessments and only Horvat, Croce and Zagrodnik (2010) made use of age-matched comparison groups with mild ID and TD. Wuang and Su (2011) considered the most confounding variables and was the only study to investigate age-related changes and compared difficulties across three different age groups. The methodology used in all three studies is relatively weak in comparison

to the methodology examining other genetic syndromes, and was considered to be 'adequate' by the quality review, thus less valid conclusions can be made.

Bruni, Cameron, Dua and Noy (2010) reported 49% of participants had 'definite' and 25% of participants had 'probable' differences in sensory modulation. Both Bruni, Cameron, Dua and Noy (2010) and Horvat, Croce and Zagrodnik (2010) studies reported the most difficulties were in under-responsive/seek sensation, auditory filtering and low weak energy, whereas, there was 'typical' performance in taste/smell, movement and visual/ auditory filtering. However, Wuang and Su (2011) reported difficulties in tactile sensitivity, whereas Bruni, Cameron, Dua and Noy (2010) reported 'typical' tactile sensitivity. Wuang and Su (2011) further reported participants with DS had poorer visual ability, which was related to lower adaptive functioning and school functioning, and sensory modulation difficulties were related with more hypotonia, lower participation in school activities, poorer adaptive functioning and a slightly lower IQ, although there was no relationship between sensory modulation and sex and age. Bruni, Cameron, Dua and Noy (2010) also reported 55% of parents spent time trying to increase their child's participation and 37% of parents reported that their child's sensory difficulties had a moderate impact on daily life.

Horvat, Croce and Zagrodnik (2010) concluded individuals with DS and ID have balance difficulties when presented with inaccurate visual, somatosensory and vestibular information. Moreover, that both groups use sensory information differently compared to TD individuals, which results in movement difficulties, although this may partly be accounted for by low muscle functioning (Horvat, Ramsey, Amestoy and

Croce, 2003). The results are congregant with authors that suggest individuals with DS have sensory difficulties, which are related to slower reaction times and slower pre-motor activities (Davis, Sparrow and Ward, 1991). The authors suggest that these difficulties may also be explained by reduced cognitive abilities and are not specific to DS, as these motor-control difficulties are also seen in individuals with ASD (Vernazza-Martin et al., 2005). Thus, suggesting the sensory modulation difficulties displayed in DS are perhaps similar to those displayed by individuals with idiopathic ASD, which is supported by Moss, Richards, Nelson and Oliver (2012). However, reliable conclusions are difficult to establish due to the methodological weakness of the articles including no idiopathic ASD comparison samples and the lack of an established consistent sensory profile found across individuals with idiopathic ASD. It is also noteworthy that individuals with DS as a group perhaps display the lowest and less severe sensory modulation difficulties, which may partly explain the low percentage of individuals who have DS and ASD.

Phelan-McDermid Syndrome

One study (Mieses et al., 2016) investigated sensory modulation in PHMDS, which used the SSP questionnaire to assess sensory modulation. The study made use of an age, IQ and ASD comparison groups. The research controlled for sex, age and IQ, though did not investigate age-related changes in sensory modulation and was overall considered to be 'good'.

The results revealed 80% of children with PHMDS and 81% of children with ASD had 'probable' or 'definite' differences in sensory modulation. Children with

PHMDS displayed ‘typical’ performance in visual/auditory sensitivity, ‘probable’ differences in taste/smell sensitivity, auditory filtering, and movement sensitivity, ‘definite’ differences in under-responsivity and low-energy/weak. Children with PHMDS had significantly fewer difficulties with taste/smell sensitivity, visual/auditory sensitivity, auditory filtering and tactile sensitivity compared to children with ASD. However, children with ASD had significantly greater difficulties in low-energy/weak symptoms compared to children with PHMDS. There were no significant differences between children with PHMDS in movement sensitivity and under-responsivity. Thus, suggesting individuals with PHMDS have different sensory modulation profiles compared to those with ASD suggesting differences are a result of genetic conditions, rather than ID or ASD symptomology. However, ASD symptomology was not controlled for, although, 95% of individuals with PHMDS met criterion for ASD. To date, this is the only research to evaluate sensory modulation in PHMDS. Future research should examine the unique ASD symptomology in PHMDS (more social interaction difficulties) and their sensory profile. It is also suggested the ‘typical’ tactile sensitivity reported perhaps may explain the lack of RRB in the syndrome (Phelan and McDermid, 2012). However, due to the high sensory modulation difficulties individuals are more likely to meet Criterion B on the DSM-5 now sensory modulation difficulties have been included.

Smith-Magensis Syndrome

Two studies examined sensory modulation in individuals with SMS (Hildenbrand and Smith, 2011; Smith, Hildenbrand and Smith, 2009). Both studies used the SP to assess sensory modulation. Smith, Hildenbrand and Smith (2001) also used a

TD twin to aid comparison. Whilst both studies considered some confounding variables, neither study considered ID and ASD symptoms. Nevertheless, Hildenbrand and Smith (2011) used a longitudinal design and compared older and younger children to provide results about age-related changes, which was not offered by Smith, Hildenbrand and Smith (2009). It is noteworthy that Smith, Hildendrand and Smith (2009) research included a single participant with SMS, which significantly limits generalizability. Both studies were considered to be 'adequate' by the quality review.

Both studies reported 'definite' differences in registration, seeking, sensitivity and avoiding and 'probable' to 'definite' differences in all area of modulation in comparison to the TD normative data and the TD twin. However, Hillenbrand and Smith (2011) reported slightly more difficulties in behavioural and emotional responses compared to Smith, Hildenbrand and Smith (2009). The studies reported different outcomes in terms of specific sensory modalities, apart from both reporting 'definite' difficulties in multisensory processing and 'probable' differences in auditory processing. However, Smith, Hildenbrand and Smith (2009) reported 'typical' ability in visual and touch processing, whereas, Hildenbrand and Smith (2011) reported 'probable' and 'definite' differences. Moreover, Smith, Hildenbrand and Smith (2009) reported 'probable' differences in vestibular processing, although, Hildenbrand and Smith (2011) reported 'definite' differences. Additionally, Smith, Hildenbrand and Smith (2009) reported 'definite' differences in oral processing, whereas Hildenbrand and Smith (2011) reported 'probable' differences. Thus, Hildenbrand and Smith (2011) reported more sensory difficulties compared to Smith, Hildenbrand and Smith (2009), except for oral processing.

Furthermore, Smith, Hildenbrand and Smith (2009) reported more difficulties in fine and gross motor skills, visual-motor integration, mobility, social function and self-care for the SMS twin, compared to the TD twin. Hildenbrand and Smith (2011) reported stereotypic behaviours in less than 50% of participants and weak muscle tone in over 50% of participants, although the relationship between these difficulties and sensory processing was not considered.

Hildenbrand and Smith (2011) reported a trend for increasing difficulties with age, which, was significant for sensory-seeking. Moreover, they reported gender and age effects affecting emotional responses, in which older females had the most difficulties. This reported age-related change may explain the more severe sensory difficulties in their sample compared to Smith, Hildenbrand and Smith's (2009) participant. Moreover, the more severe difficulties in oral processing reported by Smith and Hildenbrand and Smith (2009) perhaps would be expected due to the participant being younger (thirty-seven-months-old), as children with ASD are also more sensitive to oral stimuli when younger (Dunn, 2001).

The research supports other anecdotal evidence of sensory modulation difficulties in SMS (Gropman, Duncan and Smith, 2006; Gropman, Elsea, Duncan and Smith, 2007; Hicks, Ferguson, Bernier and Lemay, 2008; Laje, Morse, Richter, Ball, Pao and Smith, 2010). However, there are inconsistencies in sensory profiles across modalities, making it difficult to determine how these sensory difficulties relate to their reported high levels of RRB, nevertheless support research which suggests their

associated constructs. Due to the high frequencies of RRBs it is suggested inclusion of sensory symptoms would not increase the number of individuals meeting criterion B in the DSM-5 criteria.

Smith-Lemli-Opitz Syndrome

One study (Tierney, Nwokoro, Porter, Freund, Ghuman and Kelley, 2001) assessed sensory modulation in SLOS using the SP. The results were compared against TD, Autism, Asperger's, DD and ADHD previously published research data, some confounding variables were considered, although, they did not examine age-related changes and was considered to be 'adequate' the quality review.

The authors reported that participants with SLOS had less social interaction, and temperament difficulties, although more difficulties in sleep and self-soothing than individuals with ASD. Furthermore, 53% of individuals met criteria for ASD, 78% had expressive language age equivalent of thirty-months or younger and 79% had receptive language age equivalent of sixteen-months or younger. The SP revealed that participants with SOLS had 'definite differences' in auditory, oral, visual and tactile sensory hyper-responsivity. The most severe difficulties were in visual processing, which was greater in comparison to individuals with ADHD, Asperger's, Autism and DD. To date, this is the only research to evaluate sensory modulation in SLOS, therefore, no conclusions can be made about the relationship between sensory modulation difficulties and their ASD symptomology, although the severity of the sensory modulation difficulties described suggest the individuals would meet criterion B of the DSM-5.

Conclusion

The review evaluated sixteen research articles examining sensory modulation in individuals with rare genetic syndromes associated with ASD symptomology and ID. The review has highlighted a range of sensory modulation difficulties across domains and syndromes. Whilst the sensory profile phenotype is more consistently described by better quality research in some syndromes, such as FXS and WS displaying predominantly hypersensitivity difficulties and AS predominantly displaying hypo-responsivity/sensory-seeking difficulties, there is a lack of research evidence to draw conclusions in other syndrome groups. Moreover, it is difficult to make comparisons of the sensory profile in genetic syndromes compared to that displayed in idiopathic ASD, due to the considerable inconsistency described in the ASD literature (Grapel, Cicchetti and Volkmar, 2015). This inconsistency could be a result of different sensory subtypes or a genuine range of sensory profiles due to internal and environmental interactions or a reflection of the inconsistencies in the research methodology, and sensory assessments lacking validation. It is also noteworthy that the systematic search found that a number of genetic syndromes, including Prader-Willi syndrome, Rett syndrome and CdLS had no research investigating the sensory profile of the syndrome, despite the high reported rates of ASD in these syndromes (Richards et al., 2015).

The review was also able to draw on the literature to hypothesise about how the DSM-5 criteria changes might impact on individuals with genetic syndromes and ASD. Firstly, it is suggested that individuals with FXS are more likely to meet criterion B due to their frequency of hyper-responsivity and less likely to meet criterion A due to their desire to communicate socially (Garrett et al., 2004). This suggestion is supported by a

large national study which found that fewer individuals met criterion A, yet a high percentages met criterion B, as a result, meant that significantly fewer individuals with FXS met criteria for DSM-5 (27.8%) compared to DSM-IV (38.7%) (Wheeler et al., 2015). Thus, it is proposed that individuals with FXS have a higher desire to communicate socially, but difficulties with hyper-sensitivity across modalities in the social environment, and social anxiety limit their communication ability (Cohen, 1995; Cohen, Vietze, Sudhalter, Jenkins and Brown, 1989; Roberts, Weisenfeld, Hatton, Heath and Kaufmann, 2007).

It is suggested that this profile of ASD symptomology and DSM-5 implications are perhaps similar for other syndromes which have a behavioural phenotype consisting of a lack of social communication difficulties such as SMS or for syndromes or an over approachable personality including AS and WS. Therefore, the DSM-5 may have led to a reduction in individuals meeting criterion A. However, the research highlights these syndromes would be more likely to meet criterion B, due to the high incidence of unusual sensory symptoms.

Individuals with DS are possibly less likely to meet both criterion A and B due to the lower frequency of social and sensory difficulties, which may reflect the low frequency of ASD symptomology in this group, although the research investigating DS had particularly weak methodology. In contrast individuals with PHMDS are perhaps more likely to meet both criteria due to the high frequency of sensory difficulties despite a lack of repetitive behaviour.

Clinical Implications

Clinicians need to be made aware of the lack of published, valid assessment tools, which have been specifically designed for individuals with ASD to evaluate sensory symptoms. Whilst it is acknowledged this task would be challenging due to the heterogeneity of individuals with ASD, this is an ongoing difficulty in the research literature due to a lack of standardised normative data for ASD populations (Hazen, Stornelli, O'Rourke, Koesterer and McDougall, 2014) [11].

It is recommended that assessments contain social and non-social items to isolate the role of sensory modulation difficulties in ASD, from the social communication symptoms. In addition, Schaaf and Lane (2015) suggested assessments need to be sensitive to age-related changes and to detect sensory symptoms in early development (2-5 years). Furthermore, that a comprehensive assessment should assess the frequency and type of sensory difficulties across multiple domains. Longitudinal assessments are also needed to measure sensory symptoms into adolescence and adulthood as these are a neglected research group. Furthermore, assessments should use multiple assessment methods, due to a lack of consistency between parent report measures and observations assessing the same sensory modality (Goldberg, Landa, Lasker, Cooper and Zee, 2000; Miller, Reisman, McIntosh and Simon, 2001). Specialist observations by clinicians are required to assess the underlying constructs displayed by specific behaviour, for example to observe if anxiety or sensory symptoms drive RRBI.

[11] The gold standard assessment of sensory symptoms for children (four-years- eight-years, eleven-months) with ASD is the Sensory Integration and Praxis Test (SIPT; Ayers, 1989). However, it takes a long time to administer, needs to be administered by a trained therapist and is only suitable for those children which can understand and follow instructions, therefore, it is not suitable for use for individuals with syndromes associated with ID.

Research has suggested that the decrease in individuals with FXS meeting criterion A of the DSM-5 is perhaps due to increased sensitivity for identifying those individuals with 'true' ASD as opposed to anxiety or sensory symptoms which restricts social engagement (Wheeler et al., 2015). If this pattern of change and symptomology is true for other genetic syndromes, which is suggested by this review, then this may lead to differences in interventions. Therefore, individuals may perhaps receive interventions more specifically targeted at anxiety or sensory management, as opposed to social communication interventions. This will also have implications for service eligibility and provision (Taheri and Perry, 2012; Wheeler et al., 2015).

Research and Theoretical Implications

Future studies should use control groups, who are matched on level of disability. Lots of research has used different methods to determine mental age, which has limited the comparisons that can be made (Ben-Sasson et al., 2009). Rogers and Ozonoff (2005) made suggestions for future research including detailed demographics of participants and a clear diagnosis, use of clinical and TD control groups and use a combination of assessment methods e.g. behavioural and physiological. Moreover, many assessments lack construct validity, especially constructs of sensory symptoms and RRBIs, therefore, the relationship between the constructs needs to be established (Baranek et al., 2014; Militerni, Bravaccio, Falco, Fico and Palermo, 2002). It is finally recommended that research should examine how the DSM-5 changes impact on ASD diagnosis for individuals with a range of genetic syndromes.

Evaluation

Whilst the review demonstrates strengths in the systematic search of the literature, it has not been able to conclusively calculate the amount of sensory symptoms across syndrome groups. The sensory literature reflects a broad range of terms and concepts even within the sensory modulation term, which perhaps reflects the unique sensory experiences of individuals (Baranek et al., 2014). However, the terms may also reflect different conceptualisations of sensory symptoms, which makes it difficult to draw comparisons between articles and consequently may have led the review to develop conclusions based on the same sensory terms, which perhaps present very different clinically for individuals. Furthermore, only one researcher evaluated the papers against the evaluation criteria, therefore inter-rater reliability was not established. Finally, the hypothesis made about the DSM-5 implications are only exploratory as the review only focused on sensory modulation as the other DSM-5 criteria were not in the remit of the review.

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CHAPTER 2

Exploring the Behavioural Phenotype of Pallister-Killian Syndrome

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Abstract

Introduction: Research has suggested individuals with Pallister-Killian Syndrome (PKS) have significant developmental delays, are non-verbal, non-mobile, have low adaptive skills, a lack of motivation to explore their environment and display challenging behaviour. However, the research has not used a comparative approach and has lacked well-validated assessment measures.

Method: Sixteen parents of individuals with PKS completed questionnaires exploring challenging behaviour, mood, activity, repetitive behaviours, ASD symptomology and sensory symptoms. This data was compared against age and ability matched individuals with Angelman syndrome (AS) and non-matched individuals with AS, Fragile X syndrome (FXS) and Cornelia de Lange syndrome (CdLS).

Results: The results revealed individuals with PKS displayed a range of abilities, but as a syndrome group they displayed a similar frequency of challenging behaviour, social communication and repetitive behaviours compared to individuals with AS. Individuals with PKS displayed lower mood and less over-activity, compared to individuals with AS. Individuals with to individuals with FXS and CdLS. Furthermore, individuals with PKS displayed less sensory seeking behaviours and more hyposensitivity behaviours compared to individuals with AS and FXS.

Discussion: The results are discussed in relation to previous research examining PKS and established behavioural phenotype research of AS, FXS and CdLS. Clinical implications focus on the assessment of ASD symptomology and timely sensory interventions.

Introduction

Pallister-Killian Syndrome (PKS) is a rare sporadic multisystem developmental disorder (Bartsch, Loitzsch, Kozlowski, Mazauric and Hickmann, 2005). The syndrome was first identified in an adult (Pallister et al., 1977) and child (Teschler-Nicola and Killian, 1981) who were reported to have mosaic isochromosome[12] 12p, which acted as a supernumerary marker chromosome. Both individuals were reported to display a similar phenotype, which was described as including: epilepsy, profound intellectual disability, "spasticity", cataracts, kyphoscoliosis and "coarse" facial features. Since this original description research has focused on physical characteristics, physical health difficulties and genetic causes, with less focus on the behavioural phenotype of the syndrome.

The percentage of cells containing the isochromosome depends on which tissue is examined (Blyth et al., 2015). Thus, the syndrome is possibly under-diagnosed due to difficulty in making a diagnosis from peripheral blood (Izumi and Krantz, 2014) and due to the wide range of ability displayed by individuals with PKS (Kostanecka Close, Izumi, Krantz and Pipan, 2012).

Leube, Majewski, Gebauer and Royer-Pokora (2003) reported an individual with tetrasomic 12p mosaic in fibroblasts and trisomy 12p mosaic in lymphocytes who had a milder phenotype (at nineteen-months this individual was able to sit, grasp objects and began to develop speech). The authors argue there is a possible more favourable prognosis in individuals with 12p PKS, rather than i(12p) mosaic, where the mosaic is

[12] An abnormal chromosome, which contains two identical arms, due to the duplication of one arm and the deletion of another.

absent in lymphocytes. However, more recent research has not confirmed genotype-phenotype associations, with some data indicating no correlation between the mosaic ratio and severity of the phenotype (Wilkens et al., 2012; Tilton, Wilkens, Krantz and Izumi, 2014).

Individuals with PKS have been reported to have numerous physical health difficulties, including structural heart differences (40%; Tilton, Wilkens, Krantz and Izumi, 2014), hypotonia (54.55%), hypermobility (40.91%), dental disruption (54.55%), seizures (72.73%; Blyth et al., 2015), early onset epilepsy (53%; Candee et al, 2012) and structural brain abnormalities (60-70%; Wilkens et al., 2012). Congenital anomalies include diaphragmatic hernia, exomphalos, anal atresia, sacral appendages and polydactyly (Bergoffen et al, 1993: Chaouachi, Ben, Ennine, Chaabouni, Sfar, Chaabouni, Marrakchi, 2010; De Oliveira, Ortega, Ciamponi, 2006: Schinzel, 1991). Gastrointestinal system disorders are also reported (52%) resulting in feeding difficulties, dysphagia, constipation and reflux (Izumi and Krantz, 2014: Wilkens et al., 2012).

Dysmorphic features include hypertelorism, epicanthic folds, flat nasal bridge, long philtrum, a large mouth, low-set posteriorly rooted ears, prominent forehead, anterior hairline, macroglossia, sparse eyebrows and eyelashes, alopecia (improving with age), micrognathia (especially in childhood), prognathia (especially in adulthood) and supernumerary nipples (Horneff, Majewski, Hildebrand, Voit, and Lenard, 1993: Genevieve et al., 2003).

Hearing impairments have also frequently been reported (75%; Kostanecka, Close, Izumi, Krantz and Pipan, 2012; 72%; Blyth et al., 2015) causing sensorineural (38%), conductive (29%) and mixed hearing loss (33%; Wilkens et al., 2012). Similarly, visual impairments are highly prevalent (72%; Blyth et al., 2015; 75%; Kostanecka, Close, Izumi, Krantz and Pipan, 2012) including myopia and hypermetropia, astigmatism or strabismus and significant visual pathway impairments, causing blindness (19%; Kostanecka, Close, Izumi, Krantz and Pipan, 2012; 40.90%; Blyth et al., 2015).

There are significant physical and developmental delays in the PKS group, specifically; growth retardation is related to elevated levels of insulin-like growth factor binding protein-2 (IGFBP2) (Izumi et al., 2015). Most individuals with PKS described in the literature who are eighteen-months-old or older have no speech (73.1%) and most individuals who are four –years-old or older are unable to walk (61.8%) (Blyth et al., 2015). Therefore, PKS was thought to be associated with severe to profound intellectual disability, although more recent literature now reports individuals with PKS with higher levels of functioning, suggesting a wider spectrum of the phenotype (Blyth et al., 2015: Kostenecka, Close, Izumi, Krantz and Pipan, 2012). For example, a four-year-old was able to speak five words but could not stand unsupported (Warburton, Anyane-Yeboa, Francke and Reynolds, 1987), whereas, adults have been reported to walk independently but could not speak (Reynolds et al., 1987: Quarrell, Hamill and Hughes, 1988). Another four-year-old was reported to be able to walk, although verbal abilities were not described (Speleman et al., 1991). Genevieve et al., (2003) reported that an individual could independently sit at seven-months, walk at twenty eight -

months and speak at three-years-old. Wilkens et al., (2012) reported that children are able to roll at ten- months, independently sit at twenty-months, independently walk at thirty-eight-months and develop speech at thirty-six-months. Moreover, one individual with PKS had a reported IQ of eighty-one (Vogel, Lyngbye, Nielsen, Pedersen and Hertz, 2009). Finally, children have been reported to function in mainstream schools, although needing specialised schooling at seven-years (Warburton, Anyane-Yeboa, Francke and Reynolds, 1987) and fifteen-years-old (Genevieve et al., 2003).

Blyth et al., (2015) population based study of twenty two individuals with PKS (age range four-months to thirty one-years) found a developmental delay in all cases, except a four-month-old. Eight of twenty individuals who were twelve-months or older were able to sit independently. Most individuals who were four-years or older were able to walk who were four- years or older, one individual who walked at youngest age was sixteen-months old. However, the authors also reported an eight-year-old learning to walk for the first time and an eighteen-year-old learning to toilet independently. Therefore, continued developmental progress can be gained, despite significant delay.

Kostenecka, Close, Izumi, Krantz and Pipan, (2012) is the only population-based study (sixteen individuals with PKS; age range: sixteen-months – nineteen-years) using a range of validated developmental assessments. The Vineland Adaptive Behavior scale (VABS) revealed that gross and fine motor skills were below an age equivalent of seven-month-old. Only two individuals were able to display purposeful hand movements; a nine-year, ten-month-old was able to hold a cup and a three-year, two-month old was able to feed herself using her fingers. Furthermore, fourteen individuals

displayed verbal language abilities at below the age equivalent of a nine-month-old using the VABS. However, a sixteen-month-old showed the highest level of verbal ability and was able to produce fifty words.

The authors also reported two individuals who were higher functioning. One individual was a six-year, seven-month female who displayed gross motor and daily living skills at the age equivalent of a twenty four-month old. She was able to walk independently, and feed and dress herself with help. She also had normal hearing and could communicate twenty words with additional use of communication gestures and the Social Communication Questionnaire (SCQ) revealed no indication of autism spectrum disorder (ASD). The second individual was a five-year, four-month old female who displayed gross motor and daily living skills at the age equivalent of a twenty four-month-old. She was able to walk and climb stairs independently. Her language abilities were at an age equivalent of a four-year, eleven-month-old, with auditory comprehension at a three-year, nine-month-old and expressive communication at a three-year, three-month-old using the VABS. She was able to speak in three or four word sentences. She had an IQ of sixty-nine using the Brief Intelligence Test. However, the SCQ indicated probable ASD and this was confirmed using the Autism Diagnosis Interviews (ADI).

Stalker, Gray, Bent-Williams and Zori (2006) reported a single case study of an individual with PKS who rolled at six months, sat at nine months, walked at fifteen-months and spoke first words at twelve-months and who had early intervention from occupational therapy, physical and speech therapies from fifteen-months-old. They also

reported good cognitive development at four years old with an IQ of eighty-three (Stanford-Binet). At age seven-years a full scale IQ was eighty-six, with verbal IQ of eighty-three and performance IQ of ninety-three (WISC III). They did note however, deficits in auditory memory and processing speed. At eleven-years old a full scale IQ was ninety-six, with fluid reasoning IQ of ninety-four and spatial visual IQ of ninety-two. At thirteen-years-old a full scale IQ of ninety-three was reported (Stanford-Binet). At fourteen-years they reported average mathematical application (standard score: ninety-one, age equivalent: twelve-years), spelling ability (standard score: 105, age equivalent: fifteen-years, six-months) and reading comprehension (standard score: ninety-one, age equivalent: eleven-years, six-months) and above average ability in reading decoding (standard score: 112, age equivalent: eighteen-years, three-month). However, the authors reported below average skills in mathematic computation (standard score: seventy-six, age equivalent: nine-years, nine-months).

There is a lack of research specifically examining the behavioural phenotype of PKS. Kostanecka, Close, Izumi, Krantz and Pipan, (2012) used the Aberrant Behavior Checklist (ABC) and identified many participants were described as "lethargic and withdrawn" (68%) and "drowsy during daily activities" (31%). This in combination with visual and hearing difficulties, hypotonia and hyposensitivity (50%), may result in an apparent lack of motivation to explore the environment, consequently contributing to developmental delays displayed by individuals. However, the authors suggest this hypothesis needs to be further researched, as well as the high levels of tactile hyposensitivity, as no research has undertaken a comprehensive sensory assessment. Furthermore, the ABC has not been standardised in children younger than six-years-old

and has limited validity in children with multiple disabilities (Aman, Singh, Stewart and Field, 1985; Kostanecka, Close, Izumi, Krantz and Pipan, (2012).

Many individuals with PKS are reported to display challenging behaviour, including self-stimulatory behaviour (45.45%; Blyth et al., 2015) and self-injurious behaviour (25%; Wilkens et al., 2012; 36.36%; Blyth et al., 2015), mostly in the form of hand biting (Blyth et al., 2015). Filloux et al., (2012) reported individuals with hypohidrosis and who experience episodes of hyperventilation would deliberately hold their breath. Additionally, two individuals without hyperventilation deliberately held their breath and one individual was also described to breath-hold, which caused seizures. High frequencies of repetitive hand and body movements have also been reported (75%; Kostanecka, Close, Izumi, Krantz and Pipan, 2012)

Blyth et al., (2015) reported 27.27% of individuals with PKS displayed features consistent with an ASD. Stalker et al (2006) also reported a 14-year-old individual with higher abilities, who had difficulties in social skills, daily living skills, had idiosyncratic speech, made repetitive movements and met diagnosis criteria for ASD. Similarly, Schinzel (1991) also reported an individual with ASD characteristics. However, none used standardised assessment and relied on clinical judgement. Whilst, Kostanecka, Close, Izumi, Krantz and Pipan (2012) used the Modified Checklist for Autism in Toddlers (M-CHAT), the Autism Diagnostic Interview Revised (ADI-R) and the SCQ to assess ASD symptomology, it was only used for individuals with a developmental age of more than 18-months-old, which excluded the majority of the sample.

Research into other genetic syndromes has revealed syndrome related behaviours, which has developed a precedent for establishing behavioural phenotype characteristics in other genetic syndromes, rather than simply classifying syndromes on the level of ID (Feinstein and Singh, 2007). The first behavioural phenotype was established for Lesch-Nyhan and Cornelia de Lange Syndromes (CdLS; Nylan, 1972). Dykens (1995) describes a behavioural phenotype as "the heightened probability or likelihood that the people with a given syndrome will exhibit certain behavioural and developmental sequelae relative to those without the syndrome" (as cited in Cook, 2009; p.146).

In summary, the research highlights a lack of an established behavioural phenotype despite three population-based studies (Wilkens et al., 2012) (Blyth et al., 2015; Kostanecka, Close, Izumi, Krantz and Pipan, 2012); Wilkens et al., 2012). This is due to a lack of formal standardised assessments suitable for individuals with ID and research to date only involves single group descriptions of PKS. More recent behavioural phenotype research has concentrated on comparative approaches (Nelson, Moss and Oliver, 2014). This comparative approach is currently missing from the PKS literature, but is critical to developing the description of a behavioural phenotype.

Therefore, comparisons needs to be made against other genetic syndromes with comparable level of disability, chronological age and gender to ensure findings are not artifacts of these characteristics (Dykens and Hadapp, 2001).

Individuals with Angelman Syndrome (AS) provide a useful comparison group, firstly due to their low adaptive ability (Peters, Beaudet, Madduri and Bacino, 2004), lack of mobility (Dan, Bouillot, Bengoetxea, Boyd and Cheron, 2001) and verbal communication (Jolleff and Ryan, 1993) allowing accurate matching of ability to participants with PKS and secondly due to the well-known behavioural phenotype of AS (see Table 1). Additional comparisons are also made with individuals with CdLS and FXS, also due to their ability and well-documented behavioural phenotype (see Table 1).

Additionally, several domains need to be assessed to determine a behavioural phenotype including, behavioural self-regulation, sensory modulation, social development, cognitive and adaptive functioning, psychiatric disorders and challenging behaviour (Tierney, Nwokoro, Porter, Freund, Ghuman and Kelley, 2001), which again is absent from the previous PKS literature.

Aims

The aim of this study is to further characterise the behavioural phenotype of PKS, specifically by assessing autism symptomology, sociability, mood, challenging behaviour, repetitive behaviour, over-activity and impulsivity and sensory experiences. The research will use assessment questionnaires appropriate for individuals with intellectual disability, which are reliable and valid. Individuals with PKS will be compared to individuals with other genetic syndromes, including AS, CdLS and FXS (Table 2.1). In addition, the study aims to explore the wellbeing of parents/carers of

individuals with PKS, by specifically assessing clinical symptoms of anxiety and depression.

Table 2.1: ***Descriptions of Angelman Syndrome, Fragile X syndrome and Cornelia de Lange Syndrome.***

Syndrome	Genetic Mechanisms	Estimated Prevalence	Behavioural Phenotype
Angelman Syndrome (AS)	Loss of functioning in the UBE3A gene on the maternally driven chromosome 15, predominantly due to deletions or imprinting errors (Kishino, Lalande and Wagstaff, 1997).	One in 10,000-20, 000 live births (Williams, 2005.	Severe ID, speech and language delays, epilepsy, sleep difficulties, ataxic gait, sensory-seeking behaviours and an excessive happy demeanour and laughing (Oliver, Horsler, Berg, Bellamy, Dick and Griffiths 2007; Williams et al., 2006). Richards et al., (2015) reported an ASD prevalence of 34%. Peters, Beaudet, Madduri and Bacino (2004) found that individuals with AS can still lack social engagement and interaction skills. However, other research has reported that individuals with AS show appropriate social reciprocity, and emotional contact (Clayton-Smith and Lann, 2003; Thompson and Bolton, 2003) and less stereotyped and repetitive behaviours compared to individuals with idiopathic ASD.
Fragile X Syndrome (FXS)	The silencing of the FMR1 gene at chromosome Xq27.3, leading to production of the Fragile X mental retardation protein (FMRP), which is associated with ID (Kaufmann and Reiss, 1999).[13]	One in 5,160 male births (more severely affected) (Coffee et al., 2009) and one in 8000 female births (Sherman, 2002).	Hyperactivity, impulsivity, attention difficulties, anxiety, shyness, aggression, moderate ID, SIB, hand-flapping and hypersensitivity (Hagerman and Hagerman, 2002). Richards et al., (2015) reported an ASD prevalence of 22%. The ASD symptomatology in FXS is different from idiopathic ASD (Kerby and Dawson, 1994). As a group, people with FXS are more able to recognise emotional expression (Turk and Cornish, 1998) and display better theory of mind skills (Mazzocco, Pennington and Hagerman, 1994).
Cornelia de Lange Syndrome (CdLS)	Predominantly (65%) due to heterozygous mutations in NIPBL on 5p13 or the SMC1A and SMC3 on Xp11.22-p11.21 and 10q24 (Liu and Baynam, 2010).	1.24 in 1000,000 births (Barisic et al., 2008).	Mild to profound ID, feeding difficulties, over-activity, mood disturbances, self-injury and stereotyped behaviours (Basile, Villa, Selicorni and Molteni, 2007; Berney, Ireland and Burn, 1999). Richards et al., (2015) reported an ASD prevalence of 43%; a high proportion compared to other genetic syndromes (Oliver, Arron, Hall and Sloneem, 2008), yet lower levels of repetitive behaviours (Oliver, Berg, Moss, Arron and Burbidge, 2011).

[13] The gene normally contains five-fifty repetitions of cytosine-guanine-guanine (CGG). Individuals with FXS have the full mutation and have more than 200 CGG sequences.

Method

Recruitment

Individuals with PKS were recruited via UNIQUE, which is a rare chromosome disorder support group. Families were contacted, inviting them to take part in the research by sending them a link to complete the questionnaires online using LimeSurvey. The invitation email was sent to fifty-two families and sixteen families gave consent and participated in the research (30.77% return rate).

Procedure

Participants were asked to complete a set of online questionnaires, which also contained information sheets, consent procedures and a background information questionnaire (Appendix 4). One follow up email was sent to remaining families about participating in the research, in an attempt to improve recruitment to the study. Ethical Approval for the study was approved by the Coventry NHS Research Ethics Committee (REC reference: 10/H1210/1) (Appendix 5).

Participants

There were sixteen individuals with PKS (Table 2.2), although one participant (ID=16) was excluded in all the analysis except for the health questionnaire due to their young age of 18-months-old, thus other assessments were not applicable. One participant (ID=7) was not included in the SCQ or the SQID analysis due to the assessments not being applicable to children under four-years of age. All participants had an adequate amount of data (missing no more than two questionnaires) and all participants reported a PKS diagnosis confirmed by a clinical geneticist. Table 2

displays the demographic characteristics of the group. The mean age of the sample was 10.57 years (SD=4.73; Range=three-twenty one years), eleven (73.33%) were male and three (20.00%) were classed as able/partly able (≥6 on the self-help subscale of the Wessex questionnaire; Kushlick, Blunden & Cox, 1973), four (26.60%) were mobile, four (26.60%) were verbal (used more than thirty words or signs), five (33.33%) had normal hearing and four (26.60%) had normal vision.

Table 2.2: ***Description of Individual Participants with Pallister-Killian Syndrome.***

ID	Clinical Diagnosis	Age	Genetic Mechanism	Gender	Verbal	Mobile	Vision	Hearing	Self Help [14]	Autism cut off[15]	SIB[16]
1	PKS	11	47,XY,+mar[9]/46,XY[6]	Male	No	No	Poor	Deaf/Almost	3	Yes	No
2	PKS	12	48,XY,i(12)(p10),+i(12)(p10)	Male	Yes	Yes	Normal	Poor	7	No	No
3	PKS	4	Additional genetic info not provided	Male	No	No	Poor	Normal	3	Yes	No
4	PKS	16	Intrachromosomal triplication of 12p. 46xytrp12pl 1.2p13113 / 46x	Male	No	No	Blind/Almost	Deaf/Almost	3	Yes	No
5	PKS	9	Missing	Male	No	No	Blind/Almost	Deaf/Almost	3	Yes	No
6	PKS	4	Missing	Male	No	No	Poor	Poor	3	Yes	Yes
7	PKS	3	47,XX,+mar	Female	No	No	Normal	Poor	3	N/A	N/A
8	PKS	13	Missing	Female	No	No	Blind/Almost	Poor	3	Yes	Yes
9	PKS	11	Missing	Male	Yes	Yes	Poor	Normal	7	No	Yes
10	PKS	21	47,XY,+i(12)(p10)dn	Male	No	No	Normal	Normal	4	Yes	Yes
11	PKS	11	47,XY,+i(12p)[3]/46,XY[6]	Male	No	No	Poor	Poor	3	Yes	Yes
12	PKS	13	Missing	Female	Yes	Yes	Normal	Normal	9	No	No

[14] Data derived from the Wessex Scale (Kushlick, Blunden and Cox, 1973).

[15] Data derived from the Social Communication Questionnaire (SCQ; Rutter, Bailey and Lord, 2003).

[16] Data derived from the Challenging Behaviour Questionnaire (CBQ; Hyman, Oliver and Hall, 2002).

13	PKS	10	47,XY,+i(12)(p10)[24]/46,XY[6]de novo	Male	No	No	Poor	Normal	4	No	No
14	PKS	12	Missing	Male	No	No	Poor	Poor	4	Yes	Yes
15	PKS	7	Missing	Female	Yes	Yes	Poor	Poor	3	No	Yes
16[17]	PKS	1	Missing	Male	No	No	Normal	Normal	3	No	No

[17] Participant excluded from analysis, due to their young age.

Comparison group participants with AS had previously participated in other research investigating their behavioural phenotype and had given consent for their data to be included in future research. The group was matched, in descending order of priority, on chronological age (+/- 3 years), self-help score (+/- 3), gender, and whether individuals were verbal and mobile obtained from the Wessex Scale. Self-help scores were utilised as a proxy measures of degree of disability. Table 3 displays the demographic characteristics of the AS group. In total there were fifteen individuals with AS. The mean age of the sample was 10.33 years (SD=4.59; Range= two-twenty years), ten (66.67%) were male and three (20.00%) were able/partly able, seven (46.67%) were mobile, one (6.67%) was verbal. No significant differences were found between the groups for age (U=.007, N_1 =11, N_2 =10, p=.934) gender (χ^2=.159, (1), p=.500), self-help (U=.077, N_1 =3, N_2 =3, p=.782), mobility (U=.708, N_1 =2, N_2 =4, p=.400) or verbal ability (χ^2= 2.160, (1), p=.142) (Table 2.3).

Table 2.3: ***Demographic Characteristics and Statistical Analyses for Participant Groups: Pallister-Killian Syndrome and Matched Individuals with Angelman Syndrome.***

		PKS N=15	AS N=15	Chi squared and Mann-Whitney U significant tests		
				χ^2/U	df	p value
Age	Mean	10.47	10.33	.007	1	.934
	(sd)	4.73	4.59			
	Range	1-21	2-20			
	Median	11	10			
	IQR	7-13	6-14			
Gender	Male	11	10	.159	1	.500
	(%)	(73.33%)	(66.67%)			
Self Help	Mean	4.13	3.93	.077	1	.782
	(sd)	1.92	1.67			
	Range	3-9	2-7			
	Median	3	3			
	IQR	3-4	3-4			
Mobility	Mean	3.33	3.87	.708	1	.400
	(sd)	1.68	1.81			
	Range	2-6	2-6			
	Median	2	4			
	IQR	2-5	2-6			
Verbal[18]	(%)	4 (26.67%)	1 (6.67%)	2.160	1	.142

As it was not possible to use the matched AS participants on every questionnaire, data from additional groups of non-matched participants with AS, FXS and CdLS were used for the Sociability Questionnaire for Intellectual Disability (SQID) and the Sensory Experience Questionnaire (SEQ). Whilst there were no significant group differences in age there were significant differences between groups in their gender distribution (χ^2=31.869, (3), p<.001), self-help skills (h=37.456, (3), p<.001); the PKS group displayed a lower ability in comparison to the FXS group (U=75.329, N_1 =3, N_2 =7, p<.001) and mobility (h=29.665, (3), p<.001); The PKS group were less

[18] Able to speak or sign more than thirty words.

mobile in comparison to the AS group (U=-37.083, , N_1 =2, N_2 =5, p<.001) and the FXS group (U=69.454, N_1 =2, N_2 =5, p<.001) (Table 2.3).

Table 2.4: ***Demographic Characteristics and Statistical Analyses for Participant Groups: Pallister-Killian Syndrome and Non-Matched Individuals with Angelman Syndrome, Fragile X Syndrome and Cornelia De Lange Syndrome.***

		PKS	AS (Non-Matched	CdLS	FXS	Chi Squared and Kruskal-Wallis Significant Tests			Post Hoc Mann-Whitney U Significant Tests		
						χ^2/h	Df	p Value	Significant PKS Direction	χ^2/h	p Value
N		15	91	28	40	6.991	3	.072	N/A	N/A	N/A
Age	Mean	10.47	7.29	7.89	9.25						
	(sd)	4.73	3.73	4.10	3.84						
	Range	1-21	2-15	2-15	2-15						
	Median	11	7	7.5	9						
	IQR	7-13	4-10	4-12	5-12						
Gender	Male (%)	11	45	17	40	31.869	3	<.001	PKS<FXS	11.503	0.004[19]
Self Help	Mean	4.13	4.96	4.68	6.65	37.456	3	<.001	PKS<FXS	75.329	<.001
	(sd)	1.92	1.48	1.81	1.53						
	Range	3-9	3-9	3-9	6-7.75						
	Median	3	4	4	7						
	IQR	3-4	4-6	3-6	3-9						
Mobility	Mean	3.33	4.74	4.29	5.63	29.665	3	<.001	PKS<AS	37.083	0.027
	(sd)	1.68	1.41	1.67	0.95				PKS<FXS	69.454	<.001
	Range	2-6	1-6	2-6	2-6						
	Median	2	5	4.5	6						
	IQR	2-5	4-6	2.25-6	6-6						

[19] Fishers exact p value reported as 50% had an expected count <5.

Measures

Parents/careers completed eleven questionnaires suitable for individuals with ID. This included the demographic questionnaire, which obtained information about age, gender, mobility, verbal ability, parent age and income and diagnosis information, including the time of diagnosis and precise genetic mechanism. Other questionnaires included the Challenging Behaviour Questionnaire (CBQ; Hyman, Oliver and Hall, 2002), the Sensory Experience Questionnaire (SEQ; Baranek, 1999), The Activity Questionnaire (TAQ; Burbidge and Oliver, 2008), the Health Questionnaire (HQ; Hall, Arron, Sloneem and Oliver, 2008), the Mood, Interest and Pleasure Questionnaire (MIPQ; Ross and Oliver, 2003), the Repetitive Behaviour Questionnaire (RBQ; Moss, Oliver, Arron, Burbidge and Berg, 2009), the Sociability Questionnaire for Intellectual Disability (SQID; Collins and Oliver, 2007), the Social Communication Questionnaire (SCQ; Rutter, Bailey and Lord, 2003) and the Wessex Questionnaire (WQ; Kushlick, Blunden and Cox, 1973). These questionnaires were parent reports of their child's health, wellbeing and behaviour. The Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983) was used to assess parents/carers own mental wellbeing (Table 2.5; Appendix 6: full assessments with copyright permission only).

Table 2.5: ***Descriptions of the Assessments and including the Psychometric Properties.***

Assessment	Authors	Description of the Assessment	Psychometric Properties
Challenging Behaviour Questionnaire (CBQ)	Hyman, Oliver and Hall (2002),	The questionnaire is in two parts. Part one assesses the presence or absence of five types of challenging behaviour; self-injury, physical aggression, verbal aggression, destruction of property and inappropriate vocalizations over the last month. It also assesses eight topographies of self-injurious behaviour (Bodfish et al., 1995). Part two determines the severity of each challenging behaviour identified in part one. Responses are on a five-point scale.	The authors reported Inter-rater reliability of .61-.89.
Hospital Anxiety and Depression Scale (HADS)	Zigmond and Snaith (1983)	A screening assessment to detect anxiety and depression in adults. It contains fourteen items in total with two scales the HADS-D (depression) and HADS-A (anxiety) containing seven items each. The questionnaire includes symptoms of physical disorders.	The measure has been reviewed to be both reliable and valid (Bjelland, Dahl, Haug and Neckelmann, 2002;Hermann, 1997). Cut off scores of 8> in each scale are suggested to identify depression/anxiety, with sensitivity and specificity of .90 (Abiodun, 1994). Although using a cut-off score of 9> in the HADS-A had sensitivity of .66 and specificity of .93. Using a cut-off score of 7> in the HADS-D had sensitivity of .66 and specificity of .97 (El Rufaie and Absood, 1995). Good internal consistency between HADS-A and HADS-D (r=.40-.74; Bjelland, Dahl, Haug and Neckelmann, 2002). Research also confirmed the two factor model (Lisspers, Nygren and Soderman, 1997). Good concurrent validity with the Beck Depression Inventory (r=.73; Lisspers, Nygren and Soderman, 1997) and the General Health Questionaire-28 (r=.50-.68; Caplan, 1994).
Sensory Experience Questionnaire-	Baranek (1999)	A forty-one-item parent report questionnaire to assess children's behavioural responses to a range of sensory activities in children aged six-months	Discriminant validity good between individuals with ASD and TD (sensitivity= 72-80%, specificity= 44-77%; Baranek, David, Poe, Stone and Watson, 2006).

Assessment	Authors	Description of the Assessment	Psychometric Properties
Short Form (version 2.1) (SEQ)		to six-years. It assesses frequency of sensory behaviours across sensory response patterns, modalities and social and non-social contexts. The first fifty-three items assess frequency of sensory behaviours on a five-point likert scale ranging from 'almost never' to 'almost always'. The final questions are not score, but give qualitative contextual information. A total score is given, plus sub-scores for three types of sensory patterns including; hyper-responsivity, hypo-responsivity, and sensory-seeking, and scores for each of the five modalities including; auditory, visual, tactile, gustatory and vestibular, and a score for social and non-social contexts. A higher score indicates more severe sensory symptoms.	Internal consistency for repetitive and sensorimotor behaviours= .83 and for insistence on sameness= .73. Test-retest reliability= .95, inter-rater reliability=.95 (Hason, Siderdis, Jackson, Porche, Campe and Huntington, 2016). The 3 responses patterns were validated in confirmatory factor analysis (Watson, Pattern, Baranek, Poe, Boyd and Lorenzi, 2009). High internal consistency for each domain; hyper-responsivity (α =.73), hypo-responsivity (α =.75), sensory seeking (α =.80), social contexts (α =.69), and non-social contexts (α =.78). Good concurrent validity with the Sensory Processing Assessment (Baranek and Costello, 2003) Also used to determine sensory patterns in children with genetic syndromes up to eighteen-years-old including Angelman syndrome (Walz and Baranek, 2006) and Fragile X Syndrome (Baranek et al., 2008).
The Activity Questionnaire (TAQ).	Burbidge and Oliver (2008).	An eighteen-item questionnaire used to assess frequency of activity. It contains three subscales measuring over activity, impulsivity and impulsive speech. Informants respond on a five-point scale ranging from zero (never/ almost never)- five (always/ almost all of the time).	The measure has good item level inter-rater reliability (range= .31-.75, mean= 0.56). Test-retest reliability (range= .60-.90, mean= 0.75) and moderate internal consistency (.50-.59) (Burbidge et al., 2010). The authors also report that factor analysis confirmed the integrity of the sub-scales.
The Health Questionnaire (HQ)	Hall, Arron, Sloneem and Oliver (2008).	A fifteen-item questionnaire, which measures the presence and severity of health difficulties total score by adding two subsections; lifetime and the last month. The assessment is based on health problems in the Tenth Revision of the International Statistical Classification of Disease and related Health Problems or ICD-10 (World Health Organisation, 1998). Responses are recorder on a three-point scale ranging from zero	The authors report the measure has good kappa coefficient inter-rater reliability for the lifetime total (=. 72, range= .32-1.00) and for the last month total (= .76, range= .32-1.00). Good internal consistency fir individuals with Rett syndrome (=.77; Clanfaglione, Clarke, Kerr, Hastings, Oliver and Felce, 2015).

Assessment	Authors	Description of the Assessment	Psychometric Properties
		(never) to three (Severe problems). There is a total score for the last month and lifetime difficulties.	
The Mood Interest and Pleasure Questionnaire-Short Form (MIPQ-S).	Ross and Oliver (2003).	A questionnaire to measure two sub scales of mood and interest and pleasure. The measure has twelve items and is based on behavioural signs in last two weeks. It has a five-point scale, with a maximum score of fourth-eight; a higher score indicates positive effect and higher interest and pleasure.	The authors report the measure has good test-retest reliability (.97), inter-rater reliability (r=.85) and internal consistency (total=.88, mood= .79, interest and pleasure=.87) The measure has good concurrent validity as it correlated highly with the lethargy and social withdrawal scale on the Aberrant Behavior Checklist (ABC: Aman, Singh, Stewart and Field, 1985; .73).
The Repetitive Behaviour Questionnaire (RBQ)	Moss, Oliver, Arron, Burbidge and Berg (2009).	A nineteen-item questionnaire used to measure repetitive behaviours using five subscales: Stereotyped behaviour, compulsive behaviour, insistence on sameness, restricted preferences and repetitive speech. Informants rate the frequency of operationally defined behaviours over the last month on a five-point Likert scale ranging from 'never' to 'more than once a day'. The assessment contains four items only applicable to verbal individuals. Thus, there are two different scoring methods for verbal and non-verbal individuals. For verbal individuals the total score range is zero to seventy-six and for non-verbal individuals the range is zero to sixty. The item level clinical cut-off score is ≥3 on an item. At the subscale level the cut off is three or more on at least one item within the subscale.	The authors report good Spearman's coefficient inter-rater reliability (.46-.80), and good Spearman's test retest reliability (61-.93). The assessment has good internal consistency for the full scale (α>.80) and for the stereotyped behaviour and compulsive behaviour subscales (α>.70), although lower consistency for the restricted preferences (α=.50), repetitive speech (α=.54) and insistence on sameness (α=.65) subscales. The assessment also has good context and concurrent validity as it correlated with the repetitive behaviour subscale from the Autism Screening Questionnaire (Berument et al., 1999) (.60; p<.001).
The Sociability Questionnaire for Intellectual Disabilities (SQID)	Collis and Oliver (2007)	An informant based questionnaire, which assesses social interaction and social anxiety with familiar and unfamiliar people. Items one to twenty-one ask how frequently individuals initiate social interaction using verbal and non-verbal strategies	The assessment has good concurrent validity with the Child Sociability Rating Scale (CSRS, Moss et al., 2013) (r=.36-.52). The SQID also has good inter-rater reliability for items 1-21 (r=.43-.80) and for questions, 22-25 (α>=.44-.96).

Assessment	Authors	Description of the Assessment	Psychometric Properties
		on a seven-point scale from rarely/never to nearly always. Items twenty-two to twenty-five ask about the use of language using a yes or no answer. It comprises twenty-five items and contains eight subscales (four familiar and four unfamiliar) including; receive interaction (receiving an interaction/being approached by another), ongoing interaction (one-on-one ongoing interaction), approach or initiate interaction (initiating an interaction with another) and performance (a group interaction). It also assesses behaviours indicative of selective mutism. The informant completes the questionnaire based on the participant's behaviour in social settings over the past two months.	Clinical cut-off points for subscales for excessive sociability (>13) and shyness (<3).
The Social Communication Questionnaire (SCQ).	Rutter, Bailey and Lord (2003).	A questionnaire used to screen for ASD symptomatology, by assessing communication, social functioning and repetitive and stereotyped patterns of behaviour. It contains forty items requiring a yes/no response. Has cut-off score for Autism (≥22) and ASD (≥15).	Using a cut-off score of fifteen the questionnaire was able to discriminate between individuals with Pervasive Developmental Disorder (PDD) and individuals with other diagnoses, with a specificity of .80 and sensitivity of .96, and between individuals with ASD from individuals with ID, with a specificity of .67 and sensitivity of .96. Using a higher cut-off score of 22 the assessment was able to discriminate between individuals with Autism and other PDD with a sensitivity of .75 and specificity of .60. The measure has good convergent validity, due to a high correlation with the Autism Diagnostic Interview (ADI) and the Autism Diagnostic Observation Schedule (ADOS: Berument et al., 1999; Bishop and Norbury, 2002). Specifically, Howlin and Karpf (2004) reported high internal consistency and concurrent validity with the ADOS and ADI with individuals with Cohen Syndrome.

Assessment	Authors	Description of the Assessment	Psychometric Properties
The Wessex Questionnaire (WQ)	Kushlick, Blunden and Cox (1973)	The questionnaire assesses the degree of ID and presence of speech. It has two overall factors; the social and incapacity (SPI) scale and the Speech, Self-help and Literacy (SSL) scale, which includes five subscales; continence, mobility, self-help skills, speech and literacy.	The authors report the measure has good inter-rater reliability for the SPI (α=0.65) and the SSL(α=0.76). Modest inter-rater reliability for each subscale (α=.54-.62) and overall classification (α=.64). Appropriate for large study questionnaire research with both children and adults (Palmer and Jenkins, 1982).

Data Analysis

Given the small sample size and resultant difficulties assessing adherence to the additional assumptions of parametric tests, non-parametric tests were utilised where possible.

Group Comparisons

In order to compare behaviours reported in the PKS group with those of the matched AS comparison group, total and subscale scores were analysed for mood (using the MIPQ), repetitive behaviours (using the RBQ) and activity (using the TAQ). A series of Mann-Whitney U tests were performed to test for group differences in the subscales between the two groups. The proportions of individuals displaying a range of challenging behaviours in each syndrome group was also compared using Chi-Squared tests and Fishers, and the severity of challenging behaviour was compared between syndrome groups using a Mann-Whitney U test (using the CBQ).

The profile of autism phenomenology (using the SCQ) in the PKS group (participants aged >4 years-old) was explored by comparing total and subscale scores with those of the AS matched syndrome group, and testing for significant differences using the Mann-Whitney U test. To investigate the prevalence of autism phenomenology in the PKS and AS matched group, the percentage of each group scoring above the cut-off for ASD ($\geq$15) and autism ($\geq$22) on the SCQ was assessed. Differences in the frequency with which individuals in the two groups scored above these cut-off scores were compared using Chi-Square tests. To further explore the sociability (using the SQID) of individuals with PKS, total and subscale scores were

compared against non-matched AS, CdLS and FXS groups using a series of Kruskal-Wallis tests and, where significant group differences were identified, post-hoc compassions were made using Mann-Whitney U tests.

Sensory experiences (using the SEQ) in PKS were explored by comparing total and subscale scores from the SEQ between the non-matched AS, CdLS and PKS group using a series of Kruskal-Wallis tests and where significant group differences were identified, post-hoc contrast were made using Mann-Whitney U tests.

Relationships between variables for participants with PKS

For participants with PKS, non-parametric correlations with age of mood, sociability and hyperactivitiy/impulsivity were undertaken. These are variables known to systematically vary with age for some other groups, such as CdLS (Berney, Ireland and Burn, 1999; Nelson, Moss and Oliver, 2014; Oliver, Berg, Moss, Arron and Burbidge, 2011) and Kleefstra Syndrome (unpublished data).

Alpha

Effects at $p<0.05$ are reported as significant. This is despite the numerous tests employed. It is acknowledged that this raises the possibility of Type I errors (rejecting the null hypothesis incorrectly). However, where samples are small, as tends to be the case for research into rare syndrome groups, there is always a substantial risk of making Type II errors (accepting the null hypothesis incorrectly) due to insufficient power. Thus, effects are reported as significant at $p < 0.05$, it must be borne in mind at the point of interpretation that caution is required, and replication in future studies is paramount.

Results

Health Questionnaire

The most frequently reported lifetime health difficulties were ear problems (n=14, 87.6%)[20], which were mostly described as moderate difficulties (n=6, 37.5%) for which eleven individuals (68.8%) needed corrective treatment. The second most frequent reported health difficulty was dental problems (n=13, 81.4%), which were mostly described as mild (n=5, 31.3%) and moderate (n=5, 31.3%), for which four individuals (25%) needed corrective treatment. Other frequent health difficulties were epilepsy/seizures (n=11, 88.8%; moderate: n=5, 31.3%), skin problems (n=10, 62.5%; mild: n=8, 50%) and gastrointestinal problems (n=8, 50%, moderate: n=4, 25%) (see Appendix 7).

Challenging Behaviour

Approximately half of the individuals with PKS displayed SIB (n=7, 46.67%) and stereotyped behaviour (n=8, 53.33%) in the last month, with lower levels of physical aggression (n=2, 13.33%) and destruction of property (n=3, 20.00%). The frequency of property destruction and physical aggression was lower than that seen for the AS group, although, there were no significant differences between groups in SIB (χ^2=0.556, (1), p=.456), destruction of property (χ^2=2.400, (1), p=.121), physical aggression (χ^2=3.968, (1), p=.109) and stereotyped behaviour (χ^2=0.130, (1), p=.713).

The PKS group's challenging behaviour is displayed with lower severity than seen for the AS group (U=5.056, N_1 =6, N_2 =9.5, p=.025) (Table 2.6).

[20] Percentages displayed for the whole sample.

Table 2.6: ***Number and Percentage of Individuals with Pallister-Killian Syndrome and Matched Individuals with Angelman Syndrome displaying Challenging Behaviour and Chi-Squared Analysis.***

	PKS N=15	AS N=15	Chi-Squared Test χ^2	df	p Value
Displayed SIB in the last month (%)	7 (46.67%)	5 (33.33%)	0.556	1	.456
Displayed Destruction of Property in the last month (%)	3 (20.00%)	7 (46.67%)	2.400	1	.121
Displayed Physical Aggression in the last month (%)	2 (13.33%)	7 (46.67%)	3.968	1	.109[21]
Displayed Stereotyped Behaviour in the last month (%)	8 (53.33%)	9 (60.00%)	0.130	1	.713

Mood

Individuals with PKS showed significantly lower scores than individuals with AS on the mood subscale (U=17.019, N_1 =14, N_2 =22.50, p<.001), interest and pleasure subscale (U=10.084, N_1 =11, N_2 =18.5, p<.001) and total MIPQ score (U=14.944, N_1 =25, N_2 =40, p<.001) (Table 2.7).

For the PKS group, there was a strong positive correlation between age and the mood subscale of the MIPQ (r_s = 0.70, p = 0.003, n = 16), indicating that older participants may be reported to display more positive mood than younger participants.

Activity

Individuals with PKS showed significantly lower scores compared to individuals with AS on the impulsivity subscale (U=4.576, N_1 =3, N_2 =7, p=.032), over-activity

[21] Fishers exact p value reported as 50% had an expected count <5.

(U=7.398, N_1 =6, N_2 =18, p=.007) and total TAQ score (U=6.945, N_1 =12, N_2 =18, p=.008) (Table 2.7).

There were no significant or near-significant correlations of any of the TAQ scores with age for the PKS group, indicating no systematic linear association with age in measures of activity.

Behaviours associated with Autism

Repetitive Behaviours

Individuals with PKS displayed a similar score to the AS group on the total RBQ score (U=0.758, N_1 =11, N_2 =12, p=.384), the stereotyped behaviour subscale (U=82.99, N_1 =8, N_2 =8, p=.191), compulsive behaviour subscale (U=111.00, N_1 =0, N_2 =0, p=.929) and the insistence on sameness subscale (U=112.00, N_1 =0, N_2 =0, p=.972) demonstrating both groups displayed similar levels of repetitive behaviour (Table 2.7).

Items typically requiring higher levels of ability were rarely endorsed by informants (e.g., repetitive questioning, n=2, 14.3%; excessive cleaning, n=1, 7.1%). However, some other items were endorsed more frequently, including object stereotypy[22] (n=7, 50.0%; all of these at least once a day), body stereotypy (n=8, 57.1%; n=7, 50.0% at least once a day) and hand stereotypy (n=9, 64.3%; n=8, 57.1% at least

[22] A term used to categories repetitive behaviors often displayed by individuals with Autism, which offer sensory automatic feedback and socially mediated reinforcement (Cunningham and Schreibman, 2008).

once per day). Also five people were reported to show a strong attachment to specific objects (n=5, 35.7%; n=4, 28.6% at least once a day).

Autism Spectrum Disorder

Individuals with PKS showed significantly higher scores compared to individuals with AS on the total SCQ (U=48.50, N_1 =23, N_2 =20, p=.021). However, there were no significant differences between the two groups on any of the subscales including Communication (U=4.576, N_1 =3, N_2 =7, p=.734), Repetitive, Restrictive and Stereotyped Behaviors (U=128.00, N_1 =13, N_2 =13, p=.178), and Reciprocal Social Interaction (U=168.00, N_1 =12, N_2 =9, p=.114) (Table 2.7).

In both groups nearly all participants (92.9%) met criteria for ASD according to the SCQ, suggesting similar prevalence rates of ASD (χ^2=0.000, (1), p=.759). However, significantly more individuals from the PKS group compared to the AS group met criteria for Autism, suggesting a higher prevalence rate of Autism for individuals with PKS (χ^2=7.337, (1), p=.007) (Table 2.8).

Table 2.7: ***Median (Inter Quartile Range) for Pallister-Killian Syndrome and Matched Individuals with Angelman Syndrome Subscales of the Challenging Behaviour Severity Score, Mood, Interest and Pleasure Questionnaire, the Repetitive Behaviour Questionnaire, the Activity Questionnaire and the Social Communication Questionnaire with Results for Mann-Whitney U Analysis.***

		PKS	AS	Mann-Whitney U Test		
				U	df	p Value
CBQ Severity	N	7	6	5.056	1	.025
	Median	6	9.5			
	IQR	3-9	8.25-11.25			
MIPQ Mood	N	15	14	17.019	1	<.001
	Median	14	22.50			
	IQR	13-16	21-23			
MIPQ Interest and Pleasure	N	15	14	10.084	1	.001
	Median	11	18.5			
	IQR	8-14	15-21.5			
MIPQ Total	N	15	14	14.944	1	<.001
	Median	25	40			
	IQR	23-30	35.5-44			
RBQ total	N	15	15	.758	1	.384
	Median	11	12			
	IQR	8-16	9-14			
RBQ- Stereotyped Behaviour	N	15	15	82.00	1	.191
	Median	8	8			
	IQR	0-12	8-12			
RBQ- Compulsive Behaviour	N	15	15	111.00	1	.929
	Median	0	0			
	IQR	0-0	0-0			
RBQ- Insistence on Sameness	N	15	15	112.00	1	.972
	Median	0	0			
	IQR	0-0	0-0			
TAQ- Impulsivity	N	15	15	4.576	1	.032
	Median	3	17			
	IQR	0-11	6-22			
TAQ- Overactivity	N	15	15	7.398	1	.007
	Median	6	18			
	IQR	2-13	15-24			
TAQ Total	N	15	15	6.945	1	.008
	Median	12	18			
	IQR	5-31	15-24			

		PKS	AS	Mann-Whitney U Test		
				U	df	p Value
SCQ- Total	N	14	14	48.50	1	.021
	Median	23	20			
	IQR	19.75-25.25	17.75-20.75			
SCQ- Communication	N	14	14	106.00	1	.734
	Median	13	13			
	IQR	8.75-13.00	11-13			
SCQ- Restricted, repetitive and stereotyped behaviours	N	14	14	128.00	1	.178
	Median	2	2.50			
	IQR	2-4.25	1-3.5			
SCQ- Reciprocal Social Interaction	N	14	14	168.00	1	.114
	Median	12	9.00			
	IQR	8.50-13.25	8.50-10.50			

Table 2.8: ***Number and Percentage of Individuals with Pallister-Killian Syndrome and Matched Individuals with Angelman Syndrome Meeting Criteria for ASD and Autism from the Social Communication Questionnaire and Chi-Squared Analysis.***

	PKS N=14	AS N=14	Chi-Squared Test χ^2	df	p. Value
Met ASD criteria from the SCQ (%)	13 (92.9%)	13 (92.9%)	0.000	1	.759[23]
Met Autism criteria from the SCQ (%)	9 (64.3%)	2 (14.3%)	7.337	1	.007

Sociability

Overall analyses for PKS, AS, FXS, and CdLS showed significant group differences on familiar (h=69.439, (3), p<.001) and unfamiliar subscales (h=84.956, (3), p<.001) of the SQID. Post hoc analysis revealed that individuals with PKS displayed lower scores compared to individuals with AS on both familiar (U=-75.401, N_1 =36, N_2 =53, p<.001) and unfamiliar subscales (U=-50.077, N_1 =28, N_2 =41, p=.004), indicating individuals with PKS were less sociable. This pattern of lower scores

[23] Fishers exact p value reported as 50% had an expected count <5.

compared to the AS group was reported on all subscales except for interaction with unfamiliar individuals (p>.050). There were no significant post hoc differences between PKS and CdLS and PKS and FXS participants, except there was a trend[24] for individuals with PKS to display significantly lower scores compared to individuals with FXS for approaching or initiating interaction with familiar others (U=-41.423, N_1 =5, N_2 =10, P=.047), implying that individuals with PKS may approach/initiate interaction with familiar others less than people with FXS do. Overall, data from the SQID suggest that individuals with PKS may display levels of sociability similar to individuals with CdLS and FXS (Table 2.9).

There were significant positive correlations with age for the PKS group on the Total Familiar (r_s = 0.55, p = 0.04, N = 14), the Familiar Approach or Initiate Interaction (r_s = 0.62, p = 0.019, N = 14), and the Unfamiliar Approach or Initiate Interaction (r_s = 0.58, p = 0.03, N = 14) subscales, indicating greater sociability in some areas with age.

[24] Caution needs to be taken when interpreting these results due to a possible type I error.

Table 2.9: ***Median (Inter Quartile Range) for Pallister-Killian Syndrome, and Non-Matched Individuals with Angelman Syndrome, Cornelia de Lange Syndrome and Fragile X Syndrome Subscales of the Sociability in Intellectual Disabilities Questionnaire with Results for Kruskal-Wallis Analysis and Post Hoc Mann-Whitney U Analysis.***

		PKS n= 13	AS n= 91	CdLS n=27	FXS n=39	Kruskal-Wallis Tests			Post Hoc Comparison: Mann-Whitney U Test			
						H	df	p	PKS Significance Direction	U	df	P Value
Familiar Total	Median IQR	36 28.50-44.50	53 49-55	44 35-48	42 36-47	69.439	3	<.001	PKS<AS	-75.401	1	<.001
Familiar Receive Interaction	Median IQR	9 8-13	13 12-14	11 9-12	11 9-12	57.416	3	<.001	PKS<AS	-57.907	1	<.001
Familiar- Interaction	Median IQR	10 9-12.50	14 13-14	12 10-13	12 11-13	42.263	3	<.001	PKS<AS	-61.852	1	<.001
Familiar- Approach or Initiate interaction	Median IQR	5 3.50-9.50	13 11-14	9 6-13	10 8-12	41.261	3	<.001	PKS<FXS PKS<AS	-41.423 -74.566	1 1	.047 <.001
Familiar- Performance	Median IQR	9 8-11	14 13-14	12 10-12	9 5-12	75.883	3	<.001	PKS<AS	-65.214	1	<.001
Unfamiliar Total	Median IQR	28 26-31	41 32-50	28 21-39	18 11-24	84.956	3	<.001	PKS<AS	-50.077	1	.004
Unfamiliar Receive Interaction	Median IQR	8 7-8.5	10 9-12	7 5-10	4 3-5	80.685	3	<.001	PKS<AS	-45.522	1	.010
Unfamiliar-	Median	8	11	8	5	60.078	3	<.001	-	-	-	-

		PKS n= 13	AS n= 91	CdLS n=27	FXS n=39	Kruskal-Wallis Tests			Post Hoc Comparison: Mann-Whitney U Test			
						H	df	p	PKS Significance Direction	U	df	P Value
Interaction	IQR	8-9	8-12	4-10	2-7							
Familiar-	Median	4	10	6	5	61.967	3	<.001	PKS<AS	-72.945	1	<.001
Approach or Initiate interaction	IQR	2.50-5	8-12	4-8	3-6							
Unfamiliar-	Median	8	11	8	3	77.488	3	<.001	PKS<AS	-40.489	1	.032
Performance	IQR	6.5-8	9-13	5-11	2-4							

Sensory Experiences

Table 2.10 displays mean SEQ subscale scores with standard deviations for the PKS and unmatched comparison groups. Mean group scores are also classified according to Baranek's (1999) classifications defined in relation to normative data for TD individuals. On average, participants with PKS displayed deficient[25] sensory experiences in hypo-responsivity and in social, and displayed typical performance in hyper-responsivity and sensory seeking and in non-social contexts (Table 2.10).

[25] Criterion cut-points based on typically developing normative data (Baranek, 1999). Hypo-responsivity: Typical Range (6-10), At Risk Range (11-12) and Deficient Range (13-30), Hyper-responsivity: Typical Range (14-29), At Risk Range (30-34) and Deficient Range (35-70), Sensory Seeking: Typical Range (13-38), At Risk Range (39-47) and Deficient Range (48-65), Social Contexts: Typical Range (10-18), At Risk Range (19-21) and Deficient Range (22-50), Non-Social Contexts: Typical Range (22-55), At Risk Range (56-65) and Deficient Range (66-110).

Table 2.10: ***Mean, Standard Deviation and Classification of Sensory Experiences in individuals with Pallister-Killian Syndrome, and Non-Matched Individuals with Angelman Syndrome, Cornelia de Lange Syndrome and Fragile X Syndrome.***

Raw Scores		PKS n=15	AS n=91	CdLS n=28	FXS n=40
Hypo-responsivity	Mean	19.20	12.37	17.32	13.83
	SD	5.75	3.43	4.46	3.99
	Classification	Deficient	At Risk	Deficient	Deficient
	Typical %	13.3%	34.1%	3.6%	20.0%
Hyper-responsivity	Mean	28.47	28.21	34.11	34.20
	SD	5.10	6.66	9.42	9.23
	Classification	Typical	Typical	At Risk	At Risk
	Typical %	53.6%	62.7%	36.0%	35.0%
Sensory Seeking	Mean	28.73	41.08	39.93	37.33
	SD	6.40	3.43	6.91	9.32
	Classification	Typical	At Risk	At Risk	Typical
	Typical %	93.3%	36.3%	46.8%	55.0%
Social Contexts	Mean	23.87	20.44	25.43	25.13
	SD	4.41	4.05	6.88	6.48
	Classification	Deficient	At Risk	Deficient	Deficient
	Typical %	20.1%	36.6%	14.4%	17.5%
Non-Social Contexts	Mean	49.73	59.42	63.54	58.53
	SD	7.08	7.95	10.04	11.07
	Classification	Typical	At Risk	At Risk	At Risk
	Typical %	73.7%	28.6%	25.2%	40.0%

There were significant differences across syndromes groups in the number of individuals scoring in the 'typical' range in all three sensory types and across social and non-social contexts ($p<.050$). Specifically, individuals with PKS had displayed significantly less sensory-seeking behaviours compared to individuals with AS ($\chi^2=16.994$, (1), $p<.001$), individuals with FXS ($\chi^2=6.362$, (1), $p=.012$) and individuals with CdLS ($\chi^2=9.197$, (1), $p=.002$). Furthermore, individuals with PKS had displayed significantly more sensory difficulties across non-social contexts compared to

individuals with AS (χ^2=11.843, (1), p=.001), individuals with FXS (χ^2=4.850, (1), p=.028) and individuals with CdLS (χ^2=9.376, (1), p=.002) (Table 2.11).

Table 2.11: ***Number of Individuals with Pallister-Killian Syndrome, and Non-Matched Individuals with Angelman Syndrome, Cornelia de Lange Syndrome and Fragile X Syndrome Scoring in the 'Typical' Category on the Sensory Experience Questionnaire with Results for the Chi-Squared Analysis.***

Raw Scores	PKS	AS	CdLS	FXS	Chi-Squared Test			Post Hoc Chi-Squared			
	n=15	n=91	n=28	n=40	χ^2	df	P	PKS Significance Direction	χ^2	df	P Value
Hypo-Responsivity	2	31	1	8	12.154	3	.007	None for PKS	N/A	N/A	N/A
Hyper-Responsivity	8	57	10	14	11.680	3	.009	None for PKS	N/A	N/A	N/A
Sensory-Seeking	14	33	13	22	18.850	3	<.001	PKS<AS	16.994	1	<.001
								PKS<FXS	6.362	1	.012
								PKS<CdLS	9.197	1	.002
Social Contexts	3	33	4	7	8.461	3	.037	None for PKS	N/A	N/A	N/A
Non-Social Contexts	11	26	7	16	13.526	3	.004	PKS>AS	11.843	1	.001
								PKS>FXS	4.850	1	.028
								PKS>CdLS	9.376	1	.002

There were significant differences between syndromes groups in their hypo-responsivity (h=36.550, (3), p<.001), hyper-responsivity (h=18.810, (3), p<.001) and sensory seeking (h=27.028, (3), p<.001). Specifically, individuals with PKS displayed higher hypo-responsivity scores compared to individuals with FXS (U=45.292, N_1 =3.50, N_2 =2.25, p=.017) and lower sensory seeking scores compared to individuals with AS (U=-70.156, N_1 =2.31, N_2 =3.15, p<.001), CdLS (U=-62.251, N_1 =2.31, N_2 =3.00, p=.001) and FXS (U=-47.958, N_1 =2.31, N_2 =3.85, p=.010). There were no significant differences between individuals with PKS and other syndrome groups in hyper-responsivity scores (p>.050).

There were also significant differences between syndrome groups in their sensory experiences in social (h=27.256, (3), p<.001) and non-social (h=21.396, (3), p<.001) contexts. Individuals with PKS displayed higher scores in comparison to individuals with AS for social context sensory experiences (U=38.722, N_1 =2.40, N_2 =2.10, p=.034). However, they displayed lower scores in comparison to individuals with AS (U=-53.125, N_1 =2.38, N_2 =2.86, P=.001), CdLS (U=-73.474, N_1 =2.38, N_2 =3.07, p<.001) and FXS (U=-46.804, N_1 =2.38, N_2 =2.79, P=.013) in non-social contexts.

There were significant differences between syndromes groups in all five sensory modalities, tactile (h=21.178, (3), p<.001), auditory (h=16.106, (3), p=.001), visual (h=25.653, (3), p=.001), olfactory (h=27.120, (3), p<.001) and vestibular (h=28.530, (3), p<.001). Specifically, individuals with PKS scored significantly lower (more typical scores) in comparison to individuals with CdLS in their tactile sensory experiences (U=-

42.542, N_1 =2.40, N_2 =2.90, p=.049). They also scored lower in comparison to individuals with FXS in their auditory sensory experiences (U=-45.162, N_1 =2.33, N_2 =2.83, p=.017). Individuals with PKS scored significantly higher scores (more abnormal scores) in comparison to individuals with AS (U=55.648, N_1 =3.50, N_2 =2.33, p>.001) and FXS (U=52.608, N_1 =3.50, N_2 =2.17, p=.003) in their visual sensory experiences. Individuals with PKS scored lower in comparison to individuals with FXS (U=-40.817, N_1 =1.67, N_2 =2.17, p<.001), CdLS (U=-52.070, N_1 =1.67, N_2 =2.33, p=.007), and AS (U=67.888, N_1 =1.67, N_2 =2.50) in their olfactory sensory experiences. Finally, individuals with PKS scored significantly lower in comparison to individuals with CdLS (U=63.463, N_1 =2.38, N_2 =3.07, p<.001), AS (U=-70.646, N_1 =1.75, N_2 =3.25, p<.001), and FXS (U=-76.592, N_1 =1.75, N_2 =3.50) in their vestibular sensory experiences (Table 2.12).

Table 2.12: ***Median (Inter Quartile Range) for Individuals with PKS, Non-Matched Individuals with Angelman Syndrome, Cornelia de Lange Syndrome and Fragile X Syndrome subscales of the Sensory Experience Questionnaire with Results for Kruskal-Wallis Analysis and Post Hoc Mann-Whitney U Analysis.***

Mean Scores		PKS	AS	CdLS	FXS	Kruskal Wallis Tests			Post Hoc Comparison: Mann-Whitney U Test			
						H	df	p Value	PKS Significance Direction	U	Df	P Value
Total SEQ	Median	2.44	2.56	2.75	2.53	13.387	3	.004	PKS<CdLS	-53.892	1	.005
	IQR	2.19-2.59	2.34-2.81	2.45-3.16	2.31-2.98							
Seeking	Median	2.31	3.15	3.00	3.85	27.028	3	<.001	PKS<FXS	-47.958	1	.010
	IQR	1.77-2.54	2.77-3.62	2.77-3.50	2.38-3.31				PKS<CdLS	-62.251	1	.001
									PKS<AS	-70.156	1	<.001
Hypo-responsivity	Median	3.50	2.00	2.92	2.25	36.550	3	<.001	PKS>AS	62.674	1	.010
	IQR	2.83-4.00	1.67-3.33	2.33-3.46	1.83-2.83				PKS>FXS	45.292	1	.017
Hyper-responsivity	Median	2.23	2.08	2.54	2.58	18.810	3	<.001	None for PKS	N/A	N/A	N/A
	IQR	1.84-2.46	1.85-2.46	2.08-3.13	2.10-3.08							
Social	Median	2.40	2.10	2.45	2.40	27.256	3	<.001	PKS>AS	38.722	1	.034
	IQR	2.20-2.70	1.70-2.20	2.13-2.93	2.10-3.08							
Non-Social	Median	2.38	2.86	3.07	2.79	21.396	3	<.001	PKS<FXS	-46.804	1	.013
	IQR	2.05-2.71	2.62-3.10	2.63-3.31	2.48-3.10				PKS<AS	-53.125	1	.001
									PKS<CdLS	-73.474	1	<.001
Tactile	Median	2.40	2.40	2.90	2.60	21.178	3	<.001	PKS<CdLS	-42.542	1	.049
	IQR	2.30-	2.20-	2.53-	2.13-2.98							

Mean Scores		PKS	AS	CdLS	FXS	Kruskal Wallis Tests			Post Hoc Comparison: Mann-Whitney U Test			
						H	df	p Value	PKS Significance Direction	U	Df	P Value
		2.80	2.70	3.38								
	Median	2.33	2.50	2.50	2.83				PKS<FXS	-45.162	1	.017
Auditory	IQR	2.17-2.67	2.33-2.83	2.21-3.00	2.50-3.33	16.106	3	.001				
	Median	3.50	2.33	2.83	2.17				PKS>AS	55.648	1	<.001
Visual	IQR	2.83-3.67	1.83-2.83	2.33-3.33	1.83-2.83	25.653	3	<.001	PKS>FXS	52.608	1	.003
	Median	1.67	2.50	2.33	2.17				PKS<FXS	-40.817	1	<.001
Olfactory	IQR	1.67-2.17	2.33-2.83	1.92-2.96	2.00-2.67	27.120	3	<.001	PKS<CdLS	-52.070	1	.007
									PKS<AS	-67.888	1	<.001
	Median	1.75	3.25	3.25	3.50				PKS<CdLS	-63.463	1	<.001
Vestibular	IQR	1.50-2.25	1.75-4.25	2.75-3.50	3.75-4.00	28.530	3	<.001	PKS<AS	-70.646	1	<.001
									PKS<FXS	-76.592	1	<.001

Parent/Carer Anxiety and Depression

The majority of parents/ carers of individuals with PKS reported borderline (n=6, 42.85%) to abnormal (n=6, 42.85%) anxiety, whilst the majority of parents/carers of individuals with AS reported normal levels of anxiety (n=12, 41.4%). Both groups of parents mostly reported normal levels depression (PKS group: n=9, 64.27%, AS group: n=20, 69.00%). There were no significant differences in anxiety and depression of parents/carers between the groups ($p>0.05$) (Table 2.13).

Table 2.13: ***Percentage Displaying Classification[26], Median (Inter Quartile Range), for Individuals with PKS and Non-Matched individuals with Angelman Syndrome, Cornelia de Lange Syndrome and Fragile X Syndrome Subscales of the Hospital Anxiety and Depression Scale with Results for Mann-Whitney U Analysis.***

Raw Scores		PKS (n=14)				AS (n=29)[27]				Mann-Whitney U	
		N	%	Median	IQR	N	%	Median	IQR	U	P Value
Anxiety	Normal	2	14.29%	10	8-11	12	41.4%	8	5-12	164.50	.316
	Borderline	6	42.85%			7	24.15%				
	Abnormal	6	42.85%			10	34.50%				
Depression	Normal	9	64.27%	6	2-9	20	69.00%	4	1-8.50	178.50	.524
	Borderline	4	28.57%			5	14.25%				
	Abnormal	1	7.15%			4	13.80%				

[26] Classification: Normal= 0-7, Borderline=8-10, Abnormal=11-21 (Zigmond and Snaith, 1983)

[27] Participants selected from the non-matched AS group, where HADS data was available. Age, Median: 9.60 years, IQR: 5.92-15.95, 69.00% mobile, 6.9% verbal.

Table 2.14: ***Table displaying Summary Results and Relative Comparisons of the Pallister-Killian Syndrome group to the Angelman Syndrome, Cornelia de Lange Syndrome and Fragile X Syndrome.***[28]

Behavioural Domain	Syndrome Group				
	Matched Comparison Group		Non-Matched Comparison Groups		
	PKS	AS	AS	CdLS	FXS
Challenging Behaviour	0	0	N/A	N/A	N/A
Mood	-	+	N/A	N/A	N/A
Interest and Pleasure	-	+	N/A	N/A	N/A
Stereotyped Behaviour	0	0	N/A	N/A	N/A
Compulsive Behaviour	0	0	N/A	N/A	N/A
Insistence on Sameness	0	0	N/A	N/A	N/A
Overactivity	-	+	N/A	N/A	N/A
Impulsivity	-	+	N/A	N/A	N/A
Autism	+	-	N/A	N/A	N/A
Social Communication	0	0	N/A	N/A	N/A
Restricted, Repetitive Behaviours and Stereotypy	0	0	N/A	N/A	N/A
Reciprocal Social Interaction	0	0	N/A	N/A	N/A
Sociability with Familiar others	-	N/A	+	0	0
Sociability with Unfamiliar others	-	N/A	+	0	0
Hyposensitivity	+	N/A	-	0	-
Hypersensitivity	0	N/A	0	0	0
Sensory-Seeking	-	N/A	+	+	+
Parent/Carer Anxiety and Depression	0	N/A	0	N/A	N/A

[28] For PKS group: += Scores higher than another group, 0=scores than same as another group, -= scores lower than another group. For other groups: += Scores higher than PKS, 0=scores than same as PKS, -= scores lower than PKS.

Discussion

This is the first study to our knowledge to explore the behavioural phenotype of PKS using a cross syndrome approach, drawing direct comparisons with behaviour reported in other genetic syndrome groups with better defined phenotypic behaviour patterns using measures with established psychometric properties with a strong history of contribution to the understanding of behavioural phenotypes (Tierney, Nwokoro, Porter, Freund, Ghuman and Kelley, 2001). Behaviour reported for fourteen individuals with PKS was, where possible, compared with that reported for fourteen people with Angelman syndrome (AS) matched on age, gender, self-help ability, mobility and verbal ability. For other measures, comparisons were made with larger groups of less well-matched individuals with AS, Cornelia de Lange syndrome (CdLS), and Fragile X syndrome (FXS), due to availability of relevant data and the relatively well-established behavioural phenotypes of these groups. This is also the first study to use the well-established autism screening tool (the SCQ) across a range of low functioning individuals with PKS, allowing further understanding of autism symptomology. Furthermore, it is also the first study to explore sociability and sensory experiences of individuals with PKS, using specific well-established questionnaires with good psychometrics.

A summary of the assessment results and how the PKS group differed to the AS, CdLS and FXS group is displayed to ease comparison (Table 2.14).

The findings indicated that the majority of individuals with PKS had very limited abilities, with absent speech and mobility and significant developmental delays consistent with the overall phenotype described in the literature (Kosteneka, Close, Izumi, Krantz and Pipan, 2012). The majority of participants also had health difficulties, and visual and hearing impairments were prevalent in the sample.

Three of the sixteen individuals appeared to display a milder phenotype in terms of their ability levels. These three participants (ages: twelve-years, eleven-years and thirteen-years old) were verbal, mobile, and displayed higher levels of self help skills. Specifically, one participant (ID: 2) was able to feed themself independently, wash and dress themself with help, speak in sentences (but chose not to), could read and write a little and understand monetary values. Another participant (ID: 9) was able to feed themself independently, wash and dress themself with help, speak in sentences, read, write and count a little. Also another participant (ID: 12) was able to feed, wash and dress themself independently, speak in sentences, read, write and count a little. Two of the three with the milder phenotype met criteria for ASD on the SCQ, although one met the more stringent criteria for autism and two displayed SIB. One of these participants was reported to have normal hearing and vision, one had poor vision and normal hearing, and the other had normal vision and poor hearing. Whilst the small N does not allow formal comparison of the behaviours shown by the three more able participants with those who are less able, the results do suggest a wide behavioural phenotype.

Blyth et al., (2015) argue the higher reported functioning is mostly in individuals born after 2000 due to more advanced antenatal imaging detecting abnormalities leading

to termination for those more profoundly affected. Kostanecka, Close, Izumi, Krantz and Pipan (2012) suggest that extent of the milder phenotype of PKS has not been established due to a lack of diagnoses in these individuals.

The current study found higher reported levels of SIB displayed by individuals with PKS (46.67%) than has been reported in previous research (25%; Wilkens et al., 2012), although lower levels of repetitive and stereotyped movements (53.33%) were reported than in other studies (75%; Kostanecka, Close, Izumi, Krantz and Pipan, 2012). Individuals with PKS generally displayed lower frequencies of destruction of property and physical aggression than the matched participants with AS, although the differences did not reach statistical significance. Aggressive behaviours are known to be a part of the behavioural profile of people with AS, although it should be noted that the AS sample studied here displayed a lower frequency of SIB (45.1%) and aggression (13.33%) than reported in previous research (73%; Arron, Oliver, Berg, Moss and Burbidge, 2011). This may reflect the lower ability selection bias of the sample, although research has reported that high impulsitivity, lower scores in social interaction and poor communication have been reported as risk markers for aggressive behaviour (Arron, Oliver, Moss, Berg and Burbidge, 2011; Cooper et al., 2009).

Individuals with PKS in the current sample displayed lower levels of SIB (46.67%) than individuals with CdLS (70.3%) and similar levels to individuals with FXS (51.3%; Davis and Oliver, 2016). Furthermore, their frequency of physical aggression (2/15; 13%) is lower compared to individuals with CdLS (40.2%) and FXS (51.3%). Participants with PKS have lower ability levels than those with CdLS and

FXS, which may be a confounding factor when making comparisons. However, challenging behaviour can be frequent for those with severe ID (69%; Davis and Oliver, 2016). It may be that, while nearly half of the sample was reported to display self-injurious behaviours, SIB is not a specific part of the phenotype of PKS.

Whilst the relatively low levels of some types of challenging behaviour displayed in PKS (e.g., physical aggression; disruption and destruction of property) might be surprising due to the high level of ID, which is a known risk factor for challenging behaviour (Cooper et al., 2009), it might be that limited physical abilities restrict the behaviours, which can be displayed. The relatively lower levels of stereotyped and repetitive behaviours (in comparison to other syndrome groups[29]) and lower levels of activity are consistent with relatively lower levels of challenging behaviours, since increased repetitive and stereotyped behaviours and activity have been reported as significant risks markers for challenging behaviours for individuals with autism (Richards, Oliver, Nelson and Moss, 2012) and a number of genetic syndromes (Oliver, Sloneem, Hall and Arron, 2009).

Individuals with PKS displayed a similar level of restrictive and repetitive behaviours to individuals with AS. Individuals with AS have been found to have lower levels of repetitive behaviours compared to other genetic syndrome groups (Moss, Oliver, Arron, Burbidge and Berg, 2009; Barry, Leitner, Clarke and Enfeld, 2005; Bonati et al., 2007; Walz, 2006). Whilst overall scores on the RBQ were comparable, it

[29] Percentages of stereotyped behavior in other syndrome groups; CdLS=57% (Hyman, Oliver, and Hall, 2002), AS= 9-84% (Summers, Allison, Lynch and Sandler, 1995), FXS= 69.2-74.2%, Lowe Syndrome= 85% and SMS= 100% (Smith and Gropman, 2001).

may be that different types of RRBs were present for the different groups. However, Moss, Oliver, Arron, Burbidge and Berg (2009) reported that individuals with AS were less likely to endorse items on the RBQ, which are considered 'higher level', that require individuals to have a level of ability, for example items which assess tidying up, hoarding and organising objects. Yet, individuals were more likely to display hand and body stereotypy, which is also similar to the individuals with PKS found in this study.

Participants with PKS were reported to display less impulsivity and overactivity. A lack of activity has been described in other research examining individuals with PKS, who have sometimes been observed to be lethargic and withdrawn, possibly to poor hearing and visual, mobility or sensory difficulties (Kostanecka, Close, Izumi, Krantz and Pipan, 2012). The research reported higher levels of over-activity and impulsivity in individuals with AS, which is comparable with previous research using TAQ. The previous research examining other syndrome groups can also be informally compared to the results here, which suggest that the PKS the lowest levels of impulsivity and over-activity, which are mostly compared to those individuals with Prader-Willi Syndrome (PWS) (Oliver, Berg, Burbidge, Arron and Moss, 2011)[30].

Unsurprisingly, the study found lower mood and interest and pleasure in individuals with PKS in comparison to individuals with AS. This is perhaps due to the unique display of laughing, smiling and a happy demeanour which characterises the AS

[30] This research: AS (over-activity); mean=18.64, sd=7.47, (impulsivity); mean=14.00, sd=9.11. PKS (over-activity); mean=9.53, sd=8.48, (impulsivity); mean=6.30, sd=8.00. Previous research: AS (over-activity); mean=19.02, (impulsivity); mean=17.48: FXS (over-activity); mean=18.77, (impulsivity); mean=16.21: CdLS (over-activity); mean=14.56, (impulsivity); mean=14.75: PWS (over-activity); mean=6.94, (impulsivity); mean=13.00 (Oliver, Berg, Burbidge, Arron and Moss, 2011).

phenotype (Walz and Benson, 2002). However, previous literature has reported other syndrome groups have a similar MIPQ scores to those found in the current study's AS group (Nelson, Moss and Oliver, 2014)[31]. Thus, indicating the higher mood and interest and pleasure in AS is perhaps not magnifying the lower mood and interest seen in the PKS group, but rather the low mood may be distinctive to the PKS phenotype. However, future research would benefit from directly comparing PKS individuals to other matched genetic syndromes using statistical analysis to draw more precise conclusions. It is hypothesised that the high levels of health difficulties and autism symptomology in the PKS group could be associated with the lower mood and interest as these constructs have been noted as risk factors for a lower mood in other genetic syndromes (Berg, Arron, Burbidge, Moss and Oliver, 2007; Kim, Szatmari, Bryson, Streiner and Wilson, 2000). However, contributing factors could also be physical difficulties and reported lack of interaction in their environment reducing their opportunity to engage in meaningful activities (Kostanecka, Close, Izumi, Krantz and Pipan, 2012).

Interestingly, there was a positive correlation of mood with age, indicating higher mood for older participants. This contrasts with the effect seen for some other groups (e.g., CdLS; Berney, Ireland and Burn, 1999; Nelson, Moss and Oliver, 2014; Oliver, Berg, Moss, Arron and Burbridge, 2011) and Kleefstra Syndrome (unpublished data; personal communication, 2016) for whom older age is associated with declining mood, interest and pleasure. Whether this is an effect which would also be seen

[31] Reported results for individuals <15 years old with CdLS (Mood, median; 20, IQR; 17-21; Interest and pleasure; median; 18, IQR; 15-20), FXS (mood; median; 21.00, IQR; 20-23; Interest and pleasure; 17, IQR; 14-20) and CdCS (Mood, median; 20, IQR; 18-22; Interest and pleasure; median; 19, IQR; 18-21) (Nelson, Moss and Oliver, 2014).

longitudinally, indicating improvement with age, remains to be addressed in future studies.

A large majority of participants with PKS met criteria for ASD on the SCQ, a well-regarded screening tool. More individuals within the PKS group (64.3%) met the more stringent criteria for autism, compared to individuals in the AS group (14.3%), suggesting the prevalence of autism may be higher in comparison to the prevalence in AS syndrome (34%; Richards et al., 2015). However, the autism assessment used was a screening measure and therefore is not a diagnostic tool. There is a lack of autism descriptions in the PKS literature and this should be a specific focus of further research using observation-based diagnostic assessments. However, as noted by Kostanecka, Close, Izumi, Krantz and Pipan (2012), there is difficulty using autism assessment methods as they are not applicable to the low levels of cognitive functioning and the normative data often represents only typically developing children.

The current study is the first to examine the sociability of people with PKS. Data indicated that individuals with PKS display greater social interaction with familiar adults compared to unfamiliar adults which is consistent with many other genetic syndromes (Nelson, Moss, Powis, Waite and Oliver, In press). Furthermore, the results demonstrated that individuals with PKS display a lack of sociability in comparison to individuals with AS, which is consistent with research describing how individuals with AS have a strong interest in social communication (Clayton-Smith, 2001; Williams et al., 2006), despite their inappropriate social reciprocity (Smith et al., 1996; Peters, Beaudet, Madduri and Bacino, 2004). Furthermore, the results in the current study are

consistent with SQID results previously reported for individuals with AS (Nelson, Moss, Powis, Waite and Oliver, In press)[32].

However, individuals with PKS displayed similar difficulties/avoidance of social interactions to individuals with CdLS and FXS, which is also consistent with previous SQID analysis for individuals with CdLS and FXS (Nelson, Moss, Powis, Waite and Oliver, In press)[33]. This suggests that individuals with PKS may also display significant shyness and social anxiety similar to individuals with CdLS and FXS (Hall, DeBarnardis and Reiss, 2006; Richards, Moss, O'Farrell, Kaur and Oliver, 2009). Sociability is not thought to be related to adaptive functioning (r=.02-.7; Nelson, Moss, Powis, Waite and Oliver, In press), indicating that comparisons between PKS and other syndromes such as CdLS and FXS may be valid in this regard. However, considering the lack of verbal communication skills in the PKS group, and suggestions that a lack of ability possibly also contributes to reduced social interaction for individuals with CdLS (Moss, Howlin, Magiati and Oliver, 2012), future research will need to determine if the lack of sociability is due to a reduced desire to engage socially/social anxiety or due to a lack of ability to do so. This reduced sociability may account for the high percentage of individuals with PKS reaching autism criteria. However, further research investigating the autism symptomology in PKS is needed.

[32] AS; n=66, mean age=15.1 years old, unfamiliar score; median=41, IQR=31-48, familiar score; median=53, IQR=48-55 (Nelson, Moss, Powis, Waite and Oliver, In press).
[33] CdLS: n=98, mean age=18.8 years old, unfamiliar score; median=26, IQR=13.50-35, familiar score; median=41.50, IQR=35-48
FXS: n=142, mean age=19.8 years old, unfamiliar score; median=15, IQR=11-25, familiar score; median=39, IQR=31-44 (Nelson, Moss, Powis, Waite and Oliver, In press).

Certain areas of sociability correlated positively with age, indicating that older participants may have shown greater levels of certain types of sociability. This is intriguing in relation to the aforementioned possible positive association of mood with age. A possible decline in sociability with age has been seen in some other syndrome groups (e.g., CdLS; Berney, Ireland and Burn, 1999; Nelson, Moss and Oliver, 2014; Oliver, Berg, Moss, Arron and Burbridge, 2011) and Kleefstra Syndrome (unpublished data). The pattern observed in the current data should be investigated further in future work.

The current study is the first to use a comprehensive assessment to explore sensory experiences in individuals with PKS using comparison groups. The results found that hypersensitivity and sensory-seeking behaviours mostly fell in the typically developing range for people with PKS. However, the data indicated hyposensitivity behaviours, across social and non-social contexts. The group specifically displayed less difficulties hypersensitivity in olfactory, vestibular, auditory and tactile domains, yet increased hypersensitivity in visual domains. Moreover, The PKS group significantly displayed the least sensory-seeking behaviours compared to the AS, CdLS and FXS groups and significantly more hypo-sensitivity behaviours compared to individuals with FXS. This finding is consistent with previous research reporting that individuals with AS display sensory-seeking behaviours (Peters, Horowitz, Barbieri-Welge, Taylor and Hundley, 2012; Walz and Baranek, 2006) and individuals with FXS display hypersensitivity (Hagerman and Hagerman, 2002; Roberts, Weisenfeld, Hatton, Heath and Kaufmann, 2007).

This finding also supports Kostanecka, Close, Izumi, Krantz and Pipan's (2012) suggestion that individuals with PKS display lethargy and withdrawal due to hyposensitivity difficulties and avoidance. It is hypothesised that individuals with PKS are passive in their coping strategies and do not attempt to adapt their sensory thresholds (Dunn, 1997; 2001). As a result, the sensory difficulties and reduced mobility in the PKS group are perhaps associated with individuals' lack of engagement with the environment, which has consequently restricted their learning and independence (Baranek et al., 2008; Baranek, Chin, Hess, Yankee, Hatton and Hooper, 2002). However, to determine the causal relationship between sensory difficulties and development, longitudinal analysis is necessary.

The final finding of the research was the high levels of reported anxiety and depression in carers/parents of both individuals with PKS and AS. This distress, including clinical symptoms of depression, stress and anger experienced by carers of children with autism has been well described in the literature (Lutz, Patterson and Klein, 2012; Sawyer et al., 2010; Stuart and McGrew, 2009). In addition, Griffith et al., (2011) reported that parents of children with AS, CdLS and CdCS experience specific difficulties in accessing medical services and general day-to-day living.

Clinical implications

The findings of the study are important in further defining the behavioural phenotype of PKS. The results have clinical implications for the assessment and intervention of behavioural difficulties. First, due to the high frequency of autism identified by the SCQ, it may be recommended that individuals with PKS undergo

autism screening to aid early identification of specific autism symptomology, which is fundamental in developing appropriate behavioural and educational programmes (Moss and Howlin, 2009).

Second, due to the hypothesis about mobility and hypo-sensitivity difficulties leading to reduced engagement in the environment and thus limiting learning opportunities, it may be useful to assess whether sensory interventions might mitigate some elements of developmental delay. Early sensory-integration interventions promoting adaptive approaches to sensory experiences could be implemented to encourage individuals to explore their environment. Whilst there is no specific research assessing such interventions with individuals with PKS, child-directed sensory interventions have been clinically useful for individuals with autism (Case-Smith, Weaver and Fristad, 2015). Finally, it is recommended that carer distress is identified early to ensure the timing of appropriate interventions (Griffith et al., 2011; Shah, Wadoo, Lattoo, 2010).

Limitations

Firstly, the possible limitations of the statistical analysis and potential Type I errors need to be acknowledged. The results and consequent clinical implications need to be taken with caution due to the use of the numerous statistical tests employed and the small sample size. Specifically, it is possible the conclusions reached were incoreectly arrived at due to statistical error and there is perhaps no (or lesser) significant difference between individuals with PKS incomparsion to individuals with other genetic syndromes. Therefore, the possible behavioural phenotype of PKS

discussed may not be valid and reliable, thus parents and clinicians may be misinformed by the research and expect individuals with PKS to exhibit certain behaviours shown by this research, despite that behaviour not being part of the PKS behavioural phenotype. This has multiple clinical and ethical implications of potential parental anxiety, misdiagnosis and implementation of non-beneficial treatment plans. It is therefore essential the results of the study are replicated to ensure their validity and families and clinicans are aware of the studies limitations.

The selection of participants may be a potential limitation to the research as participants were only recruited via parent support organisations, which may particularly attract families who have a child with particular characteristics. Therefore results may not be representative of all individuals with PKS. Additionally, as use of multiple fully matched comparison groups was not possible, it needs to be noted that different demographic or ability levels may have accounted for the difference in behaviours between the PKS group and the other syndrome groups. In addition, some differences in comparisons may be due to the characteristics of the AS phenotype and not specifically due to a unique PKS phenotype. Whilst the use of comparison groups is a strength of the study, the selection of the matched AS sample on characteristics such as ability may mean that this group is not representative of AS more generally. As a result, the findings should not be taken as a definite phenotype for the PKS group. Future research needs to make further direct comparisons between other matched ability syndrome groups. Moreover, future research should consider investigating behaviours shown by different specific genetic mechanisms in PKS, as this study included all individuals with PKS as a group despite differences in specific genetics (Dykens, 1995).

As this was a cross-sectional survey study data were available for only one time point. This means that possible associations with age should be followed up with future longitudinal studies. This is fundamental to assess in future research as behavioural phenotypes are not static and this methodology would allow identification of specific risk markers such as hyposensitivity, which may contribute to increased difficulties or delays as children develop (Nelson, Moss and Oliver, 2014). For example, some individuals with FXS display an increase of autism symptomology and social avoidance (Hatton et al., 2006) and reduced adaptive functioning (Fisch, Simensen and Schroer, 2002) with age.

Data are also based on parent report assessments only. Future research would benefit from the use of observational to strength the reliability of the results and investigate gene-environment interactions. This study was the first to use the SCQ for a range of individuals with PKS, including those with a lower cognitive ability. Although the SCQ is only recommended for individuals with a mental age of two years or older (Rutter, Bailey and Lord, 2003), research has suggested it is suitable for individuals who are less able (Lee, David, Rusyniak, Landa and Newschaffer, 2007).

Finally, this identification of a wide spectrum of the phenotype has also been reported in other studies, which describe distinct individuals with a high level of functioning and ability (Genevieve et al., 2003; Warburton, Anyane-Yeboa, Francke and Reynolds, 1987; Wilkens et al., 2003). Differences in presentation may relate to genetic factors (Leube, Majewski, Gebauer and Royer-Pokora, 2003). Unfortunately,

the current study was limited by lack of direct genetic testing leading to reliance on parental report and/or information available via UNIQUE. For two of three most able participants, genetic information beyond diagnosis of PKS was not available. Future research needs to develop a precise understanding of how the molecular mechanisms relate to the full PKS phenotypic spectrum described in the literature (Izumi and Krantz, 2014).

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CHAPTER 3

Public Dissemination Document:

Exploring Sensory symptoms across Rare Genetic Syndromes and Exploring the Behavioural Phenotype of Pallister-Killian Syndrome

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Literature Review: Exploring Sensory symptoms across Rare Genetic Syndromes

Introduction

Autism Spectrum Disorder (ASD) was previously diagnosed by clinicians assessing individual's behaviour, including their social interactions, communication skills, imagination and repetitive behaviours. However, national guidance (DSM-5; APA, 2013) has changed and clinicians now need to additionally assess individual's sensory symptoms before a diagnosis can be made.

Individuals with ASD have a range of sensory difficulties across different modalities (Schaaf and Lane, 2015). These could be hypo-sensitivity (individuals are slower to respond to sensory stimuli), or hyper-sensitivity (individuals experience more intense sensory experiences) (Dunn, 2001). In individuals with ASD the difficulties are displayed inconsistency across different modalities including, touch, sight, taste, smell and hearing (Lane, Dennis and Geraghty, 2011).

The changes in the diagnostic criteria not only has implications for individuals with ASD, but also for individuals with rare genetic syndromes and intellectual disability as many individuals with genetic syndromes also have ASD symptoms (Richards, Jones, Groves, Moss and Oliver, 2015). Therefore, it is important to assess sensory symptoms in a range of genetic syndromes.

Method

Research databases were searched to identify all published papers that investigated sensory symptoms in a range of genetic syndromes. Sixteen papers were identified that investigated sensory symptoms in seven syndromes; Angelman syndrome (AS), Down syndrome (DS), Fragile X syndrome (FXS), Phelan-Mc Dermid syndrome (PHMDS), Smith-Lemli-Opitz syndrome (SLOS), Smith Magensis syndrome (SMS) and Williams syndrome (WS). Each paper was evaluated against a number of different criteria, which helped determine how well the research was conducted and how reliable the results were.

Main Results

1. All of the syndrome groups displayed a range of sensory difficulties.
2. Some of the research reviewed was not completed to a high standard, therefore the results could not be reliably used to draw conclusions about each syndrome.
3. The most reliable research showed the individuals with FXS and WS had hyper-sensitivity difficulties and individuals with AS had hypo-sensitivity difficulties.
4. Not all genetic syndromes displayed the same sensory difficulties and responded to different modalities in different ways.

Conclusion

The findings show that the assessment of sensory symptoms in genetic syndromes will have implications for co-morbid diagnoses of ASD. Specifically, suggesting that some syndromes may be more be more likely to met criteria for a diagnosis of ASD, whereas some syndromes will be less likely. The research as a whole had a lack of

comparison groups, often only used one method of assessing sensory symptoms and did not follow individuals up to determine how their sensory symptoms changed as they grew older.

Research Study: Exploring the Behavioural Phenotype of Palllister-Killian Syndrome (PKS)

Introduction

Pallister-Killian syndrome (PKS) is a rare genetic disorder first identified in 1977 (Pallister et al., 1977). Much of the research into the syndrome has concentrated on the their physical health difficulties and the underlying genetics. There has been a lack of research describing the 'behavioural phenotype' of PKS. A behavioural phenotype is a set of behaviours, which are more likely to be displayed by individuals with one specific syndrome compared to individuals with different genetic syndromes (Dykens, 1995). For example, research has reported that the Angelman Syndrome (AS) group behavioural phenotype includes, sensory-seeking, a happy demeanour, excessive laughing and a desire to communicate with others (Williams et al., 2006). To date previous research investing the behaviour of the syndrome have used less reliable assessment measures and not compared individuals with PKS to other individuals with other genetic syndromes. Therefore, there is a need to further investigate the behavioural phenotype of PKS using more reliable assessments and comparing results to other syndrome groups (Nelson, Oliver and Moss, 2014).

Method

Sixteen Parents of individuals with PKS completed online questionnaires exploring challenging behaviour, mood, activity, repetitive behaviours, ASD symptomology, sensory symptoms and parental anxiety and depression. This data was compared against individuals with other genetic syndromes including AS, Fragile X syndrome (FXS) and Cornelia de Lange syndrome (CdLS). Some of the individuals in the comparison syndrome groups were matched by their age and ability to participants with PKS, to be more confident the results found were not due to these factors and more likely due to the syndrome difference. Although, it was not possible to match all individuals in all syndrome comparison groups.

Main Results

1. Individuals with PKS have developmental delays and are mostly not independent mobile and are unable to speak.
2. Individuals with PKS displayed the same level of challenging behaviour as individuals with AS.
3. Individuals with PKS displayed behaviour which suggested they had a lower mood and less interest and pleasures compared to individuals with AS.
4. Individuals with PKS displayed the same level of repetitive behaviours as individuals with AS.

5. Individuals with PKS were less active and impulsive compared to individuals with AS.
6. More individuals with PKS met screening criteria for Autism than individuals with AS.
7. Individuals with PKS were less sociable compared to individuals with AS, but displayed similar sociability to individuals with FXS and CdLS.
8. Individuals with PKS showed more hyposensitivity difficulties compared to individuals with AS and FXS and less sensory-seeking behaviours compared to individuals with AS, FXS and CdLS.
9. Parents/carers of individuals with PKS had similar levels of anxiety and depression as parents/carers of individuals with AS.

Discussion

The research suggests that the behavioural phenotype of PKS may include low mood, lack of interest and engagement, reduced activity, a lack of sociability, hyposensitivity difficulties and autism. However, there were some individuals who displayed a less severe phenotype. The results highlight the importance of ASD assessments and timely sensory interventions (Griffith et al., 2011).

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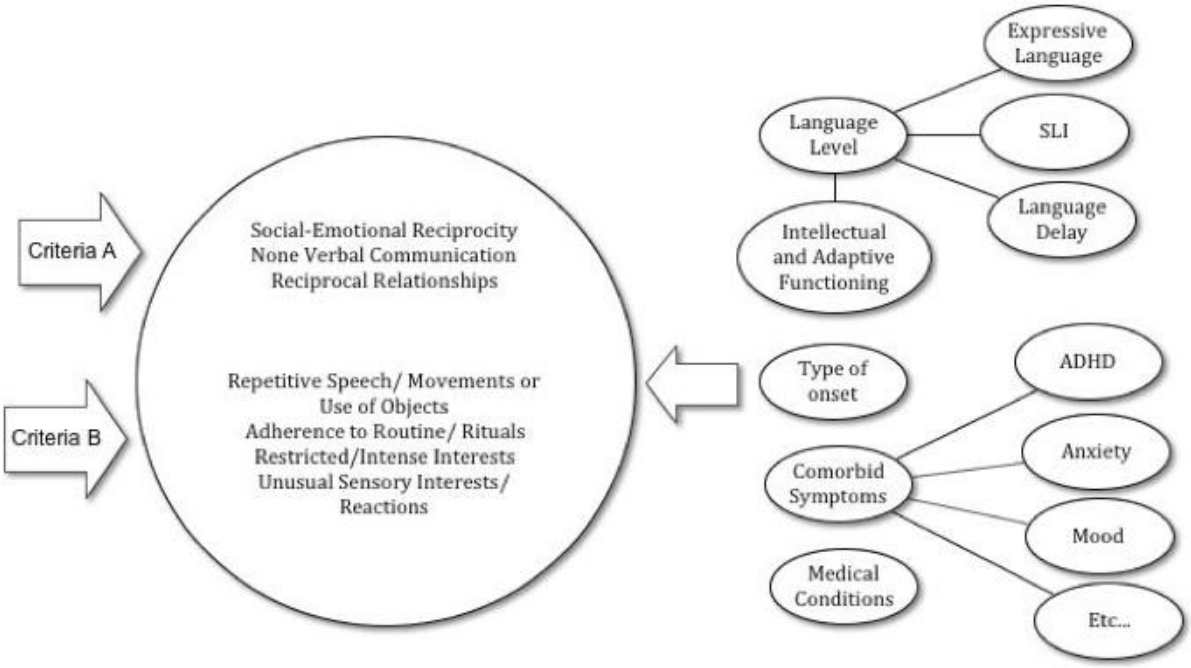
Appendix 1: Criteria and Associated Features with ASD taken from Grzadzinski, Huerta and Lord (2013).



Appendix 2: The Percentage of ASD Symptomology in a Range of Genetic Syndromes Associated with Intellectual Disability.

Syndrome	Percentage of ASD comorbidity	
	Richards (2015)	Zafeirous, Ververi, Dafoulis, Kalyva and Vargiami (2013)
Angelman Syndrome	34%	50-61%
CHARGE Syndrome	30%	28-68%
Chromosome 22q11.2 Deletion Syndrome	11%	-
Chromosome 2q37 Deletion Syndrome	-	24-50%
Cohen's Syndrome	54%	25-93%
Cornelia de Lange Syndrome	43%	46-67%
Down Syndrome	16%	16-19%
Fragile X Syndrome	22%	15-52%
Klineflter Syndrome	-	11-27%
Neurofibromatisis Type 1	18%	4% (Autism)
Noonan's Syndrome	15%	-
Phelan- McDermid Syndrome	-	50%
Potocki-Lupski Syndrome	-	>65%
Prader Willi Syndrome	-	19-36%
Rett Syndrome	61%	
Smith-Lemli-Opitz Syndrome	-	53-57%
Smith-Magenis Syndrome	-	68.4%
Soto Syndrome	-	68%
Timothy Syndrome	-	80%
Tuberous Sclerosis Complex	36%	5-61% (~50%)
Turner Syndrome	-	3% (Autism)
Velocardiofacial Syndrome	-	14-50%
William's Syndrome	12%	50%

Appendix 3: Explanation of the Development of the Quality Assessment Framework

Sensory Assessment

Richards et al., (2015) criteria for ASD assessment was changed to assess sensory modulation methods. Methods which have not been validated or used in previous studies, lack reliability and validity, specifically, criterion validity due to difficulties in overlapping constructs (Gabriel et al., 2008). Therefore, conclusions are limited and results can be used only as a screening, exploratory assessment of sensory modulation. Assessments, which have been previously used and offer psychometric properties, are considered more reliable and valid. However, there is often a lack of consistency between parent reports, observation methods and physiological data (Goldberg, Landa, Lasker, Cooper and Zee, 2000), thus, a combination of these methods offered the most comprehensive assessment (Rogers and Ozonoff, 2005). However, it is noteworthy that no sensory assessment has currently been validated for individuals with rare genetic syndromes.

As a result, a broad quality criterion of sensory modulation assessments was constructed. The sensory assessments used in the research were either ranked 'red', 'yellow', 'orange' or 'green'. Red was assigned to studies where no information was specified or reported on the type of sensory assessment conducted. A red symbol was also assigned to studies where clinician judgement alone was used to assess sensory modulation, without reference to any specified tools or diagnostic criteria. A yellow symbol was assigned when an assessment method was used, but it had not been previously used in other research and thus lacked validation, e.g. SRAF-SSI. A yellow

symbol was also given if a validated assessment measure was used, although it had not been validated or previously used in individuals with ID or ASD, or was being used for participants out of the normative age range. An orange symbol was assigned for studies that employed validated assessment measures, which had been validated or used previously for individuals with ID or ASD and was used for participants within the normative age range. Finally, a green symbol was assigned if studies used consensus from multiple assessments, and that *at least one* of these assessments would have obtained an orange symbol in isolation.

Comparison Group

The CASP framework (CASP, 2014) questions if control participants are matched and discusses the importance of comparison participants, selection methods and eligibility criteria. Therefore, comparison to normative data is less comprehensive compared to the studies, which have recruited their own participants. Furthermore, Young and Solomon (2009) highlight the importance of appropriate comparison groups, suggesting that the only difference between groups should be the syndrome diagnosis. This difficulty has also been discussed in the sensory modulation literature, specifically; suggesting that research needs to include age or IQ matched comparison groups (Ben-Sasson et al., 2009).

A criterion for comparison groups was developed. The comparison participants/data used in the research were ranked from 'red', 'yellow', 'orange' and 'green' with a symbol of red being assigned to studies where no information was specified or reported about comparison groups/data. A symbol of yellow was assigned when a comparison

could be made to published normative data or data in other research articles. A symbol of orange was assigned for studies that recruited and assessed a comparison group, which either contained TD individuals or those with ID, ASD or another genetic difficulty or syndrome, which was recruited by the research paper. Finally, a symbol of green was assigned if studies recruited and assessed a comparison group, which was matched at least on one domain e.g. chronological age or ID, which was recruited by the research paper.

Confounding Variables

The CASP framework (CASP, 2014) questions what confounding factors were accounted for and if they were considered in the design and analysis of the study. Moreover, Young and Solomon (2009) and von Elm, Altman, Egger, Pocock, Gotzsche and Vandenbroucke, (2007) recommend considering if important confounding factors were identified and accurately assessed. Confounding variables have also been considered in the literature and there is debate regarding the contribution of age, ID, repetitive behaviours, attention, social communication and mental health have on sensory modulation (e.g. Boyd et al., 2010; Militerni, Bravaccio, Falco, Fico and Palermo, 2002; Simonoff, Pickles, Charman, Candler, Locas and Baird, 2008; Watson et al., 2011).

Therefore, a criterion for assessment of confounding variables was developed. The assessment of confounding variables in the research was ranked ‘red’, ‘yellow’, ‘orange’ and ‘green’, with a red symbol assigned to studies where no information was specified or reported about confounding variables. A symbol of yellow was assigned

when at least one known confounding variables were assessed, but only used to describe participant sample, e.g. descriptions of age, or IQ, but no analysis was completed. A symbol of orange was assigned for studies were at least one known confounding variable was assessed and the relationship between constructs were considered e.g. correlational analysis between sensory modulation and repetitive behaviour assessment or age, functional ability. However, confounding variables were not controlled for in sensory analysis. Finally, a symbol of green was assigned if studies assessed known confounding variables and they were controlled for in the analysis.

Developmental Changes

The CASP framework (CASP, 2014) questions if participants were followed up and if the length of follow-up was long enough. Moreover, the sensory modulation literature suggests that studies use longitudinal methodology to determine how sensory symptoms develop and change with age (Schaaf and Lane, 2015).

A criterion for assessment for assessing developmental changes was developed. The assessment for developmental changes in the research was ranked 'red', 'yellow', 'orange' or 'green', with a symbol of red assigned to studies where no information was specified or reported about age-related changes. A symbol of yellow was assigned when retrospective data was collected, e.g. interviewing parents/carers about the development and changes in sensory modulation. A symbol of yellow was also given if correlational data was analysed between age and sensory modulation. A symbol of orange was assigned for studies, which made comparisons between specific age ranges e.g. recruiting both younger and older individuals with a syndrome and comparing sensory

modulation between the two age groups. Finally, a symbol of green was assigned if studies were longitudinal and assessed the same participants over a length of time.

Appendix 4: Participant Invitation, Consent Forms, Information Sheets and Background Information Questionnaire.

The Cerebra Centre for Neurodevelopmental Disorders

UNIVERSITY OF BIRMINGHAM

April 2016

Dear Parent,

We are writing to inform you of a new research project that is being carried out at the Cerebra Centre for Neurodevelopmental Disorders at the University of Birmingham. We would like to invite you and the person you care for to take part in this new research project. Briefly, the research is a questionnaire study looking at different behaviours in children and adults with Pallister-Killian syndrome that have received minimal attention within the literature.

We have contacted you through Unique. Your personal details will not be known to us unless you decide to take part in the study. There is an information sheet enclosed that gives you more details about why the research is being carried out and what participation will involve. If you feel it is appropriate you may wish to discuss the research with the person you care for before a decision is made about taking part.

There is an information sheet enclosed that gives you more details about why the research is being carried out and what it will involve. If you and your child/person you care for would like to take part in the study then please complete the enclosed consent form and questionnaire pack and return them in the pre-paid envelope provided.

Please read the information sheets before completing the questionnaires and if you are unclear about any aspect of the study or have any questions then contact Professor Chris Oliver at the address below or on

Thank you for your time and we look forward to hearing from you.

Yours sincerely

Chris Oliver
Professor of Neurodevelopmental Disorders

Consent Form A : For individuals who are able to provide consent to participate in the study

Understanding behaviour and family adjustment in individuals with neurodevelopmental disorders

Study Director: Professor Chris Oliver

SECTION 1: Please complete this section if you are a person with Pallister-Killian syndrome:

1. Has somebody else explained the project to you? YES/NO
2. Do you understand what the project is about? YES/NO
3. Have you asked all of the questions you want? YES/NO
4. Have you had your questions answered in a way you understand? YES/NO
5. Do you understand it is OK to stop taking part at any time? YES/NO
6. Are you happy to take part? YES/NO

If any answers are 'no' or you don't want to take part, don't sign your name!

If you do want to take part, you can write your name below

You can also choose if you want to say 'yes' to these questions:

7. If your Dr asks to see your results from this project is that OK? YES/NO
8. Are you happy for us to contact you again in the future? YES/NO

Your name:_____

Date:_____

The person who explained this project to you needs to sign too. If you are under the age of 16, this should be your parent/guardian.

Print name:_____ Sign:_____
Date:_____

<u>SECTION 2:</u> Please complete this section if you are a parent/carer/guardian of a person with PKS

who has provided their consent to participate in the study. **Please initial box…**

1. I confirm that I have read and understood the information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation and that of my child/person I care for is voluntary and that I am free to withdraw at any time without giving any reason, without my or that of my child's/person I care for's medical care or legal rights being affected. ☐

3. I understand that relevant sections of my child's/person I care for's GP medical notes or records confirming genetic diagnosis and health status may be looked at by members of the Cerebra Centre for Neurodevelopmental Disorders research team at the University of Birmingham, where it is relevant to this research project. I give permission for these individuals to have access to these records. ☐

4. I agree to my child's/person I care for's GP being informed of my participation and that of my child/person I care for's in the study, where access to my child's/person I care for's medical records is required. ☐

5. I agree to take part in the above study. ☐

Optional clause: The statement below is <u>optional</u>:

1. I agree to the University of Birmingham research team sharing my research data with any professionals or clinicians working with me and the person I care for should they request to see them. ☐

Print Name: _____
Telephone number: _____

Address: _____
Email: _____

Relationship to participant: _____
Signature: _____
Date: _____

<u>SECTION 3:</u> This is <u>optional</u> and allows you to provide consent for us to keep your personal details on the Regular Participant Database. See section titled 'Regular Participant Database' in the information sheet.

Please initial box…

1. I have read and understood the section titled 'Regular Participant Database' and I would like my personal details to be added to the database. ☐

2. I understand that my name and contact details will be kept by the research team at the University of Birmingham in accordance with the provisions of the Data Protection Act 1998 and I will be contacted by an approved member of the team with information about future research that I and the person I care for may like to participate in. ☐

3. I understand that if my details are held on the database it will be possible for the research team to trace the results of the assessments that I complete in this project back to me and my child/person I care for so that they can look at changes over time if I take part in future projects. ☐

4. I understand that even after I have agreed for my details to be added to the database, I can request that they be removed by contacting Chris Oliver on [redacted] or by post at the School of Psychology, University of Birmingham, Edgbaston, B15 2TT. ☐

5. I understand the Professor Chris Oliver holds ultimate responsibility for the database. ☐

Print Name: _____Signature: _____Date: _____

<u>Consent Form B:</u> For Children under the age of 16 who are <u>not</u> able to provide consent.

<u>Understanding behaviour and family adjustment in individuals with neurodevelopmental disorders</u>

Study Director: Professor Chris Oliver

SECTION 1: Please complete this section if you are a parent/ guardian of a child (under 16 years) with Pallister-Killian syndrome who is not able to provide consent.

Please initial box…

1. I confirm that I have read and understood the information sheet dated 01.02.2010 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation and that of my child/person I care for is voluntary and that I am free to withdraw at any time without giving any reason, without my or that of my child's/person I care for's medical care or legal rights being affected. ☐
3. I understand that relevant sections of my child's/person I care for's GP medical notes or records confirming genetic diagnosis and health status may be looked at by members of the Cerebra Centre for Neurodevelopmental Disorders research team at the University of Birmingham, where it is relevant to this research project. I give permission for these individuals to have access to these records. ☐
4. I agree to my child's/person I care for's GP being informed of my participation and that of my child/person I care for's in the study, where access to my child's/person I care for's medical records is required. ☐
5. I agree to take part in the above study. ☐

Optional clause: The statement below is <u>optional</u>:

6. I agree to the University of Birmingham research team sharing my research data with any professionals or clinicians working with me and the person I care for should they request to see them. ☐

Print Name: _____Name of person you care for_____

Address:_____Email: _____

Telephone number:_____Relationship to participant: _____

Signature: _____Date: _____

SECTION 2: This is optional and allows you to provide consent for us to keep your personal details on the Regular Participant Database. See section titled 'Regular Participant Database' in the information sheet.

Please initial box…

6. I have read and understood the section titled 'Regular Participant Database' and I would like my personal details to be added to the database. ☐

7. I understand that my name and contact details will be kept by the research team at the University of Birmingham in accordance with the provisions of the Data Protection Act 1998 and I will be contacted by an approved member of the team with information about future research that I and the person I care for may like to participate in. ☐

8. I understand that if my details are held on the database it will be possible for the research team to trace the results of the assessments that I complete in this project back to me and my child/person I care for so that they can look at changes over time if I take part in future projects. ☐

9. I understand that even after I have agreed for my details to be added to the database, I can request that they be removed by contacting Chris Oliver on [redacted] or by post at the School of Psychology, University of Birmingham, Edgbaston, B15 2TT. ☐

10. I understand the Professor Chris Oliver holds ultimate responsibility for the database. ☐

Print Name: _____Signature: _____Date: _____

<u>Consent Form C</u>: For individuals over the age of 16 who are not able to provide consent.

<u>Understanding behaviour and family adjustment in individuals with neurodevelopmental disorders</u>

Study Director: Professor Chris Oliver

SECTION 1: Please read the following statements:

Please initial box…

1. I (your name)_____have been consulted about (name of participant)_____'s participation in the above research project. I have had the opportunity to ask questions about the study and understand what is involved. ☐
2. In my opinion he/she would have no objection to taking part in the above study. ☐
3. I understand that I can request he/she is withdrawn from the study at any time without giving any reason and without his/her care or legal rights being affected. ☐
4. I understand that relevant sections of his/her GP medical notes or records confirming genetic diagnosis and health status may be looked at by members of the Cerebra Centre for Neurodevelopmental Disorders research team at the University of Birmingham, where it is relevant to this research project. I give permission for these individuals to have access to these records. ☐
5. I agree to his/her GP being informed of their participation in the study, where access to medical records is required. ☐
6. I agree to take part in the above study. ☐

Optional clause: The statement below is <u>optional</u>:

7. I agree to the University of Birmingham research team sharing his/her research data with any professionals or clinicians working with them should they request to see them. ☐

Print Name: _____ Telephone number:_____

Address:_____

Email: _____

Relationship to participant_____
Signature: _____Date: _____

SECTION 3: This is optional and allows you to provide consent for us to keep your personal details on the Regular Participant Database. See section titled 'Regular Participant Database' in the information sheet.

Please initial box…

11. I have read and understood the section titled 'Regular Participant Database' and I would like my and the person I care for's personal details to be added to the database. ☐

12. I understand that my name and contact details will be kept by the research team at the University of Birmingham in accordance with the provisions of the Data Protection Act 1998 and I will be contacted by an approved member of the team with information about future research that I and the person I care for may like to participate in. ☐

13. I understand that if my details are held on the database it will be possible for the research team to trace the results of the assessments that I complete in this project back to me and the person I care for so that they can look at changes over time if we take part in future projects. ☐

14. I understand that even after I have agreed for my details to be added to the database, I can request that they be removed by contacting Chris Oliver on [redacted] or by post at the School of Psychology, University of Birmingham, Edgbaston, B15 2TT. ☐

15. I understand the Professor Chris Oliver holds ultimate responsibility for the database. ☐

Print Name: _____Signature: _____
Date: _____

The Cerebra Centre for Neurodevelopmental Disorders
UNIVERSITY OF BIRMINGHAM

Understanding behaviour in Neurodevelopmental Disorders: Information Sheet

Please read this information carefully before deciding whether you wish to take part in the study. If you have any further questions please contact Professor Chris Oliver on [redacted]. If you have any medical/ other problems which make it difficult for you to read this information, please contact Professor Chris Oliver for a verbal explanation of the research.

When you are happy that you have all of the information you need to be able to decide whether or not you and the person you care for would like to take part in the study, please complete the enclosed consent form and questionnaire pack return them to us in the prepaid envelope provided

Background

We would like to invite you to take part in a questionnaire study being conducted at the Centre for Neurodevelopmental Disorders, University of Birmingham. This research work, which is led by Professor Chris Oliver, looks at a range of behaviours, skills and impairments in individuals with Pallister-Killian syndrome including: Repetitive behaviour, Hyperactivity, Mood, Challenging behaviour, Social functioning and Health. We will also ask some questions that are related to family well-being and the impact that having a child with a disability has on the family.

We hope that this information will enable us to further understand the behaviours, skills and impairments associated with Pallister-Killian syndrome including challenging behaviour, social functioning, mood, hyperactivity and health and the impact that these behaviours have on the family. The more people that take part in this research, the more meaningful the results will be. A good response will provide new and valuable information about Pallister-Killian syndrome. In the future we hope to follow up the progress of the people who take part in this study. However, participation in this stage of the project will **not** mean that you are obliged to participate in further surveys in the future.

Aims of the study

1. To further our understanding of challenging behaviour, repetitive behaviour, hyperactivity, mood and social functioning in individuals with Pallister-Killian syndrome.
2. To understand what happens with regard to these behaviours as children and adults develop.
3. To understand what, if any, changes may occur with regard to these behaviours when the individuals reach a certain age.
4. To understand the impact of having a child with a disability has on the family.

What will happen if you and your child/the person you care for decide(s) to participate?

Where will the research take place?
The research will involve completing the enclosed questionnaire pack. This can be completed by you in your own time.

Who will be involved in collecting the data?
Members of the research team at the Cerebra Centre for Neurodevelopmental disorders including Professor Chris Oliver, Dr Alice Wheelham and Miss Claire Edwards
How long will participation in the study take?
The questionnaire pack will take approximately 45 minutes to complete.

In the future you may be asked if you would like to complete the questionnaire again so that we can start to understand what happens to people with Pallister-Killian syndrome across their lifetime. We will only contact you with this invitation if you have previously agreed to be contacted by the research team at the University of Birmingham with information about research studies conducted by the team.

Sometimes after you have completed the questionnaire, we may need to contact you again in order to clarify any information that you have provided or to ask you for further information regarding the diagnosis of the person you care for. This helps us to ensure that our data is as useful and as accurate as possible. If this happens then we would contact you again within 6 months of receiving your questionnaire pack to ask whether or not you would be willing to provide us with the extra information.

What will participants be required to do during the study?
We will ask parents and caregivers to complete the enclosed questionnaire pack and return it to us alongside the consent form in the pre-paid envelope provided.

Are there any risks that individuals taking part in the study might face?
There will not be any risks associated with participation in this study.

What are the potential benefits for participants from taking part?
You will receive a personalised feedback regarding your child/ the person you care for. This study will help us to find out more about the lives of people with Pallister-Killian syndrome and the difficulties that these people face. The results might help us to improve things for people with Pallister-Killian syndrome in the future.

Where will data be stored?
The data collected will be kept in locked or password protected storage at the University of Birmingham. Only members of the research team at the University of Birmingham will have access to information that we collect about you. Information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.

If you/ the person you care for decide(s) to participate, what will happen after that participation?
You and your child/ person you care for will receive an individual feedback report describing the results of all of the assessments that were carried out during the study. If requested, this feedback report will be circulated to other interested individuals.

Descriptions of research findings will be published in newsletters of the relevant family support groups and educational institutions involved. Any request for advice concerning the person you care for will be referred to Professor Chris Oliver, Clinical Psychologist.

The researchers will publish the findings from the study in scientific journals and will present the results at relevant conferences.

What will happen to the data afterwards?
The information that you provide will be locked in a filing cabinet at the University of Birmingham or held on a password protected database. Participants will be identified by a unique number so that the information you provide us with cannot be traced to your personal details. You will be able to decide whether or not you want to make your research data available to any professionals or clinicians working with you and the person you care for should they wish to see it. This is optional and will not affect your participation in the current study. If you agree to this, then your research data will only be made available to relevant clinicians or professionals should they contact us directly and request to see it. If you do not agree to this then research data will not be made available to anyone other than the research team at the University of Birmingham.

After 6 months of receiving your questionnaire pack, your personal details will be ***destroyed unless you tell us otherwise.*** This means that we would no longer be able to trace the results of your assessments back to you. ***The section below on 'The Regular Participant Database Information'*** gives information about a database that we use to store the personal details of some participants. Please read this section in order to decide if you would like to join that database.

Regular Participant Database Information:

What is the regular participant database?
We have a database that we keep in the Cerebra Centre where we store the names and contact details of some previous participants. If you would like us to, we can add your details to this database. We would use this information for two things:

1) We will contact you with information about future research work to find out whether or not you would like to participate.
2) It is often important to find out how things change over time. By keeping your details we would be able to trace the results of the previous assessments that you have done with us back to you. This means that if you take part in other studies with us we would be able to look at how things have changed over time.

Who would have access to my details?
Only approved members of out research team would have access to your details. We would not share your details with anyone outside the research team.

When would I be contacted?
You would only be contacted by an approved member of the research team when we are starting another study or phase of a study that we think you might like to participate in or when we need to clarify some information that you have provided us with from participation in a research study.

What happens if I decide that I want my details to be added to the database but then I change my mind?
All you would need to do is contact Chris Oliver on at the School of Psychology, University of Birmingham, Edgbaston, Birmingham, B15 2TT. Your details would be removed from the database immediately.

Consent
After having read all of the information and having received appropriate responses to any questions that you may have about the study you and the person you care for will be asked to give your and your child's/ person you care for's consent to participate in the study if you decide that you do wish to participate. The section below on ***'Giving consent'*** will explain this process. We need to receive consent from/ on behalf of potential participants in order for them to participate.

Withdrawal
Even after consent has been granted, participants can request to be withdrawn from the study at any time, without giving a reason. Even after participation has taken place, consent can be withdrawn and any data collected will be destroyed. This will not restrict the access of you/ the person you care for to other services and will not affect their right to treatment.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. Please contact Chris Oliver on in the first instance. If you remain unhappy and wish to complain formally, you can contact: Professor Chris Miall; Head of School; School of Psychology, University of Birmingham, Birmingham, B15 2TT, by email: hos.psychology@contacts.bham.ac.uk or by phone on 0121 414 4931

Confidentiality

The confidentiality of participants will be ensured. If published, information on the participant will be presented without reference to their name or any other identifying information. All personal details will be kept separately from the information collected so that it will only be possible to connect results to individuals via a special code. This will ensure that results are kept anonymous. In the unlikely event of any evidence of abuse being identified, this information will be disclosed by the research workers.

Review
The study has been approved by Coventry NHS Research Ethics Committee. For any queries or concerns regarding the ethical approval of this study please contact Pauline Pittaway on 02476967529 quoting study reference number: 10/H1210/1.

Further information
If you would like any more information about the study please contact Professor Chris Oliver on Or write to Chris Oliver, School of Psychology, University of Birmingham, Edgbaston, Birmingham, B15 2TT.

Giving consent

Now it is up to you whether you decide that you and your child/the person you care for would like to participate. The decision about whether or not to take part in the study must be 'informed'. This means that anyone making the decision must understand exactly what is involved in the study, what will be required from participants and why.

IMPORTANT:

You need to decide whether your child/the person you care for is able to understand enough about the study to make an 'informed' decision independently about whether or not they would like to participate and to communicate this decision to you. If you are unsure whether or not your child/person you care for is able to understand enough to make a decision independently then we can provide you with some guidelines to help you to assess this A symbol information sheet can also be made available to you if this would be of help. Please contact Professor Chris Oliver request a copy of this.

Please choose from one of the following options:

1. My child/ the person I care for is <u>able to understand</u> what is involved in the study and what will be required from them if they participate and has communicated their decision to me:

If you think that the person ***<u>is</u>* able** to understand enough about the study in order to make an 'informed'
decision and they decide that they would like to participate then please ensure that they complete **Section 1 of <u>Consent Form A coloured YELLOW</u>** enclosed, or that you complete it with them, on their behalf. A parent/carer will need to complete **Section 2 of <u>Consent From A coloured YELLOW</u>** in order to indicate that they also agree to participate in the study. *A symbol information sheet can be made available in order to support your child/person you care for in making this decision if it would be of help.* Please contact the research team if you would like a copy of the symbol consent form or if you need us to adapt this information further, in order to suit your child's needs. Please return the consent form along with the questionnaire pack to us in the prepaid envelope provided.

2. My child/ the person I care for is <u>unable to understand</u> what is involved in the study and what will be required from them if they participate (either because they are too young to understand or because they are unable to understand) and cannot communicate their decision to me:

If you are reading this information on behalf of someone you care for who is under the age of 16 years and you decide that the person ***is not*** able to make an 'informed' and independent decision about whether or not they would like to participate, then we would like to ask you to decide whether or not you think that it is in your child's best interests for them to participate in the study and whether you would like to provide your consent to participation on their behalf. If you would like your child/person you care for to participate in this study, please complete **Consent Form B coloured PURPLE** enclosed. Please return the consent form along with the questionnaire pack to us in the prepaid envelope provided.

UNIVERSITY OF BIRMINGHAM

The Cerebra Centre for Neurodevelopmental Disorders

Understanding behaviour in Neurodevelopmental Disorders: Information Sheet

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When you are happy that you have all of the information you need to be able to decide whether or not you and the person you care for would like to take part in the study, please complete the enclosed consent form and questionnaire pack return them to us in the prepaid envelope provided

Background

We would like to invite you to take part in a questionnaire study being conducted at the Centre for Neurodevelopmental Disorders, University of Birmingham. This research work, which is led by Professor Chris Oliver, looks at a range of behaviours, skills and impairments in individuals with Pallister-Killian syndrome including: Repetitive behaviour, Hyperactivity, Mood, Challenging behaviour, Social functioning and Health. We will also ask some questions that are related to family well-being and the impact that having a child with a disability has on the family.

We hope that this information will enable us to further understand the behaviours, skills and impairments associated with Pallister-Killian syndrome including challenging behaviour, social functioning, mood, hyperactivity and health and the impact that these behaviours have on the family. The more people that take part in this research, the more meaningful the results will be. A good response will provide new and valuable information about Pallister-Killian syndrome. In the future we hope to follow up the progress of the people who take part in this study. However, participation in this stage of the project will **not** mean that you are obliged to participate in further surveys in the future.

Aims of the study

5. To further our understanding of challenging behaviour, repetitive behaviour, hyperactivity, mood and social functioning in individuals with Pallister-Killian syndrome.
6. To understand what happens with regard to these behaviours as children and adults develop.
7. To understand what, if any, changes may occur with regard to these behaviours when the individuals reach a certain age.
8. To understand the impact of having a child with a disability has on the family.

What will happen if you and your child/the person you care for decide(s) to participate?

Where will the research take place?
The research will involve completing the enclosed questionnaire pack. This can be completed by you in your own time.

Who will be involved in collecting the data?
Members of the research team at the Cerebra Centre for Neurodevelopmental disorders including Professor Chris Oliver and Dr Alice Wheelham and Miss Claire Edwards.

How long will participation in the study take?
The questionnaire pack will take approximately 45 minutes to complete.

In the future you may be asked if you would like to complete the questionnaire again so that we can start to understand what happens to people with Pallister-Killian syndrome across their lifetime. We will only contact you with this invitation if you have previously agreed to be contacted by the research team at the University of Birmingham with information about research studies conducted by the team.

Sometimes after you have completed the questionnaire, we may need to contact you again in order to clarify any information that you have provided or to ask you for further information regarding the diagnosis of the person you care for. This helps us to ensure that our data is as useful and as accurate as possible. If this happens then we would contact you again within 6 months of receiving your questionnaire pack to ask whether or not you would be willing to provide us with the extra information.

What will participants be required to do during the study?
We will ask parents and caregivers to complete the enclosed questionnaire pack and return it to us alongside the consent form in the pre-paid envelope provided.

Are there any risks that individuals taking part in the study might face?
There will not be any risks associated with participation in this study.

What are the potential benefits for participants from taking part?
You will receive a personalised feedback regarding your child/ the person you care for. This study will help us to find out more about the lives of people with Pallister-Killian syndrome and the difficulties that these people face. The results might help us to improve things for people with Pallister-Killian syndrome in the future.

Where will data be stored?
The data collected will be kept in locked or password protected storage at the University of Birmingham. Only members of the research team at the University of

Birmingham will have access to information that we collect about you. Information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.

If you/ the person you care for decide(s) to participate, what will happen after that participation?

You and your child/ person you care for will receive an individual feedback report describing the results of all of the assessments that were carried out during the study. If requested, this feedback report will be circulated to other interested individuals. Descriptions of research findings will be published in newsletters of the relevant family support groups and educational institutions involved. Any request for advice concerning the person you care for will be referred to Professor Chris Oliver, Clinical Psychologist.

The researchers will publish the findings from the study in scientific journals and will present the results at relevant conferences.

What will happen to the data afterwards?

The information that you provide will be locked in a filing cabinet at the University of Birmingham or held on a password protected database. Participants will be identified by a unique number so that the information you provide us with cannot be traced to your personal details. You will be able to decide whether or not you want to make your research data available to any professionals or clinicians working with you and the person you care for should they wish to see it. This is optional and will not affect your participation in the current study. If you agree to this, then your research data will only be made available to relevant clinicians or professionals should they contact us directly and request to see it. If you do not agree to this then research data will not be made available to anyone other than the research team at the University of Birmingham.

After 6 months of receiving your questionnaire pack, your personal details will be ***destroyed unless you tell us otherwise.*** This means that we would no longer be able to trace the results of your assessments back to you. ***The section below on 'The Regular Participant Database Information'*** gives information about a database that we use to store the personal details of some participants. Please read this section in order to decide if you would like to join that database.

Regular Participant Database Information:

What is the regular participant database?

We have a database that we keep in the Centre where we store the names and contact details of some previous participants. If you would like then we can add your details to this database. We would use this information for two things:

3) We will contact you with information about future research work to find out whether or not you would like to participate.
4) It is often important to find out how things change over time. By keeping your details we would be able to trace the results of the previous assessments that you have done with us back to you. This means that if you take part in other studies with us we would be able to look at how things have changed over time.

Who would have access to my details?

Only approved members of out research team would have access to your details. We would not share your details with anyone outside the research team.

When would I be contacted?
You would only be contacted by an approved member of the research team when we are starting another study or phase of a study that we think you might like to participate in or when we need to clarify some information that you have provided us with from participation in a research study.

What happens if I decide that I want my details to be added to the database but then I change my mind?
All you would need to do is contact Chris Oliver on [redacted] or at the School of Psychology, University of Birmingham, Edgbaston, Birmingham, B15 2TT. Your details would be removed from the database immediately.

Consent
After having read all of the information and having received appropriate responses to any questions that you may have about the study you and the person you care for will be asked to give your and your child's/ person you care for's consent to participate in the study if you decide that you do wish to participate. The section below on ***'Giving consent'*** will explain this process. We need to receive consent from/ on behalf of potential participants in order for them to participate.

Withdrawal
Even after consent has been granted, participants can request to be withdrawn from the study at any time, without giving a reason. Even after participation has taken place, consent can be withdrawn and any data collected will be destroyed. This will not restrict the access of you/ the person you care for to other services and will not affect their right to treatment.

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. Please contact Chris Oliver on [redacted] in the first instance. If you remain unhappy and wish to complain formally, you can contact: Professor Chris Miall; Head of School; School of Psychology, University of Birmingham, Birmingham, B15 2TT, by email: hos.psychology@contacts.bham.ac.uk or by phone on 0121 414 4931

Confidentiality
The confidentiality of participants will be ensured. If published, information on the participant will be presented without reference to their name or any other identifying information. All personal details will be kept separately from the information collected so that it will only be possible to connect results to individuals via a special code. This will ensure that results are kept anonymous. In the unlikely event of any evidence of abuse being identified, this information will be disclosed by the research workers.

Review
The study has been approved by Coventry NHS Research Ethics Committee. Ref: 10/H1210/01. Tel: 01527 587688

Further information

If you would like any more information about the study please contact Professor Chris Oliver on [redacted] Or write to Chris Oliver, School of Psychology, University of Birmingham, Edgbaston, Birmingham, B15 2TT.

Giving consent

Now it is up to you whether you decide that you and your child/the person you care for would like to participate. The decision about whether or not to take part in the study must be 'informed'. This means that anyone making the decision must understand exactly what is involved in the study, what will be required from participants and why.

IMPORTANT:

You need to decide whether your child/the person you care for is able to understand enough about the study to make an 'informed' decision independently about whether or not they would like to participate and to communicate this decision to you. If you are unsure whether or not your child/person you care for is able to understand enough to make a decision independently then we can provide you with some guidelines to help you to assess this A symbol information sheet can also be made available to you if this would be of help.

Please choose from one of the following options:

3. My child/ the person I care for is <u>able to understand</u> what is involved in the study and what will be required from them if they participate and has communicated their decision to me:

If you think that the person ***is* able** to understand enough about the study in order to make an 'informed' decision and they decide that they would like to participate then please ensure that they complete **Section 1 of <u>Consent Form A coloured YELLOW</u>** enclosed, or that you complete it with them, on their behalf. A parent/carer will need to complete **Section 2 of <u>Consent From A coloured YELLOW</u>** in order to indicate that they also agree to participate in the study. A symbol information sheet can be made available in order to support your child/person you care for in making this decision if it would be of help. Please contact the research team if you would like a copy of the symbol consent form or if you need us to adapt this information further, in order to suit your child's needs. Please return the consent form along with the questionnaire pack to us in the prepaid envelope provided.

4. My child/ the person I care for is <u>over the age of 16</u> and <u>cannot understand</u> what is involved in the study or cannot communicate their decision to me:

If you are reading this information on behalf of someone you care for who is **<u>over the age of 16</u>** and you decide that the person ***<u>is not</u>*** able to make an 'informed' decision about whether or not they would like to participate, then we would like to invite you to act as a 'personal consultee' (or 'nominated consultee' where an unpaid carer e.g. parent, legal guardian etc is not able to act as a 'personal consultee') for that person. Please read the enclosed 'Personal and Nominated Consultee Information Sheet' coloured **PINK**. Once you have finished reading the 'Personal and Nominated Consultee Information Sheet' please decide whether or not you feel able to act as a personal or nominated consultee for the person you care for.

If you feel able to act as a personal or nominated consultee for the person you care for please think about whether the person would decide to participate if they were able to make an 'informed' decision themselves about whether or not to participate. If you decide that the person would decide to participate, please complete **Consent Form *C* coloured BLUE** enclosed and return it to us alongside the questionnaire pack in the prepaid envelope provided.

ID_____

BACKGROUND INFORMATION

Please tick or write your response to these questions concerning background details:

1. **Today's date:** _____

2. **Gender:** Male ☐ Female ☐

3. **Date of Birth**: ___/___/____ **Age:_____**

4. **Is the person you care for verbal?** (i.e. more than 30 signs/words in their vocabulary)

   Yes/No (delete as appropriate)

5. **Is the person you care for able to walk unaided?**

   Yes/No (delete as appropriate)

6. **Has the person you care for been diagnosed with a syndrome?** Yes/No (delete as appropriate)

If yes, please indicate which syndrome in 5a. and answer questions 6 to 8. If no, please move on to question 9

6.a

Cornelia de Lange syndrome	☐	Cri du Chat syndrome	☐
Prader-Willi syndrome	☐	Rubinstein Taybi syndrome	☐
Fragile X syndrome	☐	Down syndrome	☐
Lowe syndrome	☐	Soto Syndrome	☐
Rubinstein-Taybi syndrome	☐	9q34 deletion	☐
8p23deletion	☐	Tuberous Sclerosis	
Pallister-Killian Syndrome	☐		

Other _____

7. **What is the genetic mechanism causing the syndrome in the person you care for?**

Uni-parental disomy	☐	Sequence repetition	☐
Deletion	☐	Translocation	☐
Unknown	☐		

Other _____

8. **When was the person you care for diagnosed?** _____

9. **Who diagnosed the person you care for?**

Paediatrician	☐	Clinical Geneticist	☐
GP	☐		

Other _____

10. Has the person you care for had any medical/health difficulties in the last six months? If yes, please give details:

_____

_____

__

In the information sheet and consent form we informed you that we may need to contact your child's/person you care for's GP in order to clarify any information regarding your child's health and diagnostic status (see consent form and information sheet for more information). If you have already indicated on the consent form that you are happy for us to do this, please complete the relevant details below:

11. Name of your child's/person you care for's

GP_____

GPAddress_____

_____

GP Telephone number_____

The following questions ask for background information about you and your family. Please tick the appropriate boxes or write in the spaces provided.

1. Are you male or female? Male ☐ Female ☐

2. What was your age in years on your last birthday? _____years

3. Please tick the highest level of your educational qualifications.

No formal educational qualifications..... ☐
Fewer than 5 GCSE's or O Level's (grades A-C), NVQ 1, or BTEC First Diploma… ☐
5 or more GCSE's or O Level's (grades A-C), NVQ 2, or equivalent…….…….. ☐
3 or more 'A' Levels, NVQ 3, BTEC National, or equivalent..... ☐
Polytechnic/University degree, NVQ 4, or equivalent..... ☐
Masters/Doctoral degree, NVQ 5, or equivalent……..... ☐

4. What is your relationship to your child with a genetic syndrome (e.g. mother, father, stepmother, grandmother, adoptive parent)?

_____

5. In total how many people currently live in your home? _____ Adults _____ Children

6. Does your child with a genetic syndrome normally live with you? Yes ☐ No ☐

If no, then where do they live?_____

7. What is your current marital status?

Married, and living with spouse..... ☐

Living with partner..... ☐

Divorced/Separated/Widowed/Single and NOT living with a partner..... ☐

If living with partner/spouse, please answer the following questions, if not, please go to question 12.

8. Is your partner male or female? Male ☐ Female ☐

9. What was their age in years on their last birthday? _____ years

10. Please tick the highest level of your partner/spouse's educational qualifications.

No formal educational qualifications..... ☐

Fewer than 5 GCSE or O Level (grades A-C), NVQ 1, or BTEC First Diploma..... ☐

5 or more GCSE or O Level (grades A-C), NVQ 2, or equivalent…… ☐

3 or more 'A' Levels, NVQ 3, BTEC National, or equivalent..... ☐

Polytechnic/University degree, NVQ 4, or equivalent..... ☐

Masters/Doctoral degree, NVQ 5, or equivalent……..... ☐

11. What is your partner/spouse's relationship to your child with a genetic syndrome (e.g., mother, father, stepmother, adoptive parent)?_____

12. Recent data from research with families of children with special needs has shown that a family's financial resources are important in understanding family member's views and experiences. With this in mind, we would be very grateful if you could answer the additional question below. We are not interested in exactly what your family income is, but we would like to be able to look at whether those with high versus lower levels of financial resources have different experiences.

What is your current total annual family income? Please include a rough estimate of total salaries and other income (including benefits) before tax and national insurance/pensions. Please tick one box only:

Less than £15,000……..……...…

☐

£15,001 to £25,000……...…….

☐

£25,001 to £35,000……..……..……

☐

£35,001 to £45,000……..…..……

☐

£45,001 to £55,000……..……..……

☐

£55,001 to £65,000……..……..…..

☐

£65,001 or more……..……..…

☐

Appendix 5: Ethical Approval Letter.

Coventry Research Ethics Committee
2nd floor West Wing
University Hospital
Clifford Bridge Road
Coventry
CV2 2DX

Telephone: 024 7696 7529
Facsimile: 024 7696 5033

22 February 2010

Professor Chris Oliver
School of Psychology
University of Birmingham
Birmingham
B15 2TT

Dear Professor Oliver

Study title:	**Understanding Behaviour and Family Adjustment in Individuals with Neurodevelopmental Disorders.**
REC reference:	**10/H1210/1**
Protocol Number:	**Version 1**

Thank you for your letter of 02 February 2010 responding to the Committee's request for further information on the above research and submitting revised documentation. Please accept my sincere apologies for the delay in writing to you the IT problem with the Research Ethics Database has only been fixed today.

The further information has been considered on behalf of the Committee by the Chairman.

Mental Capacity Act 2005

The members of the committee present approved the supplementary application on the basis described in the documentation submitted. I confirm that the committee has approved this research project for the purposes of the Mental Capacity Act 2005. The committee is satisfied that the requirements of section 31 of the Act will be met in relation to research carried out as part of this project on, or in relation to, a person who lacks capacity to consent to taking part in the project.

Confirmation of ethical opinion

The research continues to have a favourable opinion from this committee. It should continue to be conducted on the basis previously approved by the committee, as amended by this supplementary application. The conditions of approval issued with the committee's original favourable opinion continue to apply.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*	
Covering Letter	Prof C Oliver	14 December 2009	
REC application	IRAS	11 December 2009	
Protocol	Version 1	01 December 2009	
Copy REC letter		06 November 2009	
Investigator CV	C Oliver	10 December 2009	
Letter of invitation to participant	Version 1 A31 Letter Unknown new research project	10 December 2009	
Letter of invitation to participant	Version 1 A31 Letter Known new phase of research	10 December 2009	
Questionnaire: Instructions & Background Information	Version 1	10 December 2009	
Questionnaire: Wessex			
Questionnaire: Social Communication			
Questionnaire: Activity			
Questionnaire: Sociability for People with Intellectual Disabilities			
Questionnaire: Health			
Questionnaire: Mood Interest & Pleasure			
Questionnaire: The CBQ			
Questionnaire: Parenting & the Family			
Questionnaire: Your feelings & emotions			
Questionnaire: Nisonger Scale			
Questionnaire: Brief-P			
Questionnaire: The RBQ			
Questionnaire: Food Related Problems			
Questionnaire: Routines Inventory			
Questionnaire: The GRQ			
Questionnaire: NCCPC-R Pain Checklist			
Questionnaire: Social Resources			
Letter of invitation to participant	Continue Project version 1 A31 Letter	10 December 2009	

The Fragile X Society syndrome group letter of support		01 June 2009	
Participant Information Sheet: A31 Consultee	Version 1	10 December 2009	
Participant Information Sheet: Symbol	Version 1	10 December 2009	
Participant Consent Form: Access to Medical Records	Version 1	10 December 2009	
Assessment of Capacity Protocol	Version 1	10 December 2009	
Interview Schedules/Topic Guides	Vineland-II Adaptive Behaviour Scales 2nd Edition		
Interview Schedules/Topic Guides	Challenging Behaviour Interview		
Evidence of insurance or indemnity	UMAL Certificate of University of Birmingham Professional Indemnity	01 August 2009	
Covering Letter	C Oliver & J Moss	02 February 2010	
Participant Consent Form: A31 Consent Known Form B	Version 2	01 February 2010	
Participant Consent Form: A31 Consent Unknown Form A	Version 2	01 February 2010	
Participant Consent Form: A31 Consent Form Unknown Form B	Version 2	01 February 2010	
Participant Consent Form: A31 Consent Unknown Form C Consultee	Version 2	01 February 2010	
Participant Consent Form: A31 Confirm Known Form A	Version 2	01 February 2010	
Response to Request for Further Information			
Participant Information Sheet: A31 Infor fu 16+	Version 2	01 February 2010	
Participant Information Sheet: A31 Info Unknown 16+	Version 2	01 February 2010	
Participant Information Sheet: A31 infor Fu <16	Version 2	01 February 2010	
Participant Information Sheet: A31 Info Unknown <16	Version 2	01 February 2010	
Participant Consent Form: A31 Consent Known Form C	Version 2	01 February 2010	

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

Feedback on the application process

Now that you have completed the application process you are invited to give your view of the service you received from the National Research Ethics Service. If you wish to make your views known please use the feedback form available on the NRES website at:

https://www.nationalres.org.uk/AppForm/Modules/Feedback/EthicalReview.aspx

We value your views and comments and will use them to inform the operational process and further improve our service.

10/H1210/1	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Stephen Keay
Chairman

E-mail: pauline.pittaway@uhcw.nhs.uk

Copy to: *Dr Brendan Laverty, University of Birmingham*

Coventry Research Ethics Committee

Attendance at Chair's Actions meeting on 02 February 2010

Mr Stephen Keay	Consultant in Reproductive Medicine	Chairman & Expert

Appendix 6: Assessments.

WESSEX Questionnaire

These items refer to the person you care for. For each question (A, B, C, D etc …), please enter the appropriate code in each box.

(Frequently = more than once a week)

A) Wetting (nights) **1** = frequently **2** = occasionally **3** = never ☐

B) Soiling (nights) **1** = frequently **2** = occasionally **3** = never ☐

C) Wetting (days) **1** = frequently **2** = occasionally **3** = never ☐

D) Soiling (days) **1** = frequently **2** = occasionally **3** = never ☐

E) Walk with help **1** = not at all **2** = not up stairs **3** = up stairs and elsewhere ☐

(note: if this person walks *by himself* upstairs and elsewhere, please also code '3' for 'walk with help')

F) Walk by himself **1** = not at all **2** = not up stairs **3** = up stairs and elsewhere ☐

G) Feed himself **1** = not at all **2** = with help **3** = without help ☐

H) Wash himself **1** = not at all **2** = with help **3** = without help ☐

I) Dress himself **1** = not at all **2** = with help **3** = without help ☐

J) Vision **1** = blind or almost **2** = poor **3** = normal ☐

K) Hearing **1** = deaf or almost **2** = poor **3** = normal ☐

L) Speech **1** = never a word **2** = odd words only **3** = sentences and normal **4** = can talk but doesn't ☐

If this person talks in sentences, is his/her speech:

1 = Difficult to understand even by acquaintances, impossible for strangers?

2 = Easily understood for acquaintances, difficult for strangers?

3 = Clear enough to be understood by anyone? ☐

M) Reads **1** = nothing **2** = a little **3** = newspapers and/or books ☐

N) Writes **1** = nothing **2** = a little **3** = own correspondence ☐

O) Counts **1** = nothing **2** = a little **3** = understands money values ☐

Please check your answers and go on to the next questionnaire.

Instructions for completing the MIPQ-S

This questionnaire contains 12 questions – <u>you should complete all 12 questions</u>. Each question will ask for your opinion about particular behaviours, which you have observed in the last 2 weeks. For every question you should circle <u>the most appropriate</u> response e.g.

6) In the last two weeks, how interested did the person appear to be in his/her surroundings?

interested all of the time	*interested most of the time*	*interested about half of the time*	*interested some of the time*	*never interested*

The Mood, Interest and Pleasure Questionnaire - Short Form

1) In the last two weeks, did the person seem…

sad all of the time	sad most of the time	sad about half of the time	sad some of the time	never sad

Please comment if anything has happened in the last two weeks which you feel might explain sadness if it has been observed (e.g. a bereavement):

2) In the last two weeks, how often did you hear positive vocalizations* when the person was engaged in activities*?

all of the time	most of the the time	about half of the time	some of the time	never

*<u>positive vocalizations</u>: e.g. laughing, giggling, "excited sounds" etc.
*<u>engaged in activities</u>: i.e. when someone is actively involved in any activity such as a mealtime, a social interaction, a self-care task or social outing etc.

3) In the last two weeks, do you think the facial expression of the person looked "flat"*…

all of the time	most of the the time	about half of the time	some of the time	never

*<u>flat expression</u>: expression seems lifeless; lacks emotional expression; seems unresponsive.

4) In the last two weeks, would you say the person…

cried every day	cried nearly every day	cried 3-4 times each week	cried once or twice each week	cried less than once each week

5) In the last two weeks, how interested did the person appear to be in his/her surroundings?

interested all of the time	interested most of the time	interested about half of the time	interested some of the time	never interested

6) In the last two weeks, did the person seem to have been enjoying life…

all of the time	most of the the time	about half of the time	some of the time	never

Please comment if there are any reasons why this person might not have been enjoying him/herself e.g. illness, being in pain, experiencing a loss etc.:

7) In the last two weeks, would you say the person smiled…

at least once every day	at least once nearly every day	3-4 times each week	once or twice each week	less than once each week

8) In the last two weeks, how disinterested did the person seem to be in his/her surroundings?

disinterested all of the time	disinterested most of the time	disinterested about half of the time	disinterested some of the time	never disinterested

9) In the last two weeks, when the person was engaged in activities*, to what extent did his/her facial expressions* suggest that s/he was interested in the activity?

interested all of the time	interested most of the time	interested about half of the time	interested some of the time	never interested

*engaged in activities: i.e. when someone is actively involved in any activity such as a mealtime, social interaction, self-care task or social outing etc.
*facial expressions: interest might be indicated by the degree to which the person's gaze is being directed at the person/things involved in an activity.

10) In the last two weeks, would you say that the person…

laughed every day	laughed nearly every day	laughed 3-4 times each week	laughed once or twice each week	laughed less than once each week

11) In the last two weeks, how often did you see gestures which appeared to demonstrate enjoyment* when the person was engaged in activities*?

all of the time	most of the the time	about half of the time	some of the time	never

*gestures which appear to demonstrate enjoyment: e.g. clapping, waving hands in excitement etc.
*engaged in activities: i.e. when someone is actively involved in any activity such as a meal time, social interaction, self-care task or social outing etc.

12) In the last two weeks, did the person's vocalizations* sound distressed…

all of the time	most of the the time	about half of the time	some of the time	never

*vocalizations: any words, noises or utterances.

THE RBQ

INSTRUCTIONS

1. The questionnaire asks about 19 different behaviours.
2. Each behaviour is accompanied by a brief definition and examples. The examples given for each behaviour are not necessarily a complete list but may help you to understand the definitions more fully.
3. Please read the definitions and examples carefully and circle the appropriate number on the scale to indicate how frequently the person you care for has engaged in each of the behaviours **within the last month**.
4. If a particular behaviour does not apply to the person you care for because they are not mobile or verbal please circle the number 0 on the scale

	Never	Once a month	Once a week	Once a day	More than once a day
1. Object stereotypy: repetitive, seemingly purposeless movement of objects in an unusual way *E.g. twirling or twiddling objects, twisting or shaking objects, banging or slapping objects.*	**0**	**1**	**2**	**3**	**4**
2. Body stereotypy: repetitive, seemingly purposeless movement of whole body or part of body (other than hands) in an unusual way. *E.g. body rocking, or swaying ,or spinning, bouncing, head shaking, body posturing..* Does not include self-injurious behaviour.	**0**	**1**	**2**	**3**	**4**
3. Hand stereotypy: repetitive, seemingly purposeless movement of hands in an unusual way. *E.g. finger twiddling, hand flapping, wigging or flicking fingers, hand posturing.* Does not include self-injurious behaviour.	**0**	**1**	**2**	**3**	**4**
4. Cleaning: Excessive cleaning, washing or polishing of objects or parts of the body *E.g. polishes windows and surfaces excessively, washes hands and face excessively,*	**0**	**1**	**2**	**3**	**4**
5. Tidying up: Tidying away any objects that have been left out. This may occur in situations when it is inappropriate to put the objects away. Objects may be put away into inappropriate places. *E.g. putting cutlery left out for dinner in the bin, removes all objects from surfaces.*	**0**	**1**	**2**	**3**	**4**
6. Hoarding: Collecting, storing or hiding objects to excess, including rubbish, bits of paper, and pieces of string or any other unusual items.	**0**	**1**	**2**	**3**	**4**
7. Organising objects: Organising objects into categories according to various characteristics such as colour, size, or function. *E.g. ordering magazines according to size, ordering toy cars according to colour, ordering books according to topic.*	**0**	**1**	**2**	**3**	**4**
8. Attachment to particular people: Continually asking to see, speak or contact a particular 'favourite' person. *E.g. continually asks to*	**0**	**1**	**2**	**3**	**4**

see or speak to particular friend, carer, babysitter or schoolteacher.

	Never	Once a month	Once a week	Once a day	More than once a day
9. Repetitive questions: Asking specific questions over and over. *E.g. always asking people what their favourite colour is, asking who is taking them to school the next day over and over*	**0**	**1**	**2**	**3**	**4**
10. Attachment to objects: Strong preference for a particular object to be present at all times. *E.g. Carrying a particular piece of string everywhere, taking a particular red toy car everywhere, attachment to soft toy or particular blanket.*	**0**	**1**	**2**	**3**	**4**
11. Repetitive phrases/signing: Repeating particular sounds, phrases or signs that are unrelated to the situation over and over. *E.g. repeatedly signing the word 'telephone'.*	**0**	**1**	**2**	**3**	**4**
12. Rituals: carrying out a sequence of unusual or bizarre actions before, during or after a task. The sequence will always be carried out when performing this task and will always occur in the same way. *E.g. turning round three times before sitting down, turning lights on and off twice before leaving a room, tapping door frame twice when passing through it.*	**0**	**1**	**2**	**3**	**4**
13. Restricted conversation: Repeatedly talks about specific, unusual topics in great detail. *E.g. conversation restricted to: trains, buses, dinosaurs, particular film, country, or sport.*	**0**	**1**	**2**	**3**	**4**
14. Echolalia: Repetition of speech that has either just been heard or has been heard more than a minute earlier. *E.g.: Mum:' Jack don't do that' Jack: 'Jack don't do that'.*	**0**	**1**	**2**	**3**	**4**
15. Preference for routine: Insist on having the same household, school or work schedule everyday. *E.g. likes to have the same activities on the same day at the same time each week, prefers to eat lunch at exactly the same time every day, wearing the same jumper everyday.*	**0**	**1**	**2**	**3**	**4**
16. Lining up or arranging objects*: Arrangement of objects into lines or patterns E.g. placing toy cars in a symmetrical pattern, precisely lining up story books,*	**0**	**1**	**2**	**3**	**4**
17. Just right behaviour: Strong insistence that objects, furniture and toys always remain in the same place. *E.g. all chairs, pictures and toys have a very specific place that cannot be changed.*	**0**	**1**	**2**	**3**	**4**
18. Completing behaviour: Insists on having objects or activities 'complete' or 'whole' *E.g. Must have doors open or closed not in between, story must be read from beginning to end, not left halfway through.*	**0**	**1**	**2**	**3**	**4**
19. Spotless behaviour: Removing small, almost unnoticeable	**0**	**1**	**2**	**3**	**4**

pieces of lint, fluff, crumbs or dirt from surfaces, clothes and objects.
E.g. Picking fluff off a jumper, removing crumbs from the kitchen table.

THE ACTIVITY QUESTIONNAIRE

Instructions:

- Please read each item carefully and circle the appropriate number on the scale, for the person you care for.
- Please ensure that you indicate a response for every item. If the particular behaviour does not apply,
  for example, if the person is not verbal or not mobile, please circle 0 on the scale.

	Never / almost never	Some of the time	Half of the time	A lot of the time	Always/ almost all the time
1. **Does the person wriggle or squirm about when seated or lying down?**	**0**	**1**	**2**	**3**	**4**
2. Does the person fidget or play with their hands and/or feet when seated or lying down?	**0**	**1**	**2**	**3**	**4**
3. **Does the person find it difficult holding still?**	**0**	**1**	**2**	**3**	**4**
4. **Does the person find it difficult to remain in their seat even when in situations where it would be expected?**	**0**	**1**	**2**	**3**	**4**
5. **Does the person prefer to be moving around or becomes**	**0**	**1**	**2**	**3**	**4**
6. **When the person is involved in a leisure activity (e.g. watching TV, playing a game etc.) do they make a lot of noise?**	**0**	**1**	**2**	**3**	**4**
7. **When the person is involved in an activity, are they boisterous and/or rough?**	**0**	**1**	**2**	**3**	**4**
8. **Does the person act as if they are "driven by a motor" (i.e. often very active)?**	**0**	**1**	**2**	**3**	**4**
9. **Does the person seem like they need very little rest to recharge their battery?**	**0**	**1**	**2**	**3**	**4**
10. **Does the person often talk excessively?**	**0**	**1**	**2**	**3**	**4**
11. **Does the person's behaviour seem difficult to manage/contain whilst out and about (e.g. in town, in supermarkets etc.)?**	**0**	**1**	**2**	**3**	**4**
12. **Do you feel that you need to "keep an eye" on the person at all times?**	**0**	**1**	**2**	**3**	**4**
13. **Does the person you care for seem to act/do things without stopping to think first?**	**0**	**1**	**2**	**3**	**4**
14. **Does the person blurt out answers before questions have been completed?**	**0**	**1**	**2**	**3**	**4**
15. **Does the person start to respond to instructions before they have been fully given or without seeming to understand them?**	**0**	**1**	**2**	**3**	**4**
16. **Does the person want things immediately?**	**0**	**1**	**2**	**3**	**4**
17. **Does the person find it difficult to wait?**	**0**	**1**	**2**	**3**	**4**
18. **Does the person disturb others because they have difficulty waiting for things or waiting their turn?**	**0**	**1**	**2**	**3**	**4**

SOCIAL COMMUNICATION QUESTIONNAIRE © Rutter et al 2003

Please circle 'yes' if <u>any</u> one of the following behaviours is present. Although you may be uncertain about whether some behaviours are present or not, please do answer 'yes' or 'no' to every question on the basis of what you think.

1. Is she/he now able to talk using short phrases or sentences? If no, skip to question 8.	**Yes**	**No**
2. Can you have a to and fro "conversation" with her/him that involves taking turns or building on what you have said?	**Yes**	**No**
3. Has she/he ever used odd phrases or said the same thing over and over in almost exactly the same way (either phrases that she/he has heard other people use or ones that she/he has made up?	**Yes**	**No**
4. Has she/he ever used socially inappropriate questions or statements? For example, has she/he ever regularly asked personal questions or made personal comments at awkward times?	**Yes**	**No**
5. Has she/he ever got her/his pronouns mixed up (e.g., saying you or she/he for I)?	**Yes**	**No**
6. Has she/he ever used words that she/he seemed to have invented or made up her/himself; put things in odd, indirect ways; or used metaphorical ways of saying things (e.g., saying hot rain for steam)?	**Yes**	**No**
7. Has she/he ever said the same thing over and over in exactly the same way or insisted that you say the same thing over and over again?	**Yes**	**No**
8. Has she/he ever had things that she/he seemed to have to do in a very particular way or order or rituals that she/he insisted that you go through?	**Yes**	**No**
9. Has her/his facial expression usually seemed appropriate to the particular situation, as far as you could tell?	**Yes**	**No**
10. Has she/he ever used your hand like a tool or as if it were part of her/his own body (e.g., pointing with your finger, putting your hand on a doorknob to get you to open the door)?	**Yes**	**No**
11. Has she/he ever had any interests that preoccupy her/him and might seem odd to other people (e.g., traffic lights, drainpipes, or timetables)?	**Yes**	**No**
12. Has she/he ever seemed to be more interested in parts of a toy or an object (e.g., spinning the wheels of a car), rather than using the object as it was intended?	**Yes**	**No**
13. Has she/he ever had any special interests that were unusual in their intensity but otherwise appropriate for her/his age and peer group (e.g., trains, dinosaurs)?	**Yes**	**No**
14. Has she/he ever seemed to be unusually interested in the sight, feel, sound, taste, or smell of things or people?	**Yes**	**No**
15. Has she/he ever had any mannerisms or odd ways of moving her/his hands or fingers, such as flapping or moving her/his fingers in front of her/his eyes?	**Yes**	**No**
16. Has she/he ever had any complicated movements of her/his whole body, such as spinning or repeatedly bouncing up and down?	**Yes**	**No**

17. Has she/he ever injured her/himself deliberately, such as by biting her/his arm or banging her/his head?	**Yes**	**No**
18. Has she/he ever had any objects (other than a soft toy or comfort blanket) that she/he had to carry around?	**Yes**	**No**
19. Does she/he have any particular friends or a best friend?	**Yes**	**No**
20. When she/he was 4 to 5, did she/he ever talk with you just to be friendly (rather than to get something)?	**Yes**	**No**
21. When she/he was 4 to 5, did she/he ever spontaneously copy you (or other people) or what you were doing (such as vacuuming, gardening, or mending things)?	**Yes**	**No**
22. When she/he was 4 to 5, did she/he ever spontaneously point at things around her/him just to show you things (not because she/he wanted them)?	**Yes**	**No**
23. When she/he was 4 to 5, did she/he ever use gestures, other than pointing or pulling your hand, to let you know what she/he wanted	**Yes**	**No**
24. When she/he was 4 to 5, did she/he nod her/his head to mean yes?	**Yes**	**No**
25. When she/he was 4 to 5, did she/he shake her/his head to mean no?	**Yes**	**No**
26. When she/he was 4 to 5, did she/he usually look at you directly in the face when doing things with you or talking with you?	**Yes**	**No**
27. When she/he was 4 to 5, did she/he smile back if someone smiled at her/him?	**Yes**	**No**
28. When she/he was 4 to 5, did she/he ever show you things that interested her/him to engage your attention?	**Yes**	**No**
29. When she/he was 4 to 5, did she/he ever offer to share things other than food with you?	**Yes**	**No**
30. When she/he was 4 to 5, did she/he ever seem to want you to join in her/his enjoyment of something?	**Yes**	**No**
31. When she/he was 4 to 5, did she/he ever try to comfort you if you were sad or hurt?	**Yes**	**No**
32. When she/he was 4 to 5, when she/he wanted something or wanted help, did she/he look at you and use gestures with sounds or words to get your attention?	**Yes**	**No**
33. When she/he was 4 to 5, did she/he show a normal range of facial expressions?	**Yes**	**No**
34. When she/he was 4 to 5, did she/he ever spontaneously join in and try to copy the actions in social games, such as The Mulberry Bush or London Bridge Is Falling Down?	**Yes**	**No**
35. When she/he was 4 to 5, did she/he play any pretend or make-believe games?	**Yes**	**No**
36. When she/he was 4 to 5, did she/he seem interested in other children of approximately the same age whom she/he did not know?	**Yes**	**No**
37. When she/he was 4 to 5, did she/he respond positively when another child approached her/him?	**Yes**	**No**
38. When she/he was 4 to 5, if you came into a room and started talking to her/him without calling her/his name, did she/he usually look up and pay attention to you?	**Yes**	**No**
39. When she/he was 4 to 5, did she/he ever play imaginative games with another child in such a way that you could tell that they each understood what the other was pretending?	**Yes**	**No**

40. When she/he was 4 to 5, did she/he play cooperatively in games that required joining in with a group of other children, such as hide-and-seek or ball games? **Yes** **No**

Hospital Anxiety and Depression Scale (Zigmond & Smaith, 1983)

This questionnaire focuses on how you feel about things. Please read each item and circle the reply underneath the item which comes closest to how you have been feeling in the past week. Do not take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought-out response.

1. I feel tense or "wound up"

Most of the time	A lot of the time	Occasionally, from time to time	Not at all

2. I still enjoy the things I used to enjoy

Definitely as much	Not quite so much	Only a little	Hardly at all

3. I get a sort of frightened feeling as if something awful is about to happen

Very definitely and quite Badly	Yes, but not too badly	A little, but it doesn't worry me	Not at all

4. I can laugh and see the funny side of things

As much as I always Could	Not quite so much now	Definitely not so much now	Not at all.

5. Worrying thoughts go through my mind

A great deal of the Time	A lot of the time	From time to time but not too often	Only occasionally

6. I feel cheerful

Not at all	Not often	Sometimes	Most of the time

7. I can sit at ease and feel relaxed

Definitely	Usually	Not often	Not at all

8. I feel as if I am slowed down

Nearly all the time	Very often	Sometimes	Not at all

9. I get a sort of frightened feeling like "butterflies" in the stomach

Not at all	Occasionally	Quite often	Very often

10. I have lost interest in my appearance

Definitely	*I don't take as much care as I should*	*I may not take quite as much care*	*I take just as much care as ever*

11. I feel restless as if I have to be on the move

Very much indeed	Quite a lot	Not very much	Not at all

12. I look forward with enjoyment to things

As much as I ever did	Rather less than I used to	Definitely less than I used to	Hardly at all

13. I get sudden feelings of panic

Very often indeed	Quite often	Not very often	Not at all

14. I can enjoy a good book, radio or TV programme

Often	Sometimes	Not often	Very seldom

Health Questionnaire

PART A

Instructions:

- Have these problems **EVER** affected your child or person you care for?
- Please rate as **0** – if the problem has never affected the person you care for, **1** – if it has been a mild problem, **2** - if the problem has been moderately serious, or **3** – if the problem has been severe.
- If the person you care for has had these problems please state whether any treatment has been implemented by circling **yes** or **no**.

	Never	Mild	Moderate	Severe
1a. Eye Problems (e.g. glaucoma / blocked tear duct/s).....	**0**	**1**	**2**	**3**
1b. Corrective surgery / medication / treatment: **yes / no**				
2a. Ear Problems (e.g. infections, glue ear)	**0**	**1**	**2**	**3**
2b. Corrective surgery / medication / treatment (e.g. grommets): **yes / no**				
3a. Dental Problems (e.g. toothache / gum problems / mouth ulcers / delayed eruption of teeth).....	**0**	**1**	**2**	**3**
3b.Dental surgery / treatment (e.g. teeth removal): **yes / no**				
4a. Cleft Palate.....	**0**	**1**	**2**	**3**
4b. Repaired: **yes / no**				
5a. Gastrointestinal Difficulties (e.g. reflux / stomach problems).....	**0**	**1**	**2**	**3**
5b. Corrective surgery / medication / treatment (e.g. nissen fundoplication): **yes / no**				
6a. Bowel Problems (e.g. obstruction).....	**0**	**1**	**2**	**3**
6b. Corrective surgery / treatment: **yes / no**				
7a. Heart Abnormalities or Circulatory Problems (e.g. congenital heart lesions or murmur).....	**0**	**1**	**2**	**3**
7b. Corrective surgery / medication / treatment: **yes / no**				
8a. Problems with Genitalia (e.g. prostate/ testicular problems i.e. undescended testes)	**0**	**1**	**2**	**3**
8b. Corrective surgery / treatment: **yes / no**				
9a. Hernia (e.g. inguinal or hiatal).....	**0**	**1**	**2**	**3**
9b. Repair / treatment: **yes / no**				
10. Limb Abnormalities (e.g. malformed arm).....	**0**	**1**	**2**	**3**
11a. Epilepsy / Seizures / Neurological Referrals.....	**0**	**1**	**2**	**3**
11b. Medication: **yes / no**				
12a. Lung or Respiratory Problems (asthma/bronchitis).....	**0**	**1**	**2**	**3**
12b. Corrective surgery / medication / treatment: **yes / no**				
13a. Liver or Kidney Problems.....	**0**	**1**	**2**	**3**
13b. Corrective surgery / medication / treatment: **yes / no**				
14a. Diabetes or Thyroid Function Problems.....	**0**	**1**	**2**	**3**
14b. Corrective surgery / medication / treatment: **yes / no**				

15a. Skin Problems (e.g. tinea, eczema, psoriasis, dry skin)…….. **0** **1** **2** **3**
15b. Medication / treatment: **yes / no**

16a. Other (please specify problem, severity from 0-3)..... **0** **1** **2** **3**
16b. Corrective surgery / medication / treatment: **yes / no**

PART B

Instructions:

- Have these medical problems affected the person you care for in the past **MONTH**
- Please rate as **0** – if your child has not been affected by this problem in the past month, **1** - if they have been mildly affected, **2** – if the problem has moderately affected your child and **3** - if your child has been severely affected by the problem.

	No	Mild	Moderate	Severe
17. Eye Problems (e.g. glaucoma / blocked tear duct/s).....	**0**	**1**	**2**	**3**
18. Ear Problems (e.g. infections, glue ear).....	**0**	**1**	**2**	**3**
19. Dental Problems (e.g. toothache / gum problems / mouth ulcers / delayed eruption of teeth).....	**0**	**1**	**2**	**3**
20. Cleft Palate.....	**0**	**1**	**2**	**3**
21. Gastrointestinal Difficulties (e.g. reflux / stomach problems).....	**0**	**1**	**2**	**3**
22. Bowel Problems (e.g. obstruction).....	**0**	**1**	**2**	**3**
23. Heart Abnormalities or Circulatory Problems (e.g. congenital heart lesions or murmur).....	**0**	**1**	**2**	**3**
24. Problems with Genitalia (e.g. prostate / testicular problems i.e. undescended testes)....	**0**	**1**	**2**	**3**
25. Hernia (e.g. inguinal or hiatal).....	**0**	**1**	**2**	**3**
26. Limb Abnormalities (e.g. malformed arm).....	**0**	**1**	**2**	**3**
27. Epilepsy / Seizures / Neurological Referrals.....	**0**	**1**	**2**	**3**
28. Lung or Respiratory Problems (asthma / bronchitis).....	**0**	**1**	**2**	**3**
29. Liver or Kidney Problems.....	**0**	**1**	**2**	**3**
30. Diabetes or Thyroid Function Problems.....	**0**	**1**	**2**	**3**
31. Skin Problems (e.g. tinea, eczema, psoriasis, dry skin).....	**0**	**1**	**2**	**3**
32. Other (please specify problem and severity from 0-3)	**0**	**1**	**2**	**3**

Appendix 7: Health Difficulties in Individuals with Pallister-Killian Syndrome.

		Never/ No n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Corrective surgery/ Treatment? n (%)
Eye Problems	Lifetime	9 (56.3%)	3 (18.8%)	3 (18.8%)	1 (6.3%)	4 (25%)
	Last Month	14 (87.5%)	2 (12.5%)	-	-	
Ear Problems	Lifetime	2 (12.5%)	5 (31.3%)	6 (37.5%)	3 (18.8%)	11 (68.8%)
	Last Month	10 (62.5%)	4 (25%)	1 (6.3%)	1 (6.3%)	
Dental Problems	Lifetime	3 (18.8%)	5 (31.3%)	5 (31.3%)	3 (18.8%)	4 (25%)
	Last Month	10 (62.5%)	4 (25%)	-	2 (12.5%)	
Cleft Palate	Lifetime	11 (68.8%)	1 (6.3%)	4 (25%)	-	3 (18.8%)
	Last Month	13 (81.3%)	1 (6.3%)	2 (12.5%)	-	
Gastrointestinal Problems	Lifetime	8 (50%)	2 (12.5%)	4 (25%)	2 (12.5%)	4 (25%)
	Last Month	11 (68.8%)	4 (25%)	1 (6.3%)	-	
Bowel Problems	Lifetime	9 (56.3%)	2 (12.5%)	3 (18.8%)	2 (12.5%)	3 (18.8%)
	Last Month	11 (68.8%)	3 (18.8%)	1 (6.3%)	1 (6.3%)	
Heart Abnormalities or Circulatory Problems	Lifetime	10 (62.5%)	5 (31.3%)	-	1 (6.3%)	2 (12.5%)
	Last Month	16 (100%)	-	-	-	
Problems with Genitalia	Lifetime	10 (62.5%)	5 (31.3%)	1 (6.3%)	-	4 (25%)
	Last Month	14 (87.5%)	2 (12.5%)	-	-	
Hernia	Lifetime	10 (62.5%)	2 (12.5%)	1 (6.3%)	3 (18.8%)	5 (31.3%)
	Last Month	14 (87.5%)	2 (12.5%)	-	-	
Limb Abnormalities	Lifetime	14 (87.5%)	-	2 (12.5%)	-	-
	Last Month	14 (87.5%)	1 (6.3%)	1 (6.3%)	-	
Epilepsy/ Seizures	Lifetime	5 (31.3%)	4 (25%)	5 (31.3%)	2 (12.5%)	7 (43.8%)
	Last Month	9 (56.3%)	4 (25%)	2 (12.5%)	1 (6.3%)	
Lung or Respiratory Problems	Lifetime	11 (68.8%)	1 (6.3%)	2 (12.5%)	2 (12.5%)	4 (25%)
	Last Month	13 (81.3%)	3 (18.8%)	-	-	
Liver or Kidney Problems	Lifetime	13 (81.3%)	1 (6.3%)	2 (12.5%)	-	3 (18.8%)
	Last Month	15 (93.8%)	-	1 (6.3%)	-	
Diabetes or Thyroid Function Problems	Lifetime	15 (93.8%)	-	-	1 (6.3%)	1 (6.3%)
	Last Month	15 (93.6%)	-	1 (6.3%)	-	
Skin Problems	Lifetime	6 (37.5%)	8 (50%)	2 (12.5%)	-	8 (50%)
	Last Month	8 (50.0%)	6 (37.5%)	1 (6.3%)	1 (6.3%)	