

**A thesis submitted to the University of Birmingham in partial fulfilment of the regulation  
for the degree of**

**DOCTOR OF CLINICAL PSYCHOLOGY (DClinPsy)**

**VOLUME I**

**Research Component**

**TOWARD A BEHAVIOURAL PHENOTYPE FOR 8P23 AND 9Q34 DELETION  
SYNDROMES**

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## OVERVIEW

This thesis comprises two volumes, representing the research and clinical elements submitted to the University of Birmingham in partial fulfilment of the degree of Doctor of Clinical Psychology (DClinPsy).

The first volume is the research component and is made up of three papers. The first paper is a review of the literature assessing the scope of the research looking at five rare genetic deletions (18p, 1q37, 2p36, 8p23 and 9q34). All of the literature published between 1967 and 2011, pertinent to these genetic deletions, was screened and categorised. Finally all of the papers that mentioned psychological or behavioural elements were reviewed. This highlighted the lack of measurement tools currently employed within the literature to assess behaviour in a manner that was replicable or reliable.

The second paper is an empirical study which honed in on two of the rare genetic deletions from the literature review (9q34 and 8p23) and began to establish a behavioural phenotype for these using established valid and reliable measures. People in both groups displayed high levels of challenging behaviour. This represents a potential cause of stress to carers, and may indicate underlying problems for the people with the genetic deletion. People in the 9q34 deletion group were overall most similar to people with Autism Spectrum Disorder (ASD), whereas people in the 8p23 group were least like people with ASD, and most like people with Down Syndrome. There were a number of exceptions to this, and there is an interesting finding in relation to people with 9q34 and ageing, discussed in detail within the paper.

Both of these papers were written with the aim of publication in the Journal of Intellectual Disability Research.

The third paper is a Public Domain Briefing Paper, this summarises both papers in language which is accessible to the general public, with the aim that Unique, the charity that supported the research, can disseminate it to the participants and use it in future publications.

The second volume is the clinical component. It consists of five Clinical Practice Reports (CPR's), these reports anonymously detail different aspects of my placements over my clinical training.

The first CPR (models) presents a 10 year old boy with a mild Learning Disability who had behavioural problems and anxiety. This report details the assessment process, and formulates his difficulties from two psychological perspectives; behavioural and psychodynamic.

The second CPR discusses a service evaluation completed within an Adult Primary Care setting exploring the types of clients referred to the service. This was looked at in order to understand how these clients' needs may be different to those traditionally expected in a Primary Care setting.

The third CPR was a case study of my work with a man who had been admitted to hospital with a severe burn. The formulation used a systemic approach to consider my client within the wider context of the hospital. Two potential points of intervention were highlighted, and as recovery from a burn is a long process, consideration was given to future therapeutic input, and the difficulties of evaluating outcomes.

The fourth CPR consisted of a single case exercise and an oral presentation. The oral presentation looked at my work with a girl in the looked after children's team. Her needs

were considered in terms of attachment and systemic models.

Finally the fifth CPR was also an oral presentation looking at my work with a 74 year old woman who had longstanding anxiety and depression. Systemic and psychodynamic models were used to assess and formulate her difficulties.

## **ACKNOWLEDGEMENTS**

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## GLOSSARY OF ABBREVIATIONS AND SYMBOLS

ADD	Attention Deficit Disorder
ADHD	Attention Deficit Hyperactivity Disorder
ASD	Autism Spectrum Disorder
BRIEF-P	The Behaviour Rating Inventory of Executive Function—Preschool Version
CBQ	Challenging Behaviour Questionnaire
CdCS	Cri du Chat Syndrome
CdLS	Cornelia de Lange Syndrome
DNA	Deoxyribonucleic Acid
DS	Down Syndrome
DSM (III/IV)	Diagnostic and Statistical Manual (III/IV)
FISH	Fluorescence in Situ Hybridisation
FXS	Fragile X Syndrome
GRQ	Gastroesophageal Reflux Questionnaire
IQ	Intelligence Quotient
LD	Learning Disability (Difficulty)
MAPH	Multiplex Amplifiable Probe Hybridisation
MIPQ-S	Mood, Interest and Pleasure Questionnaire Short-form (MIPQ-S)
MRI	Magnetic Resonance Imaging
MW	Mann Whitney
NHS	National Health Service
OCD	Obsessive Compulsive Disorder
PWS	Prader Willi Syndrome
RTS	Rubinstein Taybi Syndrome
RBQ	Repetitive Behaviour Questionnaire
TAQ	The Activity Questionnaire
SCQ	Social Communication Questionnaire
SQID	Sociability Questionnaire for Intellectual Disabilities
WISC (III/IV)	Wechsler Intelligence Scale for Children (III/IV)
$\chi^2$	Chi Square
$v$	Degrees of Freedom
Q1-Q3	Interquartile Range
$\bar{x}$	Mean
$\bar{x}d$	Mean Difference
$\tilde{x}$	Median
$r_s$	Spearman's Rho
$\sigma$	Standard Deviation
$\sigma_{\bar{x}}$	Standard Error of the Mean

**THE FOCUS AND SCOPE OF LITERATURE ON  
RARE GENETIC DELETION SYNDROMES**

## 1.1 Abstract

Many people with rare microdeletion syndromes have an intellectual disability and may display a range of difficult behaviours. Research shows that these factors can contribute to carer stress and associated mental health problems. Currently, there are no reviews that assess the quality and scope of the literature looking at rare genetic deletions.

This review looked at five rare genetic deletions (18p, 1p36, 2q37, 8p23 and 9q34). The papers retrieved (n=300) from these were categorised initially into overarching themes (molecular analysis, physical, psychological, conference and review). The majority of these papers involved molecular analysis or physical components. However, there was a general increase over time in the number of papers that had some description of psychological components. A more detailed analysis assessed the contribution of the 'psychological' papers (n=31) to the literature, focussing on the measurement and description of behaviour.

There was just one paper whose sole aim was to look at behaviour in relation to a genetic deletion. The majority relied upon clinical descriptions of behaviour with very few of the studies employing any form of standardised measure. Given the importance of behaviour to carers and health professionals, recommendations are made about how to encompass psychological factors in future studies.

## **1.2 Introduction**

### **1.2.1 Overview of Rare Genetic Deletions**

Rare genetic deletions are increasingly likely to be detected following recent advances in genetic analysis, such as high-resolution chromosome banding and molecular chromosome analysis using fluorescence in situ hybridisation (FISH) (Babovic-Vuksanovic, Jenkins, Ensenaer et al., 2004; White, Sterrenburg, van Ommen, den Dunnen & Breuning, 2003). Genetic deletions can have a variety of detrimental physical, developmental and psychological affects upon the person, collectively described as a microdeletion syndrome. Many people who have previously been diagnosed as having an intellectual disability, with no known cause, are now being diagnosed as having a microdeletion syndrome (Baker et al., 2002; Cans et al., 1999; de Vries, Winter, Schinzel & van Ravenswaaij-Arts, 2003). Alongside this development, numerous syndromes associated with intellectual disability have been described as having developmental, cognitive and behavioural profiles associated with them (Skuse, 2002; O'Brien, 2006). Behavioural phenotypes are sets of behaviours that appear more commonly than would be expected in comparison to people of the same chronological and/or mental age without the syndrome (Dykens, 1995).

### **1.2.2 Parental Stress**

Parents raising a child with an intellectual disability may experience higher levels of stress and associated mental health problems than parents whose children are typically developing (Ingersoll & Hambrick, 2011; Qin et al., 2009; Singer & Floyd, 2006). There are a number of contributory factors, including a lack of knowledge and support (Qin et al., 2009; Tehee, Honan & Hevey, 2009), challenging behaviours (Ekas & Whitman, 2010; Lecavalier, Leone &

Wiltz, 2006; Myers, Mackintosh & Goin-Kochel, 2009) including aggression, destructiveness and self-injury (e.g., Ingersoll & Hambrick, 2011), the child's social ability (e.g., Smith, Oliver & Innocenti, 2001), level of impulsivity, the presence of autism (Abbeduto et al., 2004; Ingersoll & Hambrick, 2011), and level of adaptive functioning (Weiss, Sullivan & Diamond, 2003).

Research suggests that enabling carers to have some control over their own situation, through education or service support for example, may lower the negative psychological impact and improve the outcome for the person with the intellectual disability and their family (Basu & Deb, 1996). This information is also of importance to health professionals who work with families not only in caring for their child but also in helping families make decisions before the birth of their child (Reish, Berry & Hirsch, 1995), and having an understanding of what may occur in the future. Additionally, knowledge of the behaviours typically seen within a syndrome may aid diagnosis (Kurosawa et al., 2005).

### **1.2.3 Rationale for Groups Chosen**

Given the emergence of new microdeletions, the developing literature on behavioural phenotypes, and the importance of the latter for families, service development and planning, it is important that the literature reflects the concerns of those people supporting children and adults with newly identified microdeletion syndromes. It is likely, however, that the current research in the field will be limited. At present there are no published reviews of the literature on rare microdeletion syndromes that might provide information on the size, quality, scope and focus of the area. For this reason it was considered important to conduct a literature review to detail the content of papers in this area.

To this end a small number of rare deletion groups with similar prevalence were identified. It was not possible to ascertain actual population prevalence rates as the genetic deletions were too rare (J. C. Barber personal communication October 6th, 2010; T. Kleefstra personal communication September 29th, 2010). Consequently, Unique (a charity that supports parents and carers of people with rare genetic deletions) was contacted and asked to provide details of the numbers of people held on their database identified as falling within different rare genetic deletion groups. There were five groups associated with an intellectual disability that had a similar prevalence. These were: 18p (n=57); 1p36 (n=160); 2q37 (n=101); 8p23 (n=157) and 9q34 (n=58). These five groups were selected for the literature review.

#### 1.2.3.1 18p

The 18p deletion syndrome was initially outlined by Grouchy, Lamy, Thieffry and Arthuis in 1963. Physically, people with an 18p syndrome typically have a round or triangular face with a broad nose, high palate, drooping eyelids, and prominent lips and ears (Babovic-Vuksanovic et al., 2004; Maranda, Lemieux & Lemyre, 2006; Voiculescu, Toder, Back, Osswald & Schempp, 1993; Zumel, Darnaude & Delicado, 1989). People in this group tend to be short in stature and often have a low body weight with large hands and flat feet (Babovic-Vuksanovic et al., 2004; Maranda et al., 2006). There are also numerous health problems associated with the syndrome including skin changes, dental problems, kidney problems, diabetes, growth hormone deficiency, heart problems and malformations within the brain (Bridge, McManus, Remmenga & Cuppage, 1989; de Ravel, Thiry & Fryns, 2005; Schober, Scheibenreiter & Frisch, 1995; Wester, Bondeson, Edeby & Anneren, 2006). Intellectual disabilities are often seen in this group alongside delayed psychomotor development,

coordination and speech (often with a poorer verbal than non-verbal performance) (Babovic-Vuksanovic et al., 2004; Maranda et al., 2006; de Ravel et al., 2005).

#### 1.2.3.2 1p36

The 1p36 deletion is the most common deletion found in humans (Heilstedt, Ballif, Howard, Kashork & Shaffer, 2003). It occurs in about 1 in 5000-10000 births (Shapira et al., 1997) and was first reported in 1980 (Hain et al.). Physically people with 1p36 deletions are characterised by low muscle tone, low stature and 'failure to thrive' (Eugster, Berry & Hirsch, 1997; Kang et al., 2007). People with a 1p36 deletion classically have distinctive facial features including, deep set eyes, straight eyebrows, late closing fontanelle, broad nose, pointed chin, and a high forehead (Battaglia et al., 2008; Gajecka, Mackay & Shaffer, 2007; Kang et al., 2007). A number of health problems are associated with the deletion including vision and hearing problems, brain abnormalities, heart problems and seizures (e.g., Kurosawa et al., 2005). Many young children also have feeding difficulties, although later difficulties associated with constantly feeling hungry often occur which may lead to obesity, and may be associated with aggression and irritability (D'Angelo et al., 2006; Tsuyusaki et al., 2010). There are many reports of severe developmental delay, particularly with respect to speech and motor development, and many individuals have intellectual disabilities (e.g., Knight-Jones et al., 2000).

#### 1.2.3.3 2q37

The deletion 2q37 was first identified in 1993 (Phelan, Rogers & Byrd). There are a wide range of effects within this deletion, from people who have no apparent symptoms (Ballif,

Kashork & Shaffer, 2000) to people with profound physical, developmental and behavioural difficulties. Physically people with a 2q37 deletion often have a depressed nasal bridge, short neck, ear asymmetry, small eyes, abnormalities of the hands and feet, and obesity (Reddy, Flannery & Farrer, 1999; Conrad et al., 1995). In terms of health; heart, lung and brain abnormalities and hernias have been reported (Reddy et al., 1999). There are also reports of behaviours which are similar to those seen in Autism Spectrum Disorder, in addition to general developmental delay (e.g., Galasso et al., 2008).

#### 1.2.3.4 8p23

People with an 8p23 deletion may present with no obvious physical differences. However, when they do they tend to have distinct facial features including a small jaw and large rotated ears (Baynam, Goldblatt & Walpole, 2008). There is a high incidence of heart problems within the syndrome, and there are reports of seizures, growth delay (Fryns, Klczkowska, Vogels & Van Den Berghe, 1989), developmental delay, intellectual disabilities and impulsive behaviour (Devriendt et al., 1999; Claeys et al., 1997).

#### 1.2.3.5 9q34

People with a 9q34 deletion tend to present with distinctive facial features including a large forehead, flat or round face, short nose, small mouth and protruding tongue (Harada et al., 2004; Sanger et al., 2005). There are also reports of heart conditions, seizures, respiratory problems, developmental delay and intellectual disabilities (Harada et al., 2004; Iwakoshi et al., 2004).

### **1.2.4 Aims of the Literature Review**

This review will consider the literature that has been published on these five rare deletion groups in order to ascertain the focus and scope of the literature. The review will be undertaken within the context of a need to identify the psychological characteristics that are associated with genetic syndromes that might inform families and service providers.

## **1.3 Method**

### **1.3.1 Search Strategy**

The Web of Science and Psycinfo was searched (1967-2011)<sup>1</sup> using the terms; '18p', '1p36', '2q37', '8p23', '9q34' OR 'Kleefstra<sup>2</sup>' AND 'deletion'. The term 'deletion' was truncated to allow inclusion of its suffix variations.

### **1.3.2 Inclusion Criteria**

All papers that reported upon the deletions of interest were included.

### **1.3.3 Process of Review**

Papers were categorised according to recurrent themes, descriptions of how the themes were defined are available in sections 1.3.3.1-1.3.3.5.

#### **1.3.3.1 Conference Presentations**

Search results that were abstracts for conference presentations were categorised as such. Most of these results appeared in subsequent papers, therefore categorising them in their own right would have led to duplicates. Also, the information available within them was

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<sup>1</sup> N.B. Search completed in March 2011, papers published after this time are not included.

<sup>2</sup> Kleefstra Syndrome is the name for 9q34.3 deletion syndrome, thus is encompassed within 9q34 deletions.

limited and would not give a comprehensive understanding of the topic area.

#### 1.3.3.2 Review or Letter

Reviews or letters were articles that were brief and did not add any new findings to the field, summarised research that already existed or suggested new directions for future research.

#### 1.3.3.3 Molecular Genetics

There is a slight overlap between this category and 'physical health'. Papers were categorised as being 'molecular genetics' if the main focus of the paper was upon the analysis of genes or chromosomes. Many of these papers described laboratory based research without contact with people, some described animal models (e.g., Perkowski & Murphy, 2011), whereas others focussed on the prenatal period (e.g., Prontera et al., 2007).

#### 1.3.3.4 Physical

In this category the focus of the literature was upon physical health problems or outlining features of a group with no mention of psychological aspects. This section also covered papers where there was a specific focus on a single aspect of health, such as analysis of DNA for its relationship to certain cancers (e.g., Tran et al., 1998), or, for example, the propensity for dental problems (Moralesperalta & Lantigua, 1994). In these instances there is the potential for the papers to be included in the molecular genetics category, the author's judgement was used to decide where the primary focus lay.

#### 1.3.3.5 Psychological

Papers were categorised as 'psychological' if there was a mention of any type of behaviour in

the title, abstract or keywords. Papers were also considered if there was evidence that there was a detailed clinical description of individuals, as it was possible there may also be a mention of a behavioural trait. Behaviour was rarely the focus of the paper, this means that all papers within this section could additionally fall into either the ‘physical’ or ‘molecular genetics’ category.

## 1.4 Results

### 1.4.1 Overview of Main Searches

Table 1 shows how the papers were identified according to deletion group and search engine. The final column shows the amount of unique references found i.e., those that remained after duplicates had been removed. The addition of the search engine PsycInfo added a total of ten unique references, for this reason additional search engines were not used.

**Table 1: Breakdown of Literature Reviews According to Group and Search Engine**

	Web of Knowledge	PsycInfo	Unique
<b>18p</b>	66	47(8)	74
<b>1p36</b>	133	74(1)	134
<b>2q37</b>	44	17(1)	45
<b>8p23</b>	32	3	32
<b>9q34</b>	25	11	25
<b>Total</b>	300	152(10)	310

Figure 1 shows how the papers were broken down initially into deletion groups and then into the categories within each of those. Finally, it gives an indication of how many people were included in those studies. Across all of the groups the majority of the papers primary focus was molecular genetics, physical aspects was the next frequent for all of the groups bar 2q37 and 8p23, the latter group had no papers categorised as ‘physical’. It may be that these deletions are less associated with specific health conditions, for example heart

conditions are associated with 8p23 but these seem to vary in their cause and may not be specific enough to warrant further study at this point. Also, the categorisation process (see 1.3.3) had some overlap between the molecular genetics and physical health categories.

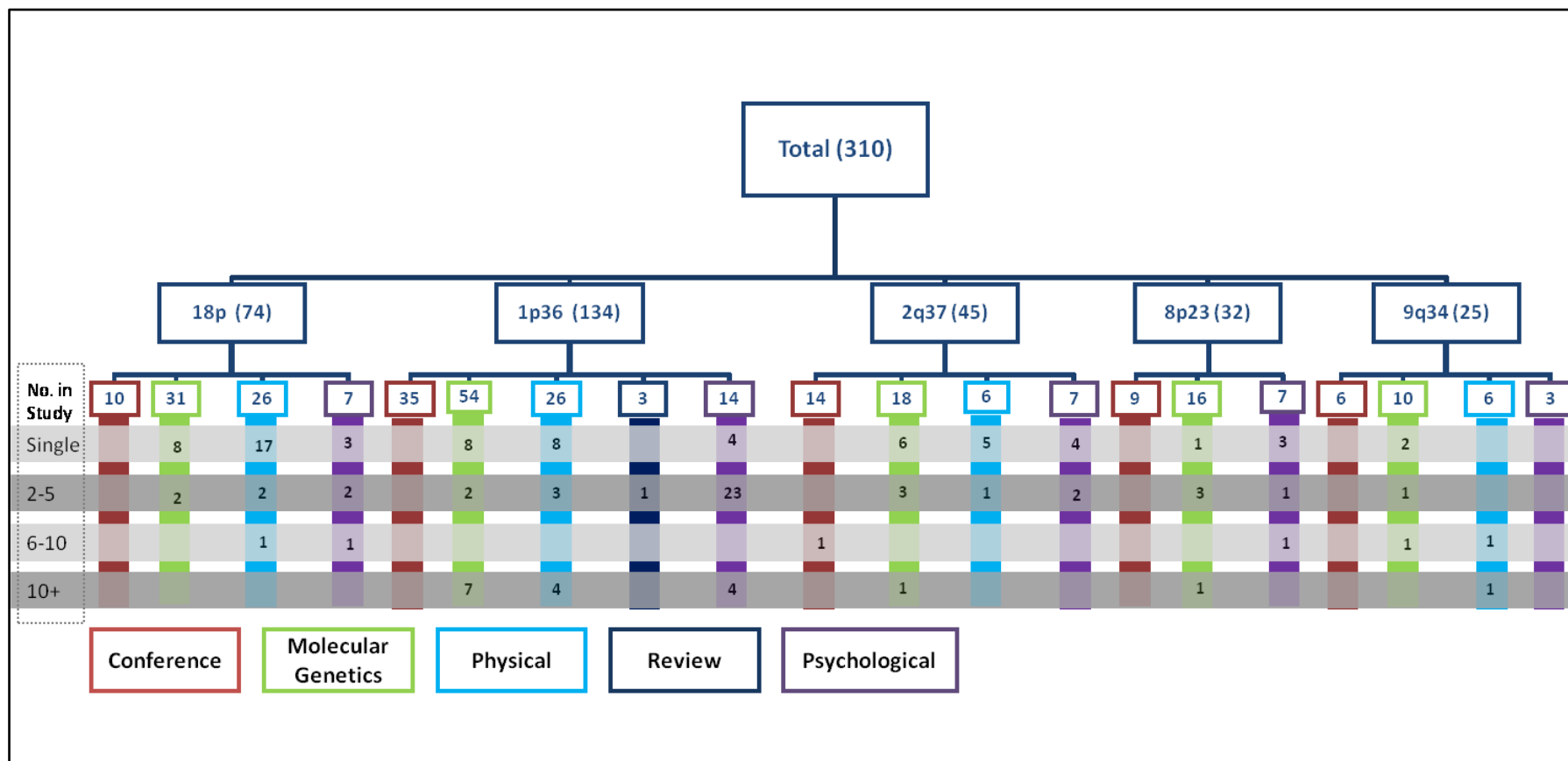


Figure 1: Pictorial Breakdown of the Literature Acquired into Deletion Groups then Categories, with Listings of the Number of Participants within Each Study

Figure 2 shows the point of focus of research over time since 1967 broken down by each of the deletion groups. As different groups were discovered at different time points these graphs have been kept separate in order to allow a clearer illustration of differences over time.

In all of the deletion groups molecular genetics is the most prominent focus; and this would be necessary in order to identify the groups. In the 18p, 1p36 and 2q37 groups 'psychological' does not feature until much later in the timescale of the research but in the 8p23 and 9q34 groups it features relatively early on, suggesting that research into recently discovered syndromes has focussed on this aspect sooner. It is possible that it also depends upon the level of different behaviours that the people with different deletions are showing, for example if the behaviour is very prominent it may be reported more frequently. 1p36 is clearly the most highly researched group with up to 50 papers produced in a single year. Although the number of papers researching 1p36 declined between 2006 and 2010, this represents a decline in molecular genetics studies with physical and behavioural studies accounting for more of the research.

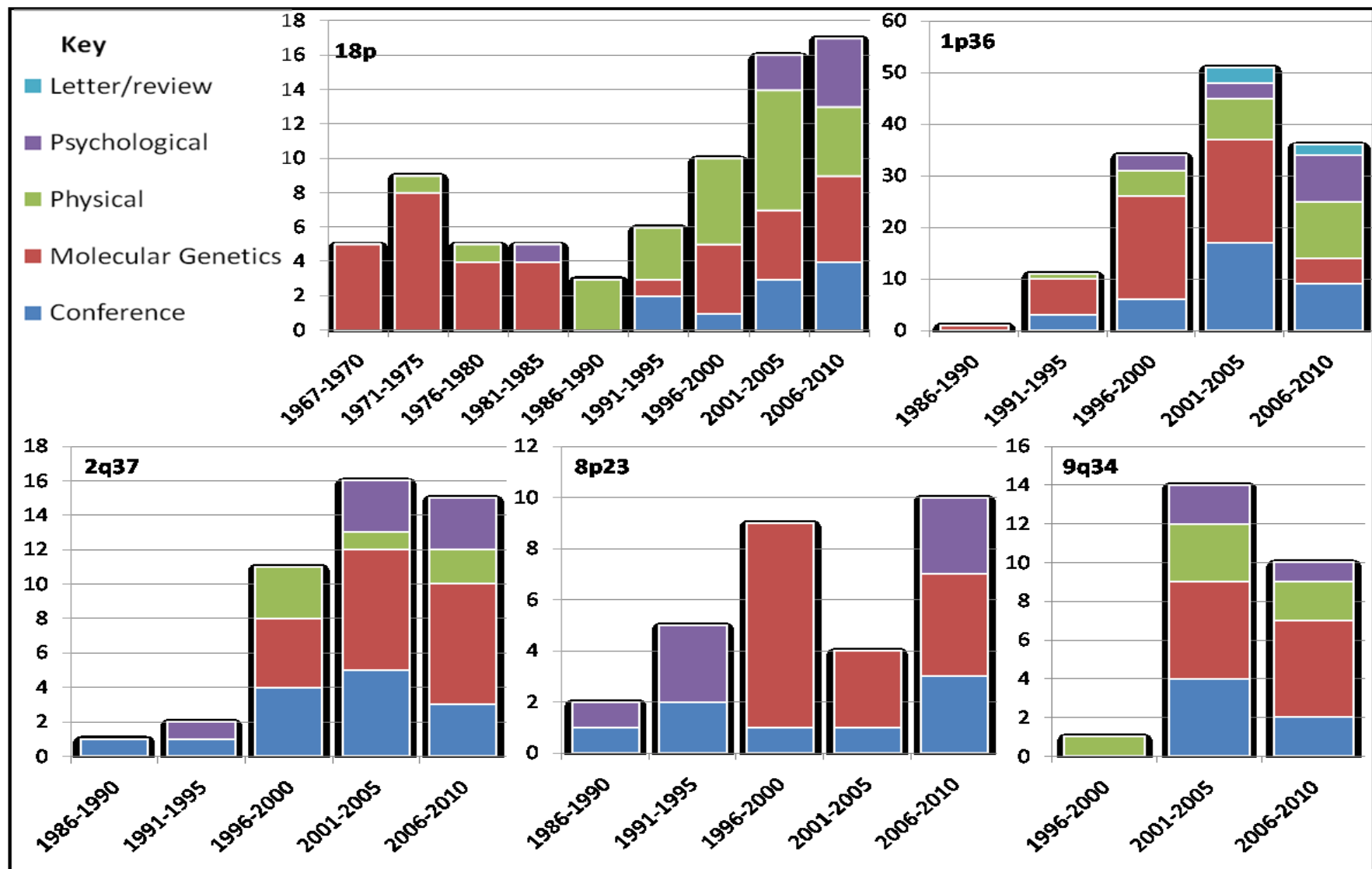


Figure 2: Distribution of Research over Time Represented Graphically by Group

### 1.4.2 Behavioural Research

In the psychological category the 38 papers were obtained and read. During this process three additional papers were added to the review<sup>3</sup>, and ten papers were removed from the psychological category as they did not mention behaviour (six of these were re-categorised as molecular genetics, one as physical), one was Italian and one was a conference presentation. The remaining 31 papers were summarised. Table 2 shows how these papers were distributed over the deletion groups.

**Table 2: Behavioural Category; Breakdown According to Category and Changes to Article Counts**

	Initial Sort	Changes	Final Count
<b>18p</b>	7	-2 (Italian (n=1), behaviour not mentioned (n=1))	5
<b>1p36</b>	14	-5 (behaviour not discussed)	9
<b>2q37</b>	7	+1 (abstract seemed more genetic)	8
		+2 (did not mention p23 in title)	
<b>8p23</b>	7	-2 (behaviour not discussed (n=1), conference abstract (n=1))	7
<b>9q34</b>	3	-1 (behaviour not discussed)	2
<b>Total</b>	38	+2, -10	31

#### 1.4.2.1 Behaviours Discussed within the Papers

Table 3-Table 7 detail the behaviours noted within the papers. They also detail any reference to development (e.g., motor and language) and any measures used<sup>4</sup>.

<sup>3</sup> One additional paper was added to the 2q37 group that had not appeared in either literature search. It appears that an erroneous space in the title may have affected its ability to be searched for. Two additional papers were added to the 8p23 group which became apparent through checking the references of existing papers.

<sup>4</sup> Please note that these comments/reviews are on the basis of coverage of behavioural components within the papers. This is very often a secondary element to the paper, therefore the primary focus of the paper may be very well established and completed. Comments on the behavioural component should not be taken as an overall comment on the quality of the paper. It is beyond the scope and the expertise of this review to comment on how effectively the authors completed their primary aim.

Table 3: 18p Psychological Factor Summary

Paper	n	Ages	Focus	Measures	Behaviour	Development
Kanjilal, Verma & Merkrebs, 1988.	1	15	Review & case report, genes.	None stated.	Age 13; 'announced that someone wanted to kill her', 'in tears and refused to speak'. Diagnosed as psychotic.	Delayed (4 years - couple of words). Language improved enormously.
Babovic-Vuksanovic et al., 2004.	1	42	Psychosis, genes.	Participant refused psychological testing.	"Mental retardation"; 6 hospitalisations as a teen for behavioural control (lack of). Age 27; 'organic delusional disorder' after major depression. Psychosis presented as 'emotional lability', tremor, insomnia, shouting, irritability, crying spells, uncharacteristic aggression, hearing voices and paranoia. Age 42; same symptoms and shouting, tracing squares in air. OCD features, anxiety, cooperative.	Psychomotor development delayed; delayed walking (2 years), delayed speech (few words at 5 years).
de Ravel, Thiry & Fryns, 2005.	2	1) 42 2) 62	Follow up; aging decline	WISC (Wechsler, 2004).	1) Feeding difficulties, mobile, 'happy', converses with everyone, 'most charming collaborative person', neurologically intact, can be 'aggressive' and 'trouble seeking' 2) 'Failure to thrive', 62 years; apathy, Parkinson type signs.	1) Poor motor control. 1 year old; psychomotor delay. Verbal IQ 39, performance IQ 57. 2) 'Severe speech disability'. Performance IQ 53. 'Poor motor control and coordination'.
Maranda, Lemieux & Lemyre, 2006.	3	1) 12, 2) 9 & mum	Family study, genes.	WISC (Wechsler, 2004).	'Neurological examination was normal'.	1) 'Developmental delay'; IQ, 40-55, 'moderate mental retardation'. 2) 'Normal early development' IQ, verbal (55-70) performance (70-85); Mother (52 and 42; verbal and non-verbal IQ).
Wester et al., 2006.	7	7-34	Family & genes.	None stated.	1) Pre-school social interaction difficulties, 'little eye contact', avoided touch, wanted routine. Now, still very slow, expressionless. 2) Social capability good	Summary of all) 5/7 language delay, 4/7 slow, 1/7 autism, 6/7 low muscle tone.

Table 4: 1p36 Psychological Factor Summary

Paper	n	Ages	Focus	Measures	Behaviour	Development
Shapira et al., 1997.	14	-	Report clinical features of pure 1p36 deletions.	Checklist compiled by reviewing the literature, and own observations.	Abusive behaviour (hand biting, banging, hitting people, throwing things).	Motor delay, mild to moderate learning disability, growth delay.
Knight-Jones et al., 2000.	4	5-19	Report clinical features and gene analysis of four children.	Case reports by paediatrician.	1) Feeding difficulties at birth 3&4) Tube fed at birth 4) Self injurious behaviour – sucking fingers. Socially responsive.	1) Birth; Feeding difficulties, low muscle tone – unable to sit without support. Age 10; feeding self, never walked independently 2) Age 1; low muscle tone, no understanding of language 3) Age 1; unable to sit unsupported. Age 7; walking. Age 9; situational understanding of language 4) Age 8; ‘profoundly delayed in all aspects of development’. Unable to sit.
Kurosawa et al., 2005.	11	0.5-17	Genetic analysis.	Medical records, Family history.	1-11) Feeding difficulties at birth 1) Aggressive 5) Panic, aggressive, self injury.	Pre and postnatal growth retardation, severe developmental delay and feeding difficulties at birth in all.
d'Angelo et al., 2006.	1	13	Similarities to Prader Willi.	Clinical interview using a standard protocol by one of the authors.	3-6 years; ‘excessive hunger causing crying and irritability’. Hyperactive. 13 years; skin picking, symptoms of ADD.	2 years; walking, 4.5 years; language. 3 years; obesity with excessive hunger. 13 years language complex, reading poor.
Hiraki et al., 2006.	2	1)20 2)16	Genetic analysis.	None stated.	2) Self-injury.	1) Motor delay (couldn't sit without support). 1.5 years; walking, language delay, 3.5 years; 3 word sentences. Graduated from high school 2). 16 years; severe developmental delay.

Table 4: (Continued)

<i>(continued)</i> Paper	n	Ages	Focus	Measures	Behaviour	Development
Kang et al., 2007.	5	1-6	Identification of a syndrome different to classical 1p36.	None stated.		Global developmental delay (motor and speech), 'failure to thrive'.
Battaglia et al., 2008.	60	0-24	Detail accurate information about syndrome.	Psychological tests (not stated which) for cognitive profile.	Behaviour problems in 28 people including; 'biting own hands and wrists', 'temper tantrums', 'reduced social interaction', 'hand washing', 'flapping', 'head shaking', 'banging', 'rocking', 'repetitive beating of objects or rolling objects', 'smelling things'.	Developmental delay, low IQ, poor language.
Rosenfeld et al., 2010.	5	2-20	Examination of critical chromosome region.	WISC III (Wechsler, 2004).	1) Hand flapping, 'sensory integration issues', 'high pain tolerance' 2) ADD, anger control, impulsivity. 3) Poor feeding during infancy. 8-10 years; excessive weight gain, overeating leading to anger and aggression when controlled. Skin picking, high pain tolerance. 4) Limited eye contact. 'Outbursts of biting, screaming, chewing clothes, rocking and skin picking'. Eats whenever he can including 'raw food, stones and dog food'. High pain tolerance.	1) Muscle weakness. 17 months; walking, first words. 'Pervasive developmental delay' 2) 'Significant developmental disability'. 17 months; walked. IQ 7 <sup>th</sup> centile. 3) 'Mildly developmentally delayed'. 15 months; walked. Difficulty with expressive language. IQ 49. 4) 3 years; walked. 4.5 years; not talking yet. 5) Global developmental delay. 2years; walked. 14 years; needs a wheelchair (>.25 mile). No speech.
Tsuyusaki et al., 2010.	2	9, 10	Looking at relationship to PWS.	Consensus Diagnostic Criteria for PWS (Holm et al., 2003).	1) Birth; tube feeding. PWS – 8.5 2) Birth; difficulty sucking. 'Temper outbursts and impulsivity' 1&2) Weight gain between 1 & 6 years, obsession with food.	1) 18 months; walked. 3 years; 'cognitive skills and motor development moderately delayed'. Repeats words. 2) Birth; psychomotor development delayed. 19 months; walked. 5 years; repeat words.

Table 5: 2q37 Psychological Factor Summary

Paper	n	Ages	Focus	Measures	Behaviour	Development
Conrad et al., 1995.	3	0.7-4	Comparison with previous literature; gene analysis.	None stated.	1) 1 year; repetitive behaviour, rocking and head movements 2) Delayed social skills, hyperactivity, repetitive behaviours 3) Ritualistic behaviour, rocking, head banging.	1) 3 months; smiled and focussed on objects. 6 months; rolled over 2) 9 months; steps. 2 years; toilet trained. 5 years; putting words together. 3) 17 months; walked. 5 years; toilet trained. Psychomotor delay.
Ghaziuddin & Burmeister, 1999.	2	1)6 2)12	Autistic features.	Parent report Cattel Infant Intelligence Scale (Cattell, 1940). Autism Behaviour Checklist (Krug et al., 1980). Autism Diagnostic Interview (Le Couteur, 1989). DSM-IV. (APA, 1994).	1) 'Self-stimulatory movements', stereotypic behaviours - tapping fingers on floor, feeling the texture of objects, turning pages of magazine. Bites own hands. 'Aloof', passive, limited interaction. Fleeting eye contact. Flat facial expression. Played with curtains. Rocking. Uttered words out of context. 2) Little social gaze, facial expression limited. 'Smiles for no apparent reason'. No imaginative play. Withdrew from children his age. 'Used parents hands to demonstrate'. Monotone speech. 'couldn't point or shake head appropriately'. Ritual of putting strings in crevices in house then removing. Distress when ritual interrupted. Sensory, sniffing food and objects, flapped hands and fingers. Liked to spin.	1) Verbal limited (2/3 words), delayed milestones. 2) Severe learning disability. Single word speech. 1&2) Both met autism cut-off on scales.
Wiktor et al., 2001.	2	1)23 2)1	Genetics and family link.	None stated.		1) Delayed motor development. 4 years; walking. 10 years; toilet trained. 19 years; IQ 28, uses gestures and odd words. Help dressing. 2) 'Development appears to be delayed'.

Table 5: (continued)

<i>(continued)</i> Paper	n	Ages	Focus	Measures	Behaviour	Development
Lukusa et al., 2004.	1	12	Genetic analysis.	None stated.	'Lack of eye contact', introversion, poor social contact/communication, limited activities and interests, obsessional, 'stereotypically busy'. Anxious when stressed, panics and run away.	At birth; sucking difficulties, developmental delay in infancy. 20 months; walking. 2.5 years; unable to talk. Mild LD.
Armstrong, Allanson, Weaver, Bevan & Hobart, 2005.	2	1)2 2)13	Genetic analysis.	Apgar scores (Apgar, 1953).	1) 'Feeding difficult' 2) 'Self stimulatory behaviour', 'Incessant chewing', 'banging', anxiety.	1) Unable to sit or roll over. 2 years; head control improved. 2) 14 months; smiled, laughed, no vocalisations. 7 years; no language, walking limited.
Kitsiou-Tzeli et al., 2007.	1	13	Genetic analysis.	Apgar scores (Apgar, 1953).	'Gregarious and friendly'.	17 months; walked with support. 2 years; Speech delay (2 words). 4 years; growth delay, walking difficulties, 2/3 word phrases, LD.
Galasso et al., 2008.	1	8	Autism and 2p.	Griffiths Mental Development Scales (Griffiths, 1970) Psychoeducational Profile– Revised (Schopler et al., 1990) Autism Diagnostic Observation Schedule (Lord et al., 1999). Vineland Adaptive Behavior Scales (Sparrow S., Balla D. & Cicchetti D., 1994).	1 year; lack of eye contact, poor social contact. 5 years; echolalia and verbal perseverations. 'Delayed social skills', 'hyperactivity', repetitive and self-injury behaviors'.	Language delayed, social skills delayed, delay on assessments between 36 and 60 months. Age 5; Griffiths Mental Development Scales, age equivalent 27.9 months. Age 7; Met criteria for autism. Impaired on all domains of the Vineland (31-43 months).
Devillard et al., 2010.	1	14	Autism, family link.	Childhood Autism Rating Scale (Schopler, Reichler, Devellis et al., 1980). Autism Diagnostic Interview– Revised (Lord et al., 1994) WISC (Wechsler, 2004).	18 months; banging head on wall, avoided eye contact, didn't respond to his name. 'Limited facial expressions'. 'Minimal interaction with other children', 'aloof', no imaginative play. Constantly active, agitated without apparent cause. 12 years; 'improved social interaction', 'interested in electronic things'. Anxiety. Poor eye contact. Voice loud and monotonous.	5 years: Motor development normal. Communication (verbal and non-verbal) delayed, meaningful phrases. Growth delay. Met cut-off for autism. IQ 46.

Table 6: 8p23 Psychological Factor Summary

Authors	n	Ages	Focus	Measures	Behaviour	Development
Fryns, Kleczkowska, Vogels & Van Den Berghe, 1989.	1	9	Case report.	WISC-R (Wechsler, 1974).	Behavioural disorders, emotional instability, obstinacy, low frustration tolerance, aggressiveness. Age 9; referred to psychiatry for behavioural disorder.	Delayed psychomotor development. 2 years; few words and walking, slight learning disability (IQ 81), speech delay and stuttering 7 years.
Hutchinson, Wilson, & Voullaire, 1992.	5	1-7	Comparison with literature, gene analysis.	None stated.	1) Affectionate, active, 'distractable', 'easily frustrated', aggressive 3) Poor feeding (early) active, poor sleep, tantrums, affectionate.	1) Fine motor and co-ordination problems, limited speech at 8 yrs. 2) slight developmental delay 3 + 4) mild / moderate developmental delay.
Pettenati et al., 1992.	3	1)7, 2)11	Genetic analysis of family.	None stated.	1) Emotional problem, 'bursts of rage', 'behavioural and emotional handicap'. Easily distracted, problems concentrating 2) Hyperactivity, organizational skills difficulties, comprehension problems, problems following directions, bedwetting.	1) IQ 68 (verbal 84, performance 55). 2 years; walking. 3 years; 2 word sentences. Visual motor and cognitive delays. 2) 15 months; walking and talking. IQ 99, specific reading disability 3) Father 'slow' (LD).
Claeys et al., 1997.	5	0-11	Behavioural phenotype.	Apgar scores (Apgar, 1953). Child Behaviour Checklist (Achenbach & Edelbrock, 1983).	1) 5 years; hospitalised with severe behavioural problems; overactive, attention problems, unruly, contrary. 7 years; hospitalised, aggression, destructive behaviour, temper tantrums, 'voluntary vomiting'. 11 years; hospital, aggressiveness, 'disobedience'. 4) 9 years; hospitalised with aggressiveness, low frustration tolerance, emotional instability, obstinacy. 16 years; 'behaviour had changed dramatically'. 5) Aggression, destructive outbursts, short attention span, hyperactivity, sleep (5 hours).	1) Motor development delayed (walking - 20 months), mild learning disability, IQ - 64 2,3) Delayed 4,5) Mild learning disability.
Devriendt, DeMars, DeCock, Gewillig, & Fryns, 1999.	9	0.5-17	Health condition associated with 8p.	WISC (Wechsler, 1991).	5) Extreme hyperactivity, impulsiveness, aggressiveness, destructiveness, sleep severely impaired. 6) Hyperactivity, concentration, impulsive, 'social skills impaired' 9) Feeding problems (in infancy).	5) Age 3; first spoken words Full IQ 73, verbal IQ 83 performance IQ 69. 6) 'Failure to thrive', mild developmental delay. 9) Failure to thrive'.

Table 6: Continued

<i>(continued)</i> Paper	n	Ages	Focus	Measures	Behaviour	Development
de Vries et al., 2001.	2	1)7 2)16	Family study, genes (cousins).	None stated.	1) Poor feeder, excellent memory, behaviour difficult at times. 2) Severe temper tantrums, head banging. Age 12; masturbating at home with no concern for other members of the household, showed genitalia to a 9 year old girl at school. Damaged property, set fire to a shed in a church, stoned the church's window, diagnosed with 'unsocialised conduct disorder'.	1) Speech and language delayed, learning disabilities 2) Motor development slightly delayed (walked 14 months). Speech normal. Mild learning disability.
Paez et al., 2008.	2	1)0.1 2)14	Genetic analysis.	Tanaka Binet test (Tanaka laboratory, 1987) - IQ 45.	2) Hyperactive during infancy.	1) Growth delay, psychomotor delay 2) Speech delay, moderate learning disability .

Table 7: 9q34 Psychological Factor Summary

Authors	n	Ages	Focus	Measures	Behaviour	Development
Sanger et al., 2005.	1	0 - 8	Description and gene analysis.	None stated.	Happy, fascinated by things that are orange.	
Papadopoulou, Sismani, Christodoulou et al., 2010.	1	2	Genetic analysis.	None stated.	Sociable and friendly.	Speech and motor delays.

#### 1.4.2.1.1 18p Deletions

The five papers within the literature which mentioned psychological components in relation to people with an 18p deletion are summarised in Table 3. Two of the studies were single case, their primary aim was to examine genetics, however one study gave a detailed report of the psychological elements that seemed pertinent to the person they were studying (Babovic-Vuksanovic et al., 2004). One of the papers was a follow up study, this allowed the authors to compare longitudinally two people who had previously been reported in the literature (de Ravel, Thiry & Fryns, 2005).

Only two of the studies used any formal measures (WISC; Weschler, 2004) and none of the studies stated how or by whom the clinical descriptions of the people with an 18p deletion had been collated.

One theme that emerged amongst these papers was a general theme of psychosis, this was mentioned in relation to two of the people with an 18p deletion (Babovic-Vuksanovic et al., 2004; Kanjilal, Verma & Merkrebs, 1988) and one paper mentioned Parkinsonian type symptoms (de Ravel, Thiry & Fryns, 2005). The onset of these was at 16 years, 27 years and between 42 and 62 years. There were also reports of 'slowness' (Wester et al., 2006).

#### 1.4.2.1.2 1p36 Deletions

Table 4 details the papers reviewed that focused on people with a 1p36 deletion and some of the behaviours they were displaying. The range of papers in this category was much broader with one study being a single case (d'Angelo et al., 2006) and one study including 60 participants (Battaglia et al., 2008). The focus of the papers has expanded somewhat with two papers actively appraising similarities between people with a 1p36 deletion and people

with Prader-Willi Syndrome (d'Angelo et al., 2006; Tsuyusaki et al., 2010). Another paper focussed on accurately detailing the clinical features present in people with a 1p36 deletion (Battaglia et al., 2008), this paper also mentions behavioural features, but does not use an established measure to do this. Only three of the nine studies used any form of psychological test and two of these were for the measurement of IQ (Battaglia et al., 2008, Rosenfeld et al., 2010, Tsuyusaki et al., 2010).

Looking at the themes that emerge from the behaviours reported, there seem to be a lot of difficulties around food, many young children had problems feeding, then in middle childhood there are reports of some of the children becoming excessively hungry. This in turn appears to be related to challenging behaviours (d'Angelo et al., 2006; Rosenfeld et al., 2010; Tsuyusaki et al., 2010).

Overall there are several reports of aggressive behaviour, symptoms of attention deficit disorder, self injury and also high pain tolerance. Almost all of the people reported in these papers had severe developmental delay, which is possibly contributing to the behaviours seen.

#### *1.4.2.1.3 2q37 Deletions*

The eight papers reviewed that discussed behaviour in people with a 2q37 deletion are summarised in Table 5. Only three of these studies failed to use any formal measure or to state how they had acquired information about behaviour (Conrad et al., 1995; Lukusa et al., 2004; Wiktor et al., 2001). Three of the studies looked specifically for the presence of autistic features and used a range of measures (Devillard et al., 2010; Galasso et al., 2008; Ghaziuddin & Burmeister, 1999). The latter study used basic screening instruments as well as

using questionnaires that assess autism spectrum disorder. With the exception of two studies, the commentary on the behaviour exhibited by people with a 2q37 deletion is detailed. From the descriptions, many features of Autism Spectrum Disorder are repeatedly reported, the studies that formally assessed autism found that all of the people (n=4) assessed were above autism cut-off. The behaviours reported by these studies such as 'lack of eye contact', 'repetitive behaviour' and 'delayed social skills' were replicated in the reports within three of the other studies (Armstrong et al., 2005; Conrad et al., 1995; Lukusa et al., 2004).

#### *1.4.2.1.4 8p23 Deletions*

Table 6 reviews the behaviours that have been cited in the literature with respect to people with 8p23 deletions. There are seven papers, one of which specifically explored behaviours in people with an 8p23 deletion (Claeys et al., 1997). This study employed the Child Behavior Checklist (Achenbach & Edelbrock, 1983). It was the only study within the papers to use a measure to directly assess behaviour, though three of the studies measured IQ using standardised measures. The studies ranged from a single case to nine participants, however the study (Devriendt et al., 1999) that assessed nine people with an 8p23 deletion only gave a detailed clinical report about three of them, noting that they had been described elsewhere.

In terms of themes that appear to arise in the descriptions there are repeated reports of challenging behaviours, in particular of 'hyperactivity', 'aggression' and 'destructiveness', though two of the papers do indicate that these may reduce over time.

#### *1.4.2.1.5 9q34 Deletions*

There were only two papers that mentioned behaviour in relation to 9q34 deletions, these were both single case studies and did not use any formal measures or state how they collated their information. The behaviours that they mentioned were 'fascinated with the colour orange', and 'happy and sociable'.

## **1.5 Discussion**

The aim of this review was to assess the literature which had been published about each of the rare genetic deletion groups of interest and to develop an understanding of which areas the literature focussed upon, and whether and how the research assessed and reported psychological or behavioural components of the syndromes.

The main focus of the current literature was either genetic analysis or physical health conditions, very few of the studies mentioned psychological aspects, and only one paper from the initial 300 papers found focussed specifically on behaviour (Claeys et al., 1997). Assessing how the literature changed over time, the papers tended to have an initial focus on molecular genetics, as might be expected as the DNA analysis is fundamental to identifying the deletion. This is followed with a gradual increase in the amount of papers published which mention physical characteristics and then psychological factors. In the more recently 'discovered' genetic deletions (8p23 and 9q34) studies mentioning behaviour appear much earlier. This is promising as it suggests that the importance of behaviour is becoming more prominent. Only 10% of the initial 300 papers retrieved through the search had any mention of psychological or behavioural traits.

Analysis of the psychological literature found that very few of the studies used any form of

standardised measurements, about a third of the papers used some form of assessment to assess IQ, and about a quarter of the papers used a standardised questionnaire. One study used five questionnaires. The lack of use of standardised measures makes comparability across studies challenging. If a behaviour is not reported it is difficult to know whether that is because it was not present, present but not assessed or because it did not seem to be of importance at the time. Although some of the studies did utilise established measures, only two studies used the same measure, making comparability across studies difficult.

The remainder of the papers reported behaviours associated with the person with the genetic deletion. Only in four cases did the authors report how this information was obtained so it is difficult to ascertain the validity and reliability of the reports. The weighting towards reporting difficult and challenging behaviours could be representative of the source that the information was obtained from, for example referrals to NHS services are more likely to have an overrepresentation of problematic behaviours. In addition, many of the descriptors of behaviours were vague, examples of this include 'aloof' and 'fascinated by the colour orange'. These descriptions are imprecise and highlight the importance of developing a consistent way of assessing people with rare genetic deletions.

### **1.5.1 Themes**

Despite the paucity of established measures, analysis of the papers that do mention behaviour found that within each deletion group there appeared to be a theme that was repeatedly reported. Each of these were problems that parents and carers would potentially find it difficult to cope with and would impact on the individual's wellbeing. There were reports of psychosis for people with 18p deletions. This was reported in two papers

(Babovic-Vuksanovic et al., 2004; Kanjilal, Verma & Merkrebs, 1988), a third paper mentioned symptoms akin to Parkinsons (de Ravel, Thiry & Fryns, 2005) and there were reports of slowness and apathy (de Ravel, Thiry & Fryns, 2005; Wester et al., 2006). Considering the limited number of papers in the area these observations warrant further investigation. Many genetic disorders are associated with neurological and psychiatric disorders, for example people with Down Syndrome are susceptible to Alzheimers disease (Oliver and Holland, 1986) and psychosis is associated with Prader-Willi (Boer et al., 2002) and Velo-cardio-facial syndromes (22q deletion; Ivanov et al., 2003, Murphy, 2002). Developing an understanding of these disorders in those with 18p deletions may ultimately aid early intervention. There were also reports of anxiety in people with 18p deletions. It could be that the psychotic presentation is related to severe anxiety. With such limited literature available this may be a finding that fails to be replicated but it does warrant investigation.

There were a number of reports of difficulties around food for people who had a 1p36 deletion. There appeared to be a time during childhood when children were excessively hungry followed by excessive eating and impaired satiety with attempts to control intake reported to lead to challenging behaviour, frustration and upset for the person with the genetic deletion (Dykens et al., 1989, Oliver & Holland, 1986; Russell & Oliver, 2003). This profile is strikingly similar to that described for Prader-Willi syndrome (Cassidy, 1997) and warrants further research.

In the studies of 2q37 and 8p23 deletions there were a number of behaviours reported that have an immediate impact on families and carers. People with a 2q37 deletion were

reported to display behaviours reminiscent of those displayed by people with ASD. Three studies used standardised measures and found that the people that they tested scored above the cut-off for Autism. Many studies have found that parents of children with ASD have higher levels of stress than parents or carers of any other disability (Abbeduto et al., 2004; Ingersoll & Hambrick, 2011). The studies highlighting behaviours found in people with an 8p23 deletion found high levels of challenging behaviour, particularly behaviours akin to those seen in ADHD. Again these behaviours are particularly stressful to parents (Ekas & Whitman, 2010; Ingersoll & Hambrick, 2011; Lecavalier, Leone & Wiltz, 2006; Myers, Mackintosh & Goin-Kochel, 2009). Intervening in challenging behaviour at its onset rather than later may reduce carer stress, thus in the long-term aiding the carers (Hastings, 2002).

### **1.5.2 Future Studies**

This review has highlighted that there are clearly behavioural differences in rare microdeletion disorders that are important to families, and has shown that the research on rare genetic deletions is, understandably, focussed on molecular genetics, or physical features. However, it is clear that psychological characteristics are of equal importance to individuals with microdeletion disorders and their families and carers. Knowledge of behaviours commonly seen in specific deletion groups may help clinicians to more readily identify those people who may need further testing (Kurosawa, 2005).

Within the papers reviewed it is clear that there are good attempts to report relevant behaviours. Indeed Babovic-Vuksanovic et al. (2004) expressed a desire to report as much as possible as they were unsure what may be pertinent in the future. In order to move the field forward in the most effective manner it is essential that researchers begin to screen all rare

genetic deletions using standardised psychological assessments. As an initial screen, adaptive behaviour may be assessed using an instrument like the Vineland Adaptive Behaviour Scale (Sparrow, Cicchetti & Balla, 2005). The most common themes within the literature for these five rare genetic deletions were challenging behaviour, ASD and ADHD traits, and sleep and feeding difficulties, these could be assessed using the SCQ (ASD; Howlin & Karpf, 2004), the Connors or the TAQ (ADHD; Conner, 2000; Burbridge & Oliver, 2008, respectively) and the CBQ (challenging behaviour; Hyman, Oliver & Hall, 2002). These questionnaires would take a relatively short time to complete and most of them could be sent to carers before an appointment or research took place, but would provide an invaluable source of information both for future research and in order to advise carers.

After the initial screening any particular behaviours that are prominent may be assessed in greater depth. This might entail assessment of psychiatric or neurological symptoms or a more focussed appraisal of, for example, eating behaviour or motor development.

### **1.5.3 Limitations of the Current Review**

This review was a brief scope of the literature with a detailed look at the papers mentioning psychological components. The initial categorisation of the papers could be defined beyond 'molecular genetics' and 'physical', and this would be better informed if all of the papers were read.

## 1.6 References

- Abbeduto, L., Seltzer, M. M., Shattuck, P., Krauss, M. W., Orsmond, G. & Murphy, M. M. (2004). Psychological Well-Being and Coping in Mothers of Youths with Autism, Down Syndrome, or Fragile X syndrome. *American Journal on Mental Retardation*, 109, 237-254.
- Achenbach, T. M. & Edelbrock, C. S. (1983). *Manual for the Child Behavior Checklist and Revised Child Behavior Profile*. Burlington, VT University of Vermont, Department of Psychiatry.
- Apgar, V. (1953). A Proposal for a New Method of Evaluation of the Newborn Infant. *Current Researches in Anesthesia and Analgesia*, 32(4), 260–267.
- American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Health Disorders* (4th ed). Washington DC: Author
- Armstrong, L., Allanson, J. E., Weaver, D. D., Bevan, C. J. & Hobart, H. H. (2005). Unrelated Patients with a Rearrangement of Chromosome 2 Causing Duplication of 2p23 and Deletion of 2q37. *American Journal of Medical Genetics Part A*, 134A(3), 299-304.
- Babovic-Vuksanovic, D., Jenkins, S. C., Ensenuer, R., Newman, D. C. & Jalal, S. M. (2004). Subtelomeric Deletion of 18p in an Adult with Paranoid Schizophrenia and Mental Retardation. *American Journal of Medical Genetics Part A*, 124A(3), 318-322.
- Baker, E., Hinton, L., Callen, D. F., Altree, M., Dobbie, A., Eyre, H.J., . . . Haan, E. (2002). Study of 250 Children with Idiopathic Mental Retardation Reveals Nine Cryptic and Diverse Subtelomeric Chromosome Anomalies. *American Journal of Medical Genetics*, 107, 285-293.
- Ballif, B.C., Kashork, C.D. & Shaffer, L.G. (2000). The Promise and Pitfalls of Telomere Region-Specific Probes. *American Journal of Medical Genetics*, 67(5), 1356-1359.
- Basu, S. & Deb, A. (1996) Parent Training in Children with Attention Deficit Hyperactivity Disorder: An Integrated Approach for Greater Effectiveness. *Indian Journal of Clinical Psychology*, 23, 184-191.
- Battaglia, A., Hoyme, E. H., Dallapiccola, B., Zackai, E., Hudgins, L., McDonald-McGinn, D., . . . Carey, J. C. (2008). Further Delineation of Deletion 1p36 Syndrome in 60 Patients: A Recognizable Phenotype and Common Cause of Developmental Delay and Mental Retardation. *Pediatrics*, 121(2), 404-410.
- Baynam, G., Goldblatt, J. & Walpole, I. (2008). Deletion of 8p23.1 with Features of Cornelia De Lange

- Syndrome and Congenital Diaphragmatic Hernia and a Review of Deletions of 8p23.1 to 8pter? A Further Locus for Cornelia de Lange Syndrome. *American Journal of Medical Genetics Part A*, 146A(12), 1565-1570.
- Beck, J., Beck, A. & Jolly, J. (2001). *Beck Youth Inventories of Emotional & Social Impairment Manual*. San Antonio: Psychological Corporation.
- Boer, H., Holland, A., Whittington, J., Butler, J., Webb, T. & Clarke, D. (2002). Psychotic Illness in People with Prader-Willi Syndrome due to Chromosome 15 Maternal Uniparental Disomy. *Lancet*, 359(9304), 135-136.
- Bridge, J. A., McManus, B. M., Remmenga, J. & Cuppage, F. P. (1989). Complete Heart Block in the 18p Syndrome: Congenital Calcification of the Atrioventricular Node. *Archives of Pathology and Laboratory Medicine*, 113, 539-541.
- Burbidge, C., & Oliver, C. (2008). *The Activity Questionnaire. Manual for Administration and Score Interpretation*. Birmingham, UK: University of Birmingham.
- Cans, C., Wilhelm, L., Baille, M., Du Mazaubrun, C., Grandjean, H., Rumeau-Rouquette, C. (1999). Aetiological Findings and Associated Factors in Children with Severe Mental Retardation. *Developmental Medicine & Child Neurology*, 41, 233-239.
- Cassidy, S. B. (1997). Prader-Willi Syndrome. *Journal of Medical Genetics*, 34, 917-923.
- Cattell, P. (1940). *The Measurement of Intelligence of Infants and Young Children*. Psychological Corporation, New York.
- Claeys, I., Holvoet, M., Eyskens, B., Adriaenssens, P., Gewillig, M., Fryns, J. P. & Devriendt, K. (1997) A Recognizable Behavioral Phenotype Associated with Terminal Deletions of the Short Arm of Chromosome 8. *American Journal of Medical Genetics*, 74, 515-520.
- Conrad B., Dewald G., Christensen E., Lopez M., Higgins J. & Pierpont, M. E. (1995). Clinical Phenotype Associated with Terminal 2q37 Deletion. *Clinical Genetics*, 48, 134–139.
- Conner, K. (2000). *Conners' Rating Scales-Revised Technical Manual*. Multi Health Systems. North Tonawanda, New York.
- d'Angelo, C. S., Da Paz, J. A., Kim, C. A., Bertola, D. R., Castro, C. I., Varela, M. C. & Koiffmann, C. P. (2006). Prader-Willi-Like Phenotype: Investigation of 1p36 Deletion in 41 Patients with Delayed Psychomotor Development Hypotonia, Obesity and/or Hyperphagia, Learning Disabilities and Behavioral Problems. *European Journal of Medical Genetics*, 49(6), 451-460.

- de Ravel, T. J. L., Thiry, P. & Fryns, J. P. (2005). Follow-up of Adult Males with Chromosome 18p Deletion. *European Journal of Medical Genetics*, 48(2), 189-193.
- Devillard, F., Guinchat, V., Moreno-De-Luca, D., Tabet, A. C., Gruchy, N., Guillem, P., . . . Betancur, C. (2010). Paracentric Inversion of Chromosome 2 Associated with Cryptic Duplication of 2q14 and Deletion of 2q37 in a Patient with Autism. *American Journal of Medical Genetics Part A*, 152A(9), 2346-2354.
- Devriendt, K., Matthijs, G., Van Dael, R., Gewillig, M., Eyskens, B., Hjalgrim, H., . . . Marynen, P. (1999). Delineation of the Critical Deletion Region for Congenital Heart Defects, on Chromosome 8p23.1. *The American Journal of Human Genetics*, 64, 1119-1126.
- de Vries, B. B., Lees, M., Knight, S. J., Regan, R., Corney, D., Flint, J., . . . Winter, R. M. (2001). Submicroscopic 8pter Deletion, Mild Mental Retardation, and Behavioral Problems Caused by a Familial t(8;20)(p23;p13). *American Journal of Medical Genetics*, 99, 314-319.
- de Vries, B. B., Winter, R., Schinzel, A. & van Ravenswaaij-Arts, C. (2003). Telomeres: A Diagnosis at the End of the Chromosomes. *Journal of Medical Genetics*, 40, 385-398.
- Dyken, E. M. (1995). Measuring Behavioral Phenotypes: Provocations from the 'New Genetics'. *American Journal on Mental Retardation*, 99, 522-532.
- Ekas, N. & Whitman, T. L. (2010). Autism Symptom Topography and Maternal Socioemotional Functioning. *American Journal on Intellectual and Developmental Disabilities*, 115(3), 234-249.
- Eugster, E. A., Berry, S. A. & Hirsch, B. (1997). Mosaicism for Deletion 1p36.33 in a Patient with Obesity and Hyperphagia. *American Journal of Medical Genetics*, 70(4), 409-412.
- Fryns, J. P., Kleczkowska, A., Vogels, A. & Van Den Berghe, H. (1989). Normal Phenotype and Slight Mental Retardation in De Novo Distal 8p Deletion (8pter-.8p23. 1:). *Annales de Genetique*, 32, 171-3.
- Gajecka, M., Mackay, K. L. & Shaffer, L. G. (2007). Monosomy 1p36 Deletion Syndrome. *American Journal of Medical Genetics Part C*. 145C, 346-356.
- Galasso, C., Lo-Castro, A., Lalli, C., Nardone, A. M., Gullotta, F. & Curatolo, P. (2008). Deletion 2q37: An Identifiable Clinical Syndrome with Mental Retardation and Autism. *Journal of Child Neurology*, 23(7), 802-806.
- Ghaziuddin, M. & Burmeister, M. (1999). Deletion of Chromosome 2q37 and Autism: A Distinct

- Subtype? *Journal of Autism and Developmental Disorders*, 29, 259-263.
- Griffiths, R. (1970). *The Abilities of Young Children*. Child Development Research Centre, London.
- Grouchy, J., Lamy, M., Thieffry, S. & Arthuis, M. (1963). Dysmorphie Complexe Avec Oligophrénie: Délétion des Bras Courts d'un Chromosome 17-18. *Comptes Rendus de l'Académie des Sciences*, 257, 3098-3102.
- Harada, N., Visser, R., Dawson, A., Fukamachi, M., Iwakoshi, M., Okamoto, N., . . . Matsumoto, N. (2004). A 1-Mb Critical Region in Six Patients with 9q34.3 Terminal Deletion Syndrome. *Journal of Human Genetics*, 49(8), 440-444.
- Hain, D., Leversha, M., Campbell, N., Daniel, A., Barr, P. A. & Rogers, J. G. (1980). The Ascertainment and Implications of an Unbalanced Translocation in the Neonate: Familial 1:15 Translocation. *Australian Paediatric Journal*, 16(3), 196-200.
- Hastings, R. P. (2002). Parental Stress and Behaviour Problems of Children with Developmental Disability. *Journal of Intellectual and Developmental Disability*, 27, 149-160.
- Heilstedt, H. A., Ballif, B. C., Howard, L. A., Kashork, C. D. & Shaffer, L. G. (2003). Population Data Suggest that Deletions of 1p36 are a Relatively Common Chromosome Abnormality. *Clinical Genetics*, 64, 310-316.
- Hiraki, Y., Fujita, H., Yamamori, S., Ohashi, H., Eguchi, M., Harada, N., . . . Matsumoto, N. (2006). Mild Craniosynostosis with 1p36.3 Trisomy and 1p36.3 Deletion Syndrome Caused by Familial Translocation T(Y;1). *American Journal of Medical Genetics Part A*, 140A(16), 1773-1777.
- Holm, V. A., Cassidy, S. B., Butler, M. G., Hanchett, J. M., Greenswag, L. R., Whitman, B. Y. & Greenberg, F. (1993). Prader-Willi Syndrome: Consensus Diagnostic Criteria. *Pediatrics*, 91, 398-402.
- Howlin, P. & Karpf, J. (2004). Using the Social Communication Questionnaire to Identify 'Autistic Spectrum' Disorders Associated with Other Genetic Conditions: Findings From a Study of Individuals with Cohen Syndrome. *Autism*, 8, 175-182.
- Hutchinson, R., Wilson, M. & Voullaire, L. (1992). Distal 8p Deletion (8p23.1-]8pter) - A Common Deletion. *Journal of Medical Genetics*, 29(6), 407-411.
- Hyman, P., Oliver, C. & Hall, S. (2002). Self-Injurious Behavior, Self-Restraint, and Compulsive Behaviors in Cornelia de Lange Syndrome. *American Journal on Mental Retardation*, 107(2), 146-154.

- Ingersoll, B. & Hambrick, D. Z. (2011). The Relationship between the Broader Autism Phenotype, Child Severity, and Stress and Depression in Parents of Children with Autism Spectrum Disorders. *Research in Autism Spectrum Disorders*, 5(1), 337-344.
- Ivanov, D., Kirov, G., Norton, N., Williams, H. J., Williams, N. M., Nikolov, I., Tzvetkova, R., Stambolova, S. M. & Murphy, K. C. (2003). Chromosome 22q11 Deletions, Velo-Cardio-Facial Syndrome and Early-Onset Psychosis Molecular Genetic Study. *British Journal of Psychiatry*, 18(3), 409-413.
- Iwakoshi, M., Okamoto, N., Harada, N., Nakamura, T., Yamamori, S., Fujita, H., . . . Matsumoto, N. (2004). 9q34.3 Deletion Syndrome in Three Unrelated Children. *American Journal of Medical Genetics Part A*, 126A(3), 278-283.
- Kang, S-H. L., Scheffer, A., Ou, Z., Li, J., Scaglia, F., Belmont, J., Lalani, Sr, . . . Bacino, C. A. (2007). Identification of Proximal 1p36 Deletions Using Array-CGH: A Possible New Syndrome. *Clinical Genetics*, 72(4), 329-338.
- Kanjilal, D., Verma, R.S. & Merkrebs, A. (1988). Clinical Manifestation of Children with a Deletion of the Short Arm of Chromosome 18 (18p-). *Dysmorphology and Clinical Genetics*, 2(4), 109-114.
- Kitsiou-Tzeli, S., Sismani, C., Ioannides, M., Bashiardes, S., Ketoni, A., Toulaitou, V., . . . Philippos, C. (2007). Array-Cgh analysis and Clinical Description of 2q37.3 De Novo Subtelomeric Deletion. *European Journal of Medical Genetics*, 50(1), 73-78.
- Knight-Jones, E., Knight, S., Heussler, H., Regan, R., Flint, J. & Martin, K. (2000). Neurodevelopmental Profile of a New Dysmorphic Syndrome Associated with Submicroscopic Partial Deletion of 1p36.3. *Developmental Medicine and Child Neurology*, 42(3), 201-206.
- Krug, D. A., Arick, J. R. & Almond, P. G. (1980). Behavior Checklist for Identifying Severely Handicapped Individuals with High Levels of Autistic Behavior. *Journal of Child Psychology and Psychiatry*, 21, 221-229.
- Kurosawa, K., Kawame, H., Okamoto, N., Ochiai, Y., Akatsuka, A., Kobayashi, M., . . . Kuroki, Y. (2005). Epilepsy and Neurological Findings in 11 Individuals with 1p36 Deletion Syndrome. *Brain and Development*, 27(5), 378-382.
- Lecavalier, L., Leone, S. & Wiltz, J. (2006). The Impact of Behaviour Problems on Care-Giver Stress in Young People with Autism Spectrum Disorders. *Journal of Intellectual Disability Research*,

50(3), 172-183.

- Le Couteur, A., Rutter, M., Lord, C., Rios, P., Robertson, S., Holdgrafer, M. & McLennan, J. D. (1989). Autism Diagnostic Interview: A Semistructured Interview for Parents and Caregivers of Autistic Persons. *Journal of Autism and Developmental Disorders*, 19, 363-387.
- Lord, C., Rutter, M., DiLavore, P. & Risi, S. (1999). *Autism Diagnostic Observation Schedule: Manual*. Los Angeles: Western Psychological Services.
- Lukusa, T., Vermeesch, J. R., Holvoet, M., Fryns, J. P. & Devriendt, K. (2004). Deletion 2q37.3 and Autism: Molecular Cytogenetic Mapping of the Candidate Region for Autistic Disorder. *Genetic Counselling*, 15(3), 293-301.
- Maranda, B., Lemieux, N. & Lemyre, E. (2006). Familial Deletion 18p Syndrome: Case Report. *BMC Medical Genetics*, 7(60), 1471-1477.
- Moralesperalta, E. & Lantigua, A. (1994) Deletion 18p Associated with a Single Maxillary Incisor - A Case-Study. *Revista Brasileira de Genetica*, 17(3), 341-343.
- Murphy, K. C. (2002). Schizophrenia and Velo-Cardio-Facial Syndrome. *The Lancet*, 359(9304), 426-430.
- Myers, B. J., Mackintosh, V. H. & Goin-Kochel, R. P. (2009) "My Greatest Joy and My Greatest Heart Ache:" Parents' Own Words on how having a Child in the Autism Spectrum has Affected their Lives and their Families' Lives. *Research in Autism Spectrum Disorders*, 3, 670-684.
- Oliver, C. & Holland, A. (1986). Down's Syndrome and Alzheimer's Disease: A Review. *Psychological Medicine*, 16, 307-322.
- O'Brien, G. (2006). Behavioural Phenotypes: Causes and Clinical Implications. *Advances in Psychiatric Treatment*, 12, 338-348.
- Paez, M. T., Yamamoto, T., Hayashi, K., Yasuda, T., Harada, N., Matsumoto, N., . . . Matsuoka, R. (2008). Two Patients with Atypical Interstitial Deletions of 8p23.1: Mapping of Phenotypical Traits. *American Journal of Medical Genetics Part A*, 146A(9), 1158-1165.
- Papadopoulou, E., Sismani, C., Christodoulou, C., Ioannides, M., Kalmanti, M. & Patsalis, P. (2010). Phenotype-Genotype Correlation of a Patient with a "Balanced" Trans Location 9;15 and Cryptic 9q34 Duplication and 15q21q25 Deletion. *American Journal of Medical Genetics Part A*, 152A(6), 1515-1522.

- Perkowski, J. & Murphy, G. (2011). Deletion of the Mouse Homolog of KCNAB2, a Gene Linked to Monosomy 1p36, Results in Associative Memory Impairments and Amygdala Hyperexcitability. *Journal of Neuroscience*, 31(1), 46-54.
- Pettenati, M. J., Rao, N., Johnson, C., Hayworth, R., Crandall, K., Huff, O. & Thomas, I. T. (1992). Molecular Cytogenetic analysis of a Familial 8p23.1 Deletion Associated with Minimal Dysmorphic Features Seizures and Mild Mental Retardation. *Human Genetics*, 89(6), 602-606.
- Phelan, M. C., Rogers, R. C. & Byrd, L. K. (1993). Albright Hereditary Osteodystrophy and Del(2)(q37) in Two Unrelated Individuals. *American Journal of Human Genetics*, 53, 484.
- Prontera, P., Aiello, V., Toschi, M., Turci, A., Gruppioni, R., Buldrini, B., . . . Sensi, A. (2007) Prenatal Diagnosis of a De Novo Satellited Chromosome 18 (18ps) Associated with 18p Deletion. *Genetic Counseling*, 18(3), 309-315.
- Qin, X-Q., Tang, C., Zhu, S-Y., Liang, Y-Y. & Zou, X-B. (2009). Parenting Stress and Related Factors in Mothers of Children with Autism. *Chinese Mental Health Journal*, 9.
- Reddy, K. S., Flannery, D. & Farrer, R. J. (1999). Microdeletion of Chromosome Sub-Band 2q37.3 in Two Patients with Abnormal Situs Viscerum. *American Journal of Human Genetics*, 84, 460-468.
- Reish, O., Berry, S. A. & Hirsch, B. (1995). Partial Monosomy of Chromosome 1p36.3: Characterization of the Critical Region and Delineation of a Syndrome. *American Journal of Medical Genetics*, 59(4), 467-475.
- Rosenfeld, J. A., Crolla, J. A., Tomkins, S., Bader, P., Morrow, B., Gorski, J., . . . Shaffer, L. G. (2010). Refinement of Causative Genes in Monosomy 1p36 Through Clinical and Molecular Cytogenetic Characterization of Small Interstitial Deletions. *American Journal of Medical Genetics Part A*, 152A(8), 1951-1959.
- Russell, H. & Oliver, C. (2003). The Assessment of Food Related Problems in Individuals with Prader-Willi Syndrome. *British Journal of Clinical Psychology*, 42, 379-392.
- Sanger, T. M., Olney, A. H., Zaleski, D., Pickering, D., Nelson, M., Sanger, W. G. & Dave, B. J. (2005). Cryptic Duplication and Deletion of 9q34.3 -> Qter in a Family with a T(9;22)(Q34.3;P11.2). *American Journal of Medical Genetics Part A*, 138A(1), 51-55.
- Schober, E., Scheibenreiter, S. & Frisch, H. (1995). 18p Monosomy with GHDeficiency and Empty

- Sella: Good Response to GH Treatment. *Clinical Genetics*, 47(5), 254-256.
- Schopler E., Reichler R. J., Bashford A., Lansing M. D. & Marcus L. M. (1990) *Individualized Assessment and Treatment for Autistic and Developmentally Disabled Children, Vol. 1: Psychoeducational Profile Revised (PEP/R)*. Pro-Ed, Austin, TX.
- Schopler, E., Reichler, R. J., Devellis, R. F. & Daly, K. (1980). Toward Objective Classification of Childhood Autism: Childhood Autism Rating Scale (CARS). *Journal of Autism and Developmental Disorders*, 10, 91–103.
- Shapira, S. K., McCaskill, C., Northrup, H., Spikes., A. S., Elder, F. F. B., Sutton, V. R., Korenberg, J. R., Greenberg, F. & Shaffer, L. G. (1997). Chromosome 1p36 Deletions: The Clinical Phenotype and Molecular Characterization of a Common Newly Delineated Syndrome. *American Journal of Human Genetics*, 61(3), 642-650.
- Singer, G. H. S. & Floyd, F. (2006). Meta-Analysis of Comparative Studies of Depression in Mothers of Children with and without Developmental Disabilities. *American Journal on Mental Retardation*, 111(3), 155-169.
- Skuse, D. H. (2002). Behavioural Phenotypes. *Psychiatry*, 1(7), 98-102.
- Smith, T. B., Oliver, M. N. I. & Innocenti, M. S. (2001). Parenting Stress in Families of Children with Disabilities. *American Journal of Orthopsychiatry*, 71(2), 257-261.
- Sparrow S., Balla D. & Cicchetti D. (1994) *Vineland Adaptive Behaviour Scale (Survey Form)*. American Guidance Service, Circle Pines, MN.
- Sparrow, S., Cicchetti, D., & Balla, D. (2005). *Vineland Adaptive Behavior Scales (2nd Edition)*. Minneapolis, MN: Pearson Assessment.
- Stevens, F. I. (1986). Vineland Adaptive Behavior Scales: Classroom Edition. *Journal of Counseling & Development*, 65(2), 112-113.
- Tanaka Laboratory (1987) *Tanaka Binet Evaluation Method*. Tanaka Shuppan Co., Ltd., Tokyo.
- Tehee, E., Honan, R. & Hevey, D. (2009). Factors Contributing to Stress in Parents of Individuals with Autistic Spectrum Disorders. *Journal of Applied Research in Intellectual Disabilities*, 22, 34-42.
- Tran, Y., Benbatoul, K., Gorse, K., Rempel, S., Futreal, A., Green, M. & Newsham, I. (1998). Novel Regions of Allelic Deletion on Chromosome 18p in Tumors of the Lung, Brain and Breast. *Oncogene*, 17(26), 3499-3505.

- Tsuyusaki, Y., Yoshihashi, H., Furuya, N., Adachi, M., Osaka, H., Yamamoto, K. & Kurosawa, K. (2010). 1p36 Deletion Syndrome Associated with Prader-Willi-Like Phenotype. *Pediatrics International*, 52(4), 547-550.
- van Duijn, G., Dijkxhoorn, Y., Noens, I., Scholte, E. & van Berckelaer-Onnes, I. (2009), Vineland Screener 0–12 years Research Version (NL). Constructing a Screening Instrument to Assess Adaptive Behaviour. *International Journal of Methods in Psychiatric Research*, 18, 110-117.
- Voiculescu, I., Toder, R., Back, E., Osswald, P. & Schempp, W. (1993). A Retrospective CISS Hybridization Analysis of a Case with de novo Translocation t(18;22) Resulting in an 18p Syndrome. *Clinical Genetics*, 43, 318-320.
- Wechsler, D. (1974). *Manual for the Wechsler Intelligence Scale for Children—Revised*. New York: Psychological Corporation.
- Wechsler, D. (1991). *The Wechsler Intelligence Scale for Children—Third Edition*. San Antonio, TX: The Psychological Corporation.
- Wechsler, D. (2004). *The Wechsler Intelligence Scale for Children—Fourth Edition*. London: Pearson Assessment.
- Weiss, J. A., Sullivan A. & Diamond, T. (2003). Parent Stress and Adaptive Functioning of Individuals with Developmental Disabilities. *Journal on Developmental Disabilities*, 10(1), 129-135.
- Wester, U., Bondeson, M. L., Edeby, C. & Anneren, G. (2006). Clinical and Molecular Characterization of Individuals with 18p Deletion: A Genotype-Phenotype Correlation. *American Journal of Medical Genetics Part A*, 140A(11), 1164-1171.
- White, S. J., Sterrenburg, E., van Ommen, G-J. B., den Dunnen, J. T. & Breuning, M. H. (2003). An Alternative to FISH: Detecting Deletion and Duplication Carriers within 24 Hours. *Journal of Medical Genetics*, 40, 113.
- Wiktor, A., Feldman, G. L., Bawle, E. V., Czarnecki, P., Conard, J. V. & Van Dyke, D. L. (2001). Deletion of 2q37 and Duplication of 10q24: Two Cases in the Same Family and Review of the Literature. *Annales de Genetique*, 44(3), 129-134.
- Zumel, R. M., Darnaude, M. T. & Delicado, A. (1989). Diaz de Bustamante, A., de Torres, M. L. & Lopez-Pajares, I. The 18p Syndrome. Report of Five Cases. *Annales of Genetics*, 32:160-163.

**TOWARD A BEHAVIOURAL PHENOTYPE FOR 8p23 AND  
9q34 DELETION SYNDROMES**

## 2.1 Abstract

There is a paucity of research examining the behaviours common to the genetic microdeletions 8p23 and 9q34. This research aimed to describe behaviours within these groups using robust and reliable questionnaires, and to compare these groups to other genetic syndromes with established behavioural phenotypes.

Participants (n=41) completed a battery of questionnaires assessing a range of behaviours including those associated with Autism Spectrum Disorder, Attention Deficit Hyperactivity Disorder, sociability and challenging behaviour.

There were high levels of challenging behaviours within both groups, possibly causing carers increased stress. People with a 9q34 deletion displayed behaviours similar to people with Autism Spectrum Disorder (ASD), including stereotyped and restricted behaviours. However, many people had higher mood, interest and pleasure ratings and were more likely to be sociable. Concerningly, there appeared to be a decline in executive functioning as children got older.

People with an 8p23 deletion were most like people with Down Syndrome in terms of their mood, levels of repetitive behaviour and sociability with unfamiliar people. They were least like people with ASD. Unlike people with Down Syndrome they were significantly less likely to be sociable with familiar people.

The study concludes by discussing the directions future research and the clinical implications.

## **2.2 Introduction**

### **2.2.1 Genetic Deletions**

A growing number of deletion syndromes are identified as being associated with intellectual disability including Smith-Magenis, Cornelia de Lange, Cri du Chat, Prader Willi, Angelman and DiGeorge Syndromes. Recent advances in detection techniques, such as high-resolution chromosome banding, molecular chromosome analysis using fluorescence in situ hybridisation (FISH) and multiplex amplifiable probe hybridisation (MAPH) (e.g., Babovic-Vuksanovic, Jenkins, Ensenauer, Newman, & Jalal, 2004; Shaw-Smith et al., 2004; White, Sterrenburg, van Ommen, den Dunnen & Breuning, 2003) have resulted in the emergence of a number of previously unrecognised microdeletion syndromes. As a consequence, an increasing number of studies are reporting associations between location and size of deletion and the resultant phenotypes with a focus on clinically important features. Within this literature are studies describing the cognitive and behavioural phenotypes associated with microdeletion syndromes. Two syndromes that have recently attracted interest are 9q34 and 8p23 deletion syndrome; both of these have been the subject of relatively little empirical research.

### **2.2.2 Behavioural Phenotypes**

Behaviours seen within microdeletion syndromes arguably result in distinctive patterns of social behaviour, specific and nonspecific cognitive impairments, and language and motor abilities known as behavioural phenotypes (O'Brien, 2006; Skuse, 2002). It is often assumed that these behaviours are the direct and indirect result of the genetic deletion, although there are clearly interactions with age, environment, and level of intellectual ability in

addition to typical individual variation (Barnard, Pearson, Rippon & O'Brien, 2002). A review of the literature on a small number of microdeletion syndromes of comparable prevalence (Grandfield, this volume), reveals a paucity of psychological research with robust methodology. Two syndromes of interest identified in the review were 8p23 and 9q34 deletion syndromes.

#### 2.2.2.1 8p23 Deletions

Children and adults with an 8p23 deletion are reported to have a range of health concerns and behavioural characteristics, with reports of heart abnormalities, hernias (Baynam, Goldblatt & Walpole, 2008; Wat et al, 2009) and distinctive facial appearance (Baynam et al. 2008; Claeys et al. 1997; Devriendt et al., 1999). There are also delays in psychomotor development and growth (Páez et al., 2008; Unique, 2009).

There are few papers examining behaviour and development but those that do report behavioural problems (de Vries et al., 2001; Devriendt et al., 1999; Wat et al., 2009), including aggression, temper outbursts possibly due to frustration (Claeys et al., 1997; de Vries et al., 2001, Unique, 2009), head banging (de Vries et al., 2001) and hyperactivity (Páez et al., 2008). One child was reported to have been diagnosed with conduct disorder (de Vries et al., 2001), in part because of 'vandalism' and inappropriate sexual behaviour. In addition, many people with an 8p23 deletion were described as having developmental delay (Devriendt et al., 1999; Wat et al., 2009), language delay (de Vries et al., 2001; Unique, 2009) and learning difficulties (de Vries et al., 2001; Devriendt et al., 1999; Páez et al., 2008; Unique, 2009).

Children with 8p23 deletions are also described as 'happy, sociable, and affectionate'

(Unique, 2009; p. 16). Although research has begun to describe behavioural sequelae of an 8p23 deletion, these tend to be attributes that are mentioned as an aside to the main study. One study used the Child Behaviour Checklist (Achenbach & Edelbrock, 1983) to assess behaviour in five children (Claeys et al., 1997). They included a very detailed clinical report on each child, but the behavioural description was relatively brief. Two other studies included assessment of IQ (Devriendt et al., 1995; Paez et al., 2008) within the clinical descriptions but the main focus of the papers was genetic analysis<sup>5</sup>.

#### 2.2.2.2 9q34 Deletions

A range of health conditions and behaviours are described in relation to adults and children with 9q34 deletions. In terms of physical attributes there is evidence of respiratory, heart and hearing problems, as well as distinctive facial features including large ears, broad nose and small mouth (Ayyash et al., 1997; Iwakoshi et al., 2004; Papadopoulou et al., 2010; Sanger et al., 2005), and delayed growth (Unique, 2009).

There are reports of developmental delay (Ayyash et al., 1997; Iwakoshi et al., 2004), including delay in both motor development and speech (Kannu, Winship & Aftimos, 2005; Sanger et al. 2005; Unique, 2009; Yatsenko et al., 2005). 9q34 deletions have also been associated with intellectual disabilities (Iwakoshi et al., 2004), 'fascination with orange things' (Sanger et al., 2005), feeding difficulties (particularly with respect to swallowing), obesity and delayed growth (Iwakoshi et al., 2004; Unique, 2009b). Other attributes included being 'a very happy child' (Sanger et al., 2005).

There is limited literature exploring behavioural characteristics within people with a 9q34

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<sup>5</sup> For a fuller review of the behavioural research see Grandfield (this volume).

deletion, and at present most of these difficulties are reported anecdotally rather than assessed formally. This makes it difficult to ascertain how common or severe highlighted behaviours may be.

### 2.2.2.3 Summary of 8p23 and 9q34 Deletions

Current research into 8p23 and 9q34 deletions has focussed primarily on identifying the genetic region affected or on identifying cases during pregnancy (see Grandfield, this volume). There is limited research investigating the effects of the deletions upon the individual's wellbeing. Where this has been the focus, research has predominantly described physical characteristics and/or health concerns for the individual. Reporting of behavioural characteristics (see 2.2.3) appears to have been limited to clinical observation rather than by the use of robust or reliable measurement.

### 2.2.3 Researching Behavioural Phenotypes in Microdeletion Syndromes

As the emerging microdeletion syndrome groups are rare, sample sizes are inevitably low. This is problematic for contrast studies that typify the approach to describing behavioural phenotypes. There are two strategies that might be pursued. Dykens (1995) proposed that behavioural phenotypes should be comparative, using adults and children who do not have the syndrome and matching participants on either chronological or mental age. Oliver, Berg, Moss, Arron and Burbidge (2010) suggest that comparing new groups with existing groups that are widely researched with a comparatively well documented behavioural phenotype, such as Down Syndrome (DS) and Autism Spectrum Disorder (Moss et al., 2008), is a feasible alternative. Groups can be selected for comparison because they are broadly similar to the syndrome of interest (Dykens 'same but different' approach). This approach is often

exploratory, requiring the use of a number of standardised measures (albeit those that have been shown to be of value in other more established groups) and non-directional hypotheses. The number of measures required in combination with the small numbers of participants means that type 2 errors might be evident. However, this kind of exploratory study may provide the foundation for future hypotheses and subsequent research of clinical value.

A second approach is to focus on individual case descriptions with high or low scores from normative samples on particular measures. This enables rich data to be collated on an individual basis and forms the initial development of an understanding of behaviour. However, it is more difficult to draw together a complete picture, and hypotheses for future research are tentative. For these reasons, in this study the first approach is adopted using previously established standardised measures that have already been used within various studies

Cornelia de Lange Syndrome, Autism Spectrum Disorder and Down Syndrome were selected for comparison to both the 8p23 and 9q34 deletion syndromes as they are well known and documented groups with established phenotypes and genotypes, thus making them good reference groups. Participants with a 9q34 deletion were also matched with Cri du Chat Syndrome, as this group shows a similar ability profile (N.B., ability profile was matched for all groups, see 2.3.3). Participants with 8p23 deletions were also matched with Rubinstein Taybi Syndrome and Fragile X Syndrome as levels of ability were similar within the groups making matching possible.

### **2.2.4 Aim**

The aim of the current study is to describe behaviours shown by participants with an 8p23 deletion or a 9q34 deletion using reliable and established measures, in order to explore a possible behavioural phenotype. A second aim is to compare and contrast these two new groups with other genetic syndromes for which behavioural phenotypes are well established.

## **2.3 Methodology**

### **2.3.1 Ethics**

Ethical review for this study was obtained from the Coventry Research Ethics Committee as part of a larger study (Appendix 3).

### **2.3.2 Recruitment**

#### **2.3.2.1 8p23 and 9q34 Deletions**

Participants were recruited via the charity Unique, a rare chromosome disorder support group for parents and carers based in the UK. Unique identified and forwarded questionnaire packs to all of the people (n=80) registered on its database with a 9q34 (n=36) or an 8p23 deletion (n=44), 41 (51.25%) questionnaires were returned.

For participants with a 9q34 deletion, 15 (42%) mothers returned the questionnaires for their child. Of these, four children were below the age of four and so were excluded as some measures are not appropriate for this age group. Eleven participants remained aged 4-44 ( $\bar{x}$  =12.45,  $\sigma$ =11.18), five were male and six were female (see Table 8).

In the 8p23 deletion group 26 (59%) parents (25 mothers, 1 father) returned questionnaires for people that they cared for, two were younger than four years old, and were excluded.

Twenty-four participants aged 4-26 ( $\bar{x}$  =11.75,  $\sigma$ =6.56) remained; 16 of which were male (see Table 9).

### 2.3.2.2 Comparison Groups

Participants with Autism Spectrum Disorder, Down Syndrome, Cornelia de Lange, Cri du Chat, Rubinstein Taybi and Fragile X Syndromes who had taken part in a similar study previously (see Moss, Oliver, Arron, Burbidge & Berg, 2009, for full details of recruitment and response rates) and agreed that their data could be used in future research, were included as comparison groups for the 9q34 and 8p23 deletion syndromes. Full details of these participants can be seen in Table 8 and Table 9.

### 2.3.3 Participant Matching

As the 9q34 and 8p23 deletion syndrome groups had different characteristics, individuals within each group were matched to individuals within the comparison groups. Participants were matched on five criteria prioritised in this order: self-help, verbal ability, mobility (these initial three criteria were based on the Wessex scale; Kushlick, Blunden & Cox, 1973; see 2.3.5.2.1), then gender and age (within 3 years if possible; collated using the demographic questionnaire; see 2.3.5.1). It was not always possible to match participants on all five of these criteria, when this was the case they were matched as closely as possible. Table 8 shows age, gender, level of hearing and vision, and level of capability in terms of speech, mobility and self help, for people with a 9q34 deletion and its comparison groups. Similarly Table 9 shows these data for people with an 8p23 deletion and its comparison groups (further statistical analyses can be seen in 2.4.1.3).

**Table 8: Demographics and Abilities for 9q34 and Comparison Groups**

n=11		9q34	ASD	DS	CdLS	CdCS
Age (years)	$\bar{x}$	12.84	12.49	12.18	13.88	13.22
	$\sigma$	11.12	11.64	10.97	9.69	9.78
	Range	4.21-44.09	4.08-45.84	5.19-43.8	6.21-39.29	5.47-39.64
Gender	% Male	45.5	90.9	54.5	36.4	27.3
Self Help <sup>*</sup>	% Partly able/able <sup>**</sup>	54.5	63.6	81.8	54.5	54.5
Mobility <sup>*</sup>	% Mobile <sup>**</sup>	81.8	100	100	81.8	81.8
Vision <sup>*</sup>	% Normal	81.8	81.80	54.5	81.8	90.9
Hearing <sup>*</sup>	% Normal	90.9	81.80	36.4	63.6	81.8
Speech <sup>*</sup>	% Verbal	100	100	81.8	100	90.9

<sup>\*</sup> Data derived from the Wessex Scale (Kushlick *et al.*, 1973).

<sup>\*\*</sup> Scores of >six on the respective subscales.

**Table 9: Demographics and Abilities for 8p23 and Comparison Groups**

n=24		8p23	ASD	DS	CdLS	FXS	RTS
Age (years)	$\bar{x}$	12.01	11.68	12.21	13.2	12.88	12.22
	$\sigma$	6.59	5.91	6.6	6.49	5.6	6.54
	Range	4.12-26.64	4.1-23.89	5.19-25.78	4.65-27.03	6.3-24.17	3.07-25.16
Gender	% Male	66.7	87.5	70.8	62.5	100	66.7
Self Help <sup>*</sup>	% partly able/able <sup>**</sup>	62.5	66.7	83.3	62.5	66.7	66.7
Mobility <sup>*</sup>	% mobile <sup>**</sup>	91.7	95.8	100	95.8	95.8	95.8
Vision <sup>*</sup>	% normal	52.2	95.8	54.2	79.2	91.3	83.3
Hearing <sup>*</sup>	% normal	91.7	95.8	50	73.9	91.3	83.3
Speech <sup>*</sup>	% Verbal	91.7	91.7	87.5	91.7	95.8	91.7

<sup>\*</sup> Data derived from the Wessex Scale (Kushlick *et al.*, 1973).

<sup>\*\*</sup> Scores of >six on the respective subscales.

### 2.3.4 Procedure

Questionnaire packs including a cover sheet (Appendix 4), covering letter (Appendix 5), information sheet (Appendix 6), consent forms (Appendix 7) and questionnaires (see 2.3.5) were sent to Unique, who then posted them to participants. If participants wished to take part in the study they were asked to return the completed packs in a postage paid envelope.

The expected time to complete all of the questionnaires should not have exceeded 60 minutes. The maximum time permitted to return the questionnaires was six weeks from posting.

### **2.3.5 Measures**

The research reported here is part of a larger study, therefore only the relevant questionnaires are mentioned in detail. The main questionnaire pack consisted of 14 questionnaires evaluating different components of behaviour and questions assessing the demographic characteristics of the participants. The questionnaires not reported are the Non-Communicating Children's Pain Checklist-Revised (Breau, McGrath, Camfield, Rosmus & Finley, 2002), the Social Motivation Questionnaire (Wilde & Oliver, unpublished), the Food Related Problems Questionnaire (Russell & Oliver, 2003), the Gastroesophageal Reflux Questionnaire (Oliver & Wilkie, unpublished), a health questionnaire (Hall, Arron, Sloneem & Oliver, 2008) and questions asking about the carers' mood and health.

#### **2.3.5.1 Demographics**

These questions (Appendix 8) covered basic details including gender, age, abilities (i.e., verbal, mobile), and diagnosis (date, age, diagnostician and any additional diagnoses).

#### **2.3.5.2 Questionnaires**

##### **2.3.5.2.1 *Wessex Scale***

The Wessex scale (Appendix 9) was developed in 1973 (Kushlick et al., 1973). Carers complete a range of questions assessing abilities. Subscales measure physical capacity (e.g., vision, hearing, mobility) and social capacity (such as communication, literacy, self-help). The scale has established reliability and validity at subscale level and has been used extensively

since its development (Kushlick et al., 1973; Palmer & Jenkins, 1982).

#### *2.3.5.2.2 Social Communication Questionnaire (SCQ)*

The SCQ (Appendix 10) was designed by Rutter, Bailey and Lord (2003) as a carer completed questionnaire which covers features linked to Autism Spectrum Disorder. Three subscales focus on communication, social interaction, and repetitive or stereotyped behaviours. The reliability and validity of the scale are robust. Additionally, research has been conducted assessing the efficacy of this scale against other more established measures (Berument, Rutter, Lord, Pickles & Bailey, 1999; Howlin & Karpf, 2004).

#### *2.3.5.2.3 The Activity Questionnaire (TAQ)*

The TAQ (Appendix 11) is a carer completed questionnaire developed by Burbridge and Oliver (2008) to assess hyperactivity and impulsivity in people with an intellectual disability. Three subscales cover overactivity, impulsive speech and impulsivity. Research indicates that this scale has robust reliability and validity (Burbridge et al., 2010). Also, recently established preliminary testing indicates high internal consistency.

#### *2.3.5.2.4 The Sociability Questionnaire for People with Intellectual Disability (SQID)*

The SQID (Appendix 12) was developed by Collis, Oliver and Moss (unpublished; Nelson, 2010) to assess a person with an intellectual disability and their level of sociability with people who are familiar or unfamiliar. This allows an indication of sociability to be established within two main subscales; social interaction and social performance. Further subscales look at whether the interaction is initiated or received within both familiar and unfamiliar interactions. This scale is relatively new and further studies are underway to assess its psychometric validity. Initial analyses suggest good reliability and validity (Nelson,

2010).

#### *2.3.5.2.5 Mood, Interest and Pleasure Questionnaire Short-form (MIPQ-S)*

Ross and Oliver initially developed the MIPQ in 2003 (Appendix 13; see also Ross, Arron & Oliver, 2008) as a carer completed scale. It is used to assess the mood and level of interest and pleasure (subscales) of a person with an intellectual disability. Development of a shorter version (used in the current study) indicated good construct validity, internal consistency and inter-rater reliability.

#### *2.3.5.2.6 Challenging Behaviour Questionnaire (CBQ)*

The CBQ (Hyman, Oliver & Hall, 2002; Appendix 14) is a carer completed questionnaire designed to explore challenging behaviour in people with an intellectual disability. The self injury component of the scale looks at eight different behaviours including ‘biting self’ and ‘hitting self on objects’. Analyses of the scale indicate strong inter-rater reliability.

#### *2.3.5.2.7 The Behaviour Rating Inventory of Executive Function—Preschool Version (BRIEF-P)*

The BRIEF-P was developed in 2003 (Gioia, Espy & Isquith; Appendix 15) to assess executive functioning within everyday contexts. Carers complete the scale on behalf of the person they are rating. In addition to an overall score (global executive composite), the scale has three main subscales: inhibitory self-control, flexibility, and emergent metacognition. It is also possible to assess a number of smaller factors (inhibition, shift, emotional control, working memory, and plan/organize). The scale has robust reliability and validity.

#### *2.3.5.2.8 The Repetitive Behaviour Questionnaire (RBQ)*

The RBQ (Moss & Oliver, 2008; Appendix 16) is a carer completed questionnaire developed

to look at repetitive behaviours in people with an intellectual disability. It consists of five subscales looking at stereotyped behaviour, compulsive behaviour, insistence on sameness, restricted preferences and repetitive language. Research has indicated that the scale has good reliability and validity (Moss & Oliver, 2008; Moss et al., 2009) and good convergent validity with the repetitive behaviour subscale of the Autism Screening Questionnaire (Berument et al., 1999).

### **2.3.6 Data Analysis**

Data were checked for skew and kurtosis by examining whether the scales fell within  $\pm 2$  standard errors. Approximately half of the scales did not meet these criteria. In addition, normality was assessed using Shapiro Wilk, as there were fewer than 2000 participants. The majority of the examined subscales evidenced statistically significant deviation from normality ( $p < 0.05$ ). It is likely that one reason for these results is the small sample sizes and homogeneity within syndrome groups within the study. Throughout this paper where normality is compromised statistical analyses are non-parametric.

## **2.4 Results**

As the primary focus of this research is how 8p23 and 9q34 deletion syndromes compare to the selected contrast groups the focus of the results are the two groups of interest. Therefore comparisons and resultant statistical analysis within the contrast groups will not be reported unless they have relevance to the current study.

### **2.4.1 Demographic Characteristics**

#### **2.4.1.1 9q34 Deletions and Comparison Groups**

Of the total 55 participants 50.9% ( $n=28$ ) were male, 74.5% ( $n=41$ ) were verbal, 61.8% ( $n=34$ )

were able (in terms of self-help) and 78.2% (n=43) were ambulant. The mean age of the participants was 12.92 years ( $\sigma=10.28$ ; range 4.08-45.84). Descriptive data are presented in Table 8.

#### 2.4.1.2 8p23 Deletions and Comparison Groups

These groups included 144 participants (age;  $\bar{x}=12.38$ ,  $\sigma=6.2$ , range 4.07-27.03), 75.7% (n=109) were male, 98.6% (n=142) were verbal, 68% (n=98) were able and 95.8% (n=138) were ambulant. Further descriptive data are in Table 9.

#### 2.4.1.3 Demographics, Sensory Impairments and Adaptive Behaviour

Parametric and non-parametric (Kruskal Wallis) ANOVAs were conducted to ascertain whether there were significant differences between the groups on any of the measures used to match participants. Gender was the only component that evidenced statistically significant differences (8p23;  $\chi(5)=14.13$ ,  $p=.013$ ; 9q34;  $\chi(4)=10.43$ ,  $p=.03$ ). Parametric post hoc (Tukeys HSD) analyses were conducted. With respect to 8p23 the analysis indicated that the Fragile X Syndrome group had statistically significantly more males than the Cornelia de Lange Syndrome group (MW=180,  $z=-3.29$ ,  $p=.001$ ). The analysis showed that within the 9q34 comparison groups the Autism Spectrum Disorder group had significantly more males than the Cri du Chat Syndrome group (MW=22,  $z=-2.96$ ,  $p=.003$ ) (a full breakdown of the post hoc tests can be seen in Appendix 1 and 2).

In addition, analyses also found differences between the 8p23 deletion group and its comparison groups for vision and hearing (8p23, vision;  $\chi(5)=22.44$ ,  $p<.001$ ; 8p23, hearing;  $\chi(5)=22.28$ ,  $p<.001$ ). The 8p23 deletion group had a greater proportion of people with normal hearing than the Down Syndrome group (MW=168,  $z=-3.14$ ,  $p=.002$ ), and their vision

was poorer than both the Autism Spectrum Disorder group (MW=155,  $z=-3.4$ ,  $p=.001$ ) and the Fragile X Syndrome group (MW=161,  $z=-2.92$ ,  $p=.004$ ).

## **2.4.2 Behavioural Characteristics**

### **2.4.2.1 9q34 Deletions**

Table 10 shows the mean rank and interquartile range for 9q34 deletions and its comparison groups and highlights statistically significant differences between the groups using Kruskal Wallis analyses. On the Challenging Behaviour Scale 54.5% (6/11) of adults and children with a 9q34 deletion were recorded as showing self-injurious or aggressive behaviour, whilst 36.4% (4/11) were reported to be destructive to property. Analysis did not indicate statistically significant differences from any of the other syndromes.

Participants with a 9q34 deletion evidenced scores on The Activity Questionnaire (Burbridge & Oliver, 2008) which were amongst the highest within the groups measured (though not statistically significantly different), showing that people with a 9q34 deletion are as impulsive as people with Cri du Chat Syndrome and have activity levels on a par with children with Autism Spectrum Disorder. In terms of mood and interest and pleasure the 9q34 deletion group were comparable to other groups in the study.

The scale assessing repetitive behaviour did not find statistically significant differences across the groups. With respect to stereotyped and restricted behaviours, participants with a 9q34 deletion were similar to those with Autism Spectrum Disorder at the high end of the scale. Furthermore, scores on compulsive behaviours were similar to those for participants with Down Syndrome. Overall people with a 9q34 deletion were at the high end of the scale.

There were significant differences between people with a 9q34 deletion and those with Cri

du Chat Syndrome on the restricted behaviour subscale of the Social Communication Questionnaire and on the overall score for the scale (indicating greater difficulty). These differences were indicated by Mann-Whitney analyses ( $z=-2.14$ ,  $p=.03$ ;  $z=-2.05$ ,  $p=.04$ , respectively). Participants with a 9q34 deletion were similar to those with Autism Spectrum Disorder on these components, though they were more congruous with Cornelia de Lange Syndrome for reciprocal social interaction.

Post hoc Mann Whitney analyses indicated that there were statistically significant differences on the total unfamiliar and the total familiar scale of the Sociability Questionnaire for Intellectual Disabilities between Autism Spectrum Disorder and 9q34 deletion syndrome ( $z=-3$ ,  $p=.002$ ,  $z=-2.53$ ,  $p=.01$ ), such that participants in the 9q34 deletion group are more likely to approach and communicate with unfamiliar and familiar people. This tendency to approach people was most like that seen in participants with Down Syndrome.

In summary, participants with a 9q34 deletion show similarities with the Autism Spectrum Disorder group on the Repetitive Behaviour Questionnaire and the Social Communication Questionnaire. However, they have higher interest and pleasure and mood scores, comparable to participants with Down and Cri du Chat Syndromes groups for their total score. Participants with a 9q34 deletion were significantly more sociable than the group of people with Autism Spectrum Disorder; comparable again to people with Down Syndrome. In terms of activity they show similar levels to those seen in Cornelia de Lange Syndrome or Cri du Chat Syndrome.

Table 10: Medians, Interquartile Range and/or Percentages, Kruskal Wallis Analyses and Positioning of 9q34 Deletions in Relation to its Comparison Groups

Scale	Component	9q34		ASD		DS		CdLS		CdCS		Kruskal-Wallis		Positioning
		<i>n</i>	$\tilde{x}$ (Q1-Q3)	<i>n</i>	$\tilde{x}$ (Q1-Q3)	<i>n</i>	$\tilde{x}$ (Q1-Q3)	<i>n</i>	$\tilde{x}$ (Q1-Q3)	<i>n</i>	$\tilde{x}$ (Q1-Q3)	$\chi^2$ ( <i>v</i> )	<i>p</i>	
CBQ	% Self-injury	11	54.5	11	36.4	10	18.2	11	81.8	10	63.6	1.41 (4)	.84	
	% aggression	11	54.5	11	63.6	10	63.6	11	72.7	11	81.8	2.08 (4)	.72	
	% property	11	36.4	11	45.5	10	10	11	81.8	11	45.5	11.12 (4)	.03	
TAQ	Impulsivity	11	17 (12-20.4)	11	11 (9-23)	11	12 (8-18)	11	14 (9-20)	11	16 (9-18)	1.44 (4)	.84	
	Overactivity	11	20 (11-25.88)	11	20 (7.88-30)	11	14 (6-24)	11	18 (11-22)	11	16 (8-23)	1.32 (4)	.86	
	Impulsive speech*	7	4 (3-11)	8	4.5 (2.25-10.5)	7	4 (3-6)	5	4 (1.5-4.5)	7	3 (1-8)	1.88 (4)	.76	
	Total Activity	11	42.88 (25.5-49)	10	27 (20.47-60.5)	10	23 (18.75-43.5)	11	36 (21-41.5)	11	33 (29-39)	1.98 (4)	.74	
MIPQ-S	Total	11	40 (30-44)	11	35 (24-39)	11	39 (38-43)	11	36 (33-37)	11	38 (36-43)	7.07 (4)	.13	
	Mood	11	21 (20-22)	11	18 (16-21)	11	22 (20-22)	11	20 (18-21)	11	21 (19-22)	8.03 (4)	.09	
	Interest & pleasure	11	18 (8-21)	11	17 (8-20)	11	18 (17-21)	11	15 (14-17)	11	18 (17-20)	6.1 (4)	.19	
RBQ	Stereotyped	11	12 (4-12)	11	10 (1-12)	11	6 (0-10)	11	8 (5-12)	11	5 (3-8)	3.36 (4)	.50	
	Compulsive	11	3 (0-4)	11	6 (1-19)	11	2 (0-4)	11	5 (3-12)	11	0 (0-8)	9.39 (4)	.05	
	Restricted	7	5 (3-12)	8	5 (0.75-10.25)	8	2.5 (0.25-6.25)	5	5 (2-9)	7	4 (1-7)	2.53 (4)	.64	
	Sameness	10	1 (0-4.25)	11	1 (0-8)	11	0 (0-2)	11	3 (1-6)	11	0 (0-3)	8.62 (4)	.07	
	Repetitive Lang	7	11 (7-12)	8	6 (1.5-11.25)	8	3 (0.5-7)	5	5 (4-9.5)	7	6 (4-8)	7.26 (4)	.12	

Table 10: (continued)

(continued)		9q34		ASD		DS		CdLS		CdCS		Kruskal-Wallis		Positioning
Scale	Component	n	$\tilde{x}$ (Q1-Q3)	n	$\tilde{x}$ (Q1-Q3)	n	$\tilde{x}$ (Q1-Q3)	n	$\tilde{x}$ (Q1-Q3)	n	$\tilde{x}$ (Q1-Q3)	$\chi^2$ (v)	p	
RBQ	Total-speech	10	19.5 (10-22.75)	11	16 (10-45)	11	12 (2-17)	11	19 (15-29)	11	11 (8-23)	6.89 (4)	.14	
	Total	10	22 (17.5-29.25)	11	21 (10-54)	11	15 (8-24)	11	26 (16-41)	11	12 (11-24)	5.95 (4)	.20	
SCQ	Communication	11	7.58 (4.88-11.38)	11	11 (7-12)	10	6.21 (2.75-10.75)	8	6.64 (2.5-10.68)	10	4.5 (2.71-7.89)	13.73 (4)	.01	CdCS<9q34= ASD
	Restricted, repetitive	11	6 (4-6)	11	6 (5-7)	11	4 (2-5)	11	4.57 (3-6)	11	4 (3-5)	10.73 (4)	.03	
	Reciprocal social interaction	11	8 (7-11)	11	11 (10-14)	10	6.5 (2-11)	8	8.5 (6-9.75)	10	3.5 (1.75-9.25)	12.73 (4)	.01	
	Total	11	22 (16-29.58)	11	29 (24-33)	10	17.5 (8.31-25)	8	18.5 (15.75-19.75)	10	13.5 (6.75-19)	14.98 (4)	.01	CdCS<9q34=ASD
	% > Cutoff	11	54.5	11	100	10	36.4	11	9.1	11	9.1	12.55 (4)	.01	
SQID	Familiar	11	49 (45-50)	11	37 (32-42)	11	53 (41-54)	2	49.5 (49-50)			11.25 (3)	.01	ASD<9q34=DS=CdLS
	Unfamiliar	11	42 (26-46)	11	25 (21-26)	11	30 (26-47)	2	41 (37-45)			11.5 (3)	.01	ASD<9q34=DS=CdLS

\* Non-verbal participants not included

#### 2.4.2.2 8p23 Deletion Syndrome

Table 11 shows the medians, interquartile range and post hoc analysis of the behavioural scales for people with an 8p23 deletion.

On the Challenging Behaviour Scale, 33.3% (8/24) of adults and children with 8p23 Deletion Syndrome were recorded as showing self-injury, 54.5% (12/22) aggressive behaviour, and 40.9% (9/22) were reported to be destructive to property. The latter two percentages were on a par with those displayed by people with Fragile X Syndrome.

In terms of activity levels, Mann Whitney analysis showed that people with an 8p23 deletion had significantly lower levels of overactivity than the Fragile X Syndrome group and the group with Autism Spectrum Disorder ( $z=2.38$ ,  $p=.02$ ;  $z=-2.13$ ,  $p=.03$ , respectively). In fact, the overactivity levels were lower for people with an 8p23 deletion than for any other group. Total activity levels fell in the middle range of the groups, being slightly higher than Rubinstein Taybi Syndrome but lower than Autism Spectrum Disorder.

With regard to mood and interest and pleasure the 8p23 deletion group were significantly higher than Autism Spectrum Disorder for the total of the scale and both subscales (total,  $z=-2.77$ ,  $p=.006$ ; mood,  $z=-2.94$ ,  $p=.003$ ; interest and pleasure,  $z=-2.35$ ,  $p=.02$ ). People in the 8p23 group had similar scores to people with Down Syndrome and Fragile X Syndrome for mood and interest and pleasure.

On the Repetitive Behaviour Questionnaire, the 8p23 deletion group had significantly lower scores than Autism Spectrum Disorder for stereotyped ( $z=-2.16$ ,  $p=.031$ ) and insistence on sameness ( $z=-2.12$ ,  $p=.033$ ) behaviours. The levels were very similar to those shown by the Down Syndrome group with the exception of repetitive speech, where the levels were in the

region of those reported in the Autism Spectrum Disorder group.

The 8p23 deletion group had significantly lower scores than the Autism Spectrum Disorder group on the Social Communication Questionnaire (restricted behaviours,  $z=-3.49$ ,  $p<.001$ ; reciprocal interaction,  $z=-4.12$ ,  $p<.001$ ; total,  $z=-4.66$ ,  $p<.001$ , and Autism Spectrum Disorder cut-off,  $z=-4.19$ ,  $p<.001$ ). The total score for the group with 8p23 deletions was close to that of the Rubinstein Taybi Syndrome group for this scale.

Post hoc Mann Whitney analyses indicated that people with 8p23 deletions had a statistically significant higher score than Autism Spectrum Disorder on the Sociability Questionnaire for Intellectual Disabilities both for familiar ( $z=-3.16$ ,  $p=.002$ ) and unfamiliar totals ( $z=-2.98$ ,  $p=.003$ ). Whilst at a similar level to Down Syndrome on the unfamiliar interaction, people with an 8p23 deletion scored significantly lower than participants with Down Syndrome on familiar interactions ( $z=-2.19$ ,  $p=.03$ ).

In summary, people with an 8p23 deletion were broadly comparable to the comparison groups for their activity levels, and their mood and interest and pleasure (though this was considerably higher than the Autism Spectrum Disorder group). For repetitive behaviours, the deletion group had a mixed profile, being very close to the Down Syndrome group for most of the subscales but on a par with autism for repetitive speech. People with an 8p23 deletion also showed similar levels to people with Down Syndrome of sociability with familiar people. People with 8p23 deletions contrasted with people with Autism Spectrum Disorder, showing significantly higher sociability, and significantly lower scores on the Social Communication Questionnaire, showing less stereotyped and sameness behaviours on the Repetitive Behaviour Questionnaire and showing much lower levels of overactivity.

Table 11: Medians, Interquartile Range and/or Percentages, Kruskal Wallis Analyses and Positioning of 8p23 Deletions in Relation to its Comparison Groups

Scale and Component		8p23 $\tilde{x}$ (Q1-Q3)		ASD $\tilde{x}$ (Q1-Q3)		DS $\tilde{x}$ (Q1-Q3)		CDLS $\tilde{x}$ (Q1-Q3)		FXS $\tilde{x}$ (Q1-Q3)		RTS $\tilde{x}$ (Q1-Q3)		Kruskal-Wallis $\chi^2$ (v) <i>p</i>		Positioning
		<i>n</i>		<i>n</i>		<i>n</i>		<i>n</i>		<i>n</i>		<i>n</i>				
CBQ	% Self-injury	24	33.3	24	58.3	23	12.5	24	50	24	58.3	24	33.3	15.22 (5)	.01	
	% Aggression	22	54.5	24	62.5	23	41.7	23	45.8	24	54.2	23	58.3	2.7 (5)	.75	
		22	40.9	24	50	23	20.8	23	54.2	23	41.7	24	58.3	8.1 (5)	.15	
	% Property															
TAQ	Impulsivity	24	14 (2.5-22)	23	19 (12-23)	24	9 (5.25-16.75)	24	10.5 (6.25-18)	24	18.5 (14.25-23.75)	23	12 (6-17)	16.6 (5)	.01	8p23=RTS=CdLS=DS<ASD=FXS
	Over-Activity	24	6.5 (2.25-19.64)	24	17.5 (11-30)	24	9 (5.25-18.75)	24	9.5 (4.25-18.25)	24	20.5 (9.25-27.75)	24	10 (3.25-16.75)	13.56 (5)	.02	
	Impulsive Speech*	15	3 (0-5)	19	5 (3-9)	17	3 (2-4.5)	13	1 (0-4)	19	3 (0-10)	17	3 (2-4.5)	8.68 (5)	.12	
	Total Activity	23	29 (9-44)	22	41 (26-57.25)	23	19 (14-37)	24	20.5 (15-36.75)	23	43 (30-59)	23	25 (14-34)	16.44 (5)	<.01	
MIPQ-S	Total	23	37 (35-43)	24	32.25 (27.25-37)	24	41 (37.25-43)	24	38 (33-41)	24	40 (34.25-42.75)	24	38.5 (34.23-42.75)	20.73 (5)	<.001	ASD<CdLS=8p23=RTS=FXS=DS ASD<CdLS=RTS=8p23=FXS=DS ASD<FXS=CdLS=RTS=8p23=DS
	Mood Interest and Pleasure	23	21 (19-22)	24	18 (16.25-19.75)	24	21.5 (20.25-23)	24	20 (18-22)	24	21.5 (19.25-23)	24	20.95 (18.5-22.75)	20.79 (5)	<.001	
		23	18 (16-21)	24	13.5 (8.5-18)	24	18 (17.25-21.75)	24	18 (15-20)	24	18 (14-20)	24	18 (15-20)	14.99 (5)	.01	
RBQ	Stereotype d	23	2 (0-8)	24	9.5 (3.5-12)	24	1.5 (0-8)	24	6 (1-10)	23	8 (3-8)	24	5.5 (0.75-11.25)	10.07 (5)	.07	DS= 8p23<ASD
	Compulsive	24	1.5 (0-5)	24	4 (1-8.5)	24	1.5 (0-5.75)	24	7.5 (2-11.75)	23	3 (0-7)	24	3.5 (0-9.25)	9.75 (5)	.08	
	Restricted	16	4 (0-7.75)	19	4 (0-11)	18	2 (0-4)	13	3 (0-8)	18	4 (0.75-8)	17	5 (2.5-7)	4.09 (5)	.54	
	Sameness	22	0 (0-2.5)	23	3 (1-4)	24	0 (0-1.75)	24	2.5 (0-4)	24	4 (1.5-7)	24	3 (0-6)	18.18 (5)	<.001	

Table 11: (Continued)

<i>(continued)</i>		<b>8p23</b> $\tilde{x}$ (Q1-Q3)	<b>ASD</b> $\tilde{x}$ (Q1-Q3)	<b>DS</b> $\tilde{x}$ (Q1-Q3)	<b>CdLS</b> $\tilde{x}$ (Q1-Q3)	<b>FXS</b> $\tilde{x}$ (Q1-Q3)	<b>RTS</b> $\tilde{x}$ (Q1-Q3)	<b>Kruskal-Wallis</b> $\chi^2$ (v) <i>p</i>		<b>Positioning</b>
<b>RBQ (cont)</b>	Repetitive Language	16 4.5 (0-7.5)	19 4 (1-10)	18 0 (0-4)	13 4 (0.5-7)	18 7 (1.75-11.25)	17 4 (2-6)	12.15 (5)	.03	
	Total-Speech	21 11 (5-19)	23 16 (9-30)	24 10.5 (1.5-15)	24 15.5 (10.25-28.5)	23 15 (10-25)	24 18.5 (6.25-31.25)	10.82 (5)	.06	
	Total	21 15 (5-27.5)	24 18 (14-34.75)	24 13 (3.25-18)	24 21.5 (11.25-32.5)	22 22.5 (12.25-40.5)	24 21 (9.5-27.25)	10.95 (5)	.05	
<b>SCQ</b>	Communication	24 6.5 (4-10.56)	24 10 (7.57-12)	20 3.13 (2-7.43)	22 7 (3.81-11.14)	23 8 (6-9.29)	19 5 (4-7.43)	23.93 (5)	<.001	DS<CdLS= <b>8p23</b> 3=FXS=ASD <b>8p23</b> =DS<RTS =FXS=ASD DS= <b>8p23</b> =CdL S=RTS<FXS=AS D DS= <b>8p23</b> =CdL S=RTS<FXS=AS D <b>8p23</b> <FXS<ASD
	Restricted, Repetitive	24 3 (0.25-4.75)	24 5 (4.25-6.75)	23 2 (1-5)	24 4.5 (2.25-6)	24 4.5 (3.25-7)	23 5 (2-7)	20.45 (5)	<.001	
	Reciprocal Interaction	23 5 (3-8)	24 11 (8-13)	20 3 (2-8.75)	22 7.5 (3-9.25)	23 9 (6-12)	18 7.5 (5.27-11)	29.59 (5)	<.001	
	Total	23 17 (8-20)	24 25 (22.25-31)	20 9 (5-20.38)	22 19.29 (9.64-21.25)	23 21 (18-28)	18 18 (15-23.25)	39.93 (5)	<.001	
	% > Cutoff	24 16.7	24 79.2	20 16.7	22 20.8	23 45.8	18 25	27.32 (5)	<.001	
<b>SQID</b>	Familiar	23 48 (39-53)	23 37 (31-42)	22 52.5 (50-55.25)	4 50.5 (49-52.75)		24 51 (41.25-54)	24.83 (4)	<.001	ASD< <b>8p23</b> <DS
	Unfamiliar	23 36 (25-48)	23 24 (15-29)	21 38 (26.5-46.5)	4 33.5 (12.25-42.75)		24 36.5 (23.5-46)	13.36 (4)	.01	ASD<RTS= <b>8p23</b> 3=DS

\* Non-verbal participants not included

### 2.4.3 Autism Spectrum Disorder and Autism

Table 12 and Table 13 show the percentage (and number) of people with 9q34 and 8p23 deletions and their comparison groups who score above the cut-off for Autism and Autism Spectrum Disorder, indicated by the Social Communication Questionnaire (see 2.3.5.2.2). In the 9q34 deletion group there is a very high percentage of people scoring at or above the cut-offs for Autism and Autism Spectrum Disorder, whereas the 8p23 deletion group score at levels comparable to those for Down Syndrome for autism but higher for the proportion reaching the cut off for Autism Spectrum Disorder.

**Table 12: Autism and ASD Cut-Offs (9q34)**

		<b>9q34</b>	<b>ASD</b>	<b>DS</b>	<b>CdLS</b>	<b>CdCS</b>
ASD	<i>n</i>	10	11	5	7	5
	%	90.9	100	45.5	63.6	45.5
Autism	<i>n</i>	6	11	4	1	1
	%	54.5	100	36.4	9.1	9.1

**Table 13: Autism and ASD Cut-Offs (8p23)**

		<b>8p23</b>	<b>ASD</b>	<b>DS</b>	<b>CdLS</b>	<b>FXS</b>	<b>RTS</b>
ASD	<i>n</i>	15	24	7	13	22	15
	%	62.5	100	29.2	54.2	91.7	62.5
Autism	<i>n</i>	4	19	4	5	11	6
	%	16.7	79.2	16.7	20.8	45.8	25

### 2.4.4 Changes with Age

Spearman's correlations were conducted to examine whether age was related to aspects of the behavioural phenotype. Table 14 shows the resultant correlation matrices. For people with a 9q34 deletion, correlations between age and both the familiar and unfamiliar subscales of the Sociability Questionnaire for Intellectual Disabilities scale were statistically significant; people that were older were less likely to evidence higher levels of sociability.

The subscales which comprise the Sociability Questionnaire for Intellectual Disabilities scale, that were also statistically significant were familiar receive interaction ( $r_s(11)=-.76$ ,  $p=.006$ ), unfamiliar receive interaction ( $r_s(11)=-.65$ ,  $p=.03$ ), interaction ( $r_s(11)=-.71$ ,  $p=.02$ ), and approach or initiate interaction ( $r_s(11)=-.66$ ,  $p=.03$ ), all of these show a negative relationship with age.

With respect to the 8p23 deletion group, the Repetitive Behaviour Questionnaire subscales stereotyped behaviour ( $r_s(23)=-.63$ ,  $p=.001$ ) and repetitive use of language ( $r_s(16)=-.64$ ,  $p=.007$ ) were significantly negatively correlated with age, indicating a decline in these behaviours as people get older. Interestingly the 9q34 deletion group evidenced a positive correlation between age and a number of subscales on the Behaviour Rating Inventory of Executive Function questionnaire, suggesting that as people age executive functioning declines. In contrast, the 8p23 deletion group show a small positive correlation on the emergent metacognition subscale indicating an increase with age, as would be expected. Also of note is that there was a significant correlation between age and self-help scores on the Wessex for the group with an 8p23 deletion, as would be expected, but the group with a 9q34 deletion did not evidence a significant correlation suggesting that age is not related to acquiring new self help skills.

Table 14: Correlations between Age and Each of the 9q34 and 8p23 Deletions

Scale	Subscale	9q34 Deletion			8p23 Deletion		
		<i>n</i>	$\bar{x}$ (Q1-Q3)	$r_s$	<i>n</i>	$\bar{x}$ (Q1-Q3)	$r_s$
SQID	Familiar Total	11	49 (45-50)	-0.69*	23	48 (39-53)	0.07
	Unfamiliar Total	11	42 (26-46)	-0.67*	23	36 (25-48)	0.22
BRIEF	Inhibition	10	18 (15-27)	0.2	21	17 (9-24)	-0.42
	Shift	10	8.5 (4.25-13.25)	0.78**	23	8 (5-15)	-0.12
	Emotional Control	10	9.5 (7.25-13)	0.51	23	8 (3-17)	-0.12
	Working Memory	10	21.5 (18.5-27)	0.53	21	18 (12.5-26)	-0.4
	Planning Organisation	10	10 (6.75-14.63)	0.82**	23	11 (5.5-14)	-0.35
	Flexibility	10	19.5 (10.75-24)	0.76*	23	16 (9-33)	-0.16
	Emergent Metacognition	10	30.5 (24.75-41.38)	0.77**	22	27.5 (13-39.25)	-0.44*
	Global Executive	10	66.5 (57.5-91.63)	0.65*	23	57 (32-91)	-0.39
RBQ	Stereotyped	11	12 (4-12)	-0.34	23	2 (0-8)	-0.63**
	Compulsive	11	3 (0-4)	-0.8	24	1.5 (0-5)	-0.19
	Restricted	7	5 (3-12)	0.13	16	4 (0-7.75)	-0.41
	Insistence on Sameness	10	1 (0-4.25)	-0.11	22	0 (0-2.5)	-0.37
	Repetitive Language	7	11 (7-12)	0.04	16	4.5 (0-7.5)	-0.64**
	Total	10	22 (17.5-29.25)	-0.15	21	15 (5-27.5)	-0.33
TAQ	Total	11	42.88 (25.5-49)	0.01	23	29 (9-44)	-0.29
SCQ	Total	11	22 (16-29.58)	0.11	23	17 (8-20)	-0.34
MIPQ	Total	11	40 (30-44)	-0.44	23	37 (35-43)	0.31
WESSEX	Self Help	11	6 (4-7)	0.17	23	6 (5-8.75)	.49*

\*  $p < .05$  \*\*  $p < .01$ 

## 2.5 Discussion

This is the first study to systematically examine behaviours in 9q34 and 8p23 deletion syndromes. The aim of this study was to measure the behaviours that are shown in these two rare deletion groups and so explore a possible behavioural phenotype. This is the first study to explore these rare genetic deletions so extensively, using standardised measures appropriate for people with an intellectual disability, and making comparisons with other well researched groups of people with genetic disorders. The information generated by this study is essential to parents supporting people with rare genetic deletions but also to health professionals both in aiding diagnosis and in helping them to support parents.

## 2.5.1 Principal Findings

### 2.5.1.1 9q34 Deletions

Analyses indicated that people with a 9q34 deletion showed a number of similarities with the Autism Spectrum Disorder group. This included, at a broad level of measurement, similarity of stereotyped and restricted behaviours and repetitive speech (the latter was higher than all of the groups who participated). In terms of Autism Spectrum Disorder cut-offs, 90.9% (10/11) of the people in the 9q34 deletion group reached the clinical cut-off for Autism Spectrum Disorder and just over 50% (6/11) reached the cut-off for Autism; this is higher than the other four (non-Autism Spectrum Disorder) groups in the research and comparable to levels reported in Cornelia de Lange and Fragile X Syndromes in similar studies employing larger sample sizes (Oliver et al., in press). Interestingly, there were some differences to the Autism Spectrum Disorder group thus suggesting an atypical profile; impulsivity and activity levels were higher, but not significantly, in the 9q34 deletion group. Higher mood and interest and pleasure ratings were also evident, although not significantly different; the Autism Spectrum Disorder group had the lowest score of all the groups and the 9q34 deletion group had the highest of all the groups.

Notably there were differences in social interaction with people, with participants with a 9q34 deletion being much more likely than those with Autism Spectrum Disorder to interact with familiar and unfamiliar people and at a level similar to that seen in people with Down Syndrome. Additionally, the levels of compulsive behaviour shown by people with a 9q34 deletion were significantly lower than those shown by people with Autism Spectrum Disorder and more akin to those seen in people with Down Syndrome. These differences in Autism Spectrum Disorder characteristics and related behaviours are reported in a number

of syndromes and indicate a potential difference in this group in the broad presentation of social behaviour (Cornish, Turk & Hagerman, 2008; Moss et al., 2008; Moss & Howlin, 2009; Mount, Charman, Hastings, Reilly & Cass, 2003).

People with 9q34 deletions showed similarities with people with Cornelia de Lange Syndrome in terms of impulsivity levels and compromised reciprocal social interaction and communication with others. It could be that impulsivity accounts for some of the disinhibition with respect to approaching strangers. It is notable that higher levels of sociability are reported in a number of syndromes in which higher levels of impulsivity are also evident, such as Smith-Magenis and Cri du Chat Syndromes.

In terms of the published literature which describes behaviour in people with a 9q34 deletion, a recent review (Grandfield, this volume) only found two papers. One paper described a child as 'happy' and 'fascinated with the colour orange' (Sanger et al., 2005) and the other described a child as 'sociable and friendly' (Papadopoulou et al., 2010). It is hard to generalise from such limited commentary, but these observations are consistent with the current findings; the report of the child being 'happy' supports the elevated mood results in relation to the Mood, Interest and Pleasure Questionnaire, 'fascinated with the colour orange' might be consistent with Autism Spectrum Disorder, whereas a report of being 'happy and sociable' supports the social interaction findings.

The results indicated that more than 50% (6/11) of the people with a 9q34 deletion displayed challenging behaviours in terms of self-injury or aggression, these behaviours are a particular source of stress to parents (e.g., Ekas & Whitman, 2010; Lecavalier, Leone & Wiltz, 2006). These levels are similar to those reported for Fragile X and Prader Willi Syndrome in

which these behaviours appear to be part of the behavioural phenotype (Arron, Oliver, Moss, Berg & Burbidge, 2011).

Analysis examining age related changes in people with a 9q34 deletion found a positive correlation with scores on the Behaviour Rating Inventory of Executive Function questionnaire and its subscales suggesting that executive functioning may decline with age. In line with this, the highlighted increase in sociability with unfamiliar adults could be indicative of increased disinhibition which is also related to executive functioning. Additionally, an increase in individuals' self help skills would typically be anticipated over time, as ability to perform basic tasks increases, however, the 9q34 deletion group failed to demonstrate this expected increase. Comparatively, the group of people with an 8p23 deletion showed a positive correlation between self help and age. These findings are based on a small sample and the study was cross-sectional rather than longitudinal, hence it is difficult to draw firm conclusions. Nevertheless, these results and the implications of this potential change with age clearly indicate that further research in this area is warranted.

#### 2.5.1.2 8p23 Deletions

Similarly to the group of adults and children with a 9q34 deletion, over half of the people with an 8p23 deletion showed challenging behaviour, particularly aggression and destruction of property. This finding is consistent with previous literature which has noted a number of challenging behaviours, including a small number of cases where the children were hospitalised or referred for psychiatric assessment because the behaviour was considered so severe (Claeys et al., 1997; Fryns, Kleczkowska, Vogels & Van Den Berghe, 1989). There was also a report of a child diagnosed with 'unsocialised conduct disorder' (de Vries et al., 2001).

In terms of group differences, most were between the people with 8p23 deletions and the group with Autism Spectrum Disorder. People with 8p23 deletions had significantly lower levels of overactivity and stereotyped behaviour and significantly higher scores for mood and interest and pleasure than people with Autism Spectrum Disorder. In addition, people with 8p23 deletions were more sociable and likely to interact with both people they knew and those who were unfamiliar. However, people with 8p23 deletions were also reported to have high levels of repetitive speech, which were similar to those seen in people with Autism Spectrum Disorder. With regard to the autism cut-off percentage scores, people with an 8p23 deletion scored amongst the lowest of the groups measured and were on a par with people with Down Syndrome (the levels of autism present in the Down Syndrome group is representative of the published literature; e.g., Kent, Evans, Paul & Sharp, 1999).

In terms of comparisons, people with 8p23 deletions had most similarities with people with Down Syndrome, they had similar mood and interest and pleasure levels, comparable overall scores on the Repetitive Behaviour Questionnaire, and a similar score for unfamiliar interaction. However, they were significantly less likely than people with Down Syndrome to be sociable with familiar people.

The overactivity levels were lower for people with an 8p23 deletion than for any other group and just significantly lower than the Fragile X Syndrome group. This contradicts some of the previously published literature where there are reports of being 'active', 'distractable' (Hutchinson, Wilson & Voullaire, 1992) and displaying 'hyperactivity' (Pettenati et al., 1992) and 'extreme hyperactivity' (Devriendt et al., 1999). People with 8p23 deletions also had relatively low scores compared to the other groups on the 'insistence on sameness' subscale

(scoring at comparable levels to people with Down Syndrome) and the total score for the Repetitive Behaviour Questionnaire. Generally across the rest of the measures people with 8p23 were not dissimilar to the other groups.

Overall, these results differ from those reported in previous literature that describes behaviours associated with individuals with 8p23 deletions. There are seven papers which mention behaviour and these are weighted toward describing challenging behaviours. However, as challenging behaviours are present in over 50% of the people within this study it could be that these are the behaviours that are most likely to be reported in the literature, as they are the ones that are most likely to access help.

### **2.5.2 Clinical Implications**

In both groups there was a high prevalence of challenging behaviour, these behaviours have an impact on carer stress levels and are likely to be amenable to change. Therefore, interventions directed at helping families with these would be invaluable. It is worth noting that even though these behaviours occur frequently in people with a genetic disorder there are interactions between the phenotype and the environment (Tunnicliffe & Oliver, 2011); directing interventions at environmental factors can have a beneficial effect for the whole family.

In the current study there were a high proportion of people with a 9q34 deletion who scored above the autism cut off on the Social Communication Questionnaire. Autism Spectrum Disorder has well established and researched therapeutic interventions, many of which may be utilised effectively.

Interestingly, people with a 9q34 deletion showed high levels of sociability with unfamiliar

adults, although this has benefits it may also be an area that puts the person with the syndrome at higher risk (Elison, Stinton & Howlin, 2010); it would therefore be useful for professionals to consider this element too.

Indications that people with a 9q34 deletion may decline over time in terms of executive functioning is an area that could have a significant impact on their wellbeing, care and the support and preparation their carers need. Where possible, professionals should therefore monitor and be aware of this possibility, through conducting standard psychological assessments and questionnaires (such as those utilised in this study) in order to monitor these effects over time.

### **2.5.3 Limitations**

This study has some potential limitations. Participants were recruited from a support group, potentially which could potentially bias the sample. However, this seems unlikely as previous studies recruiting in this manner have replicated research, in terms of behavioural outcomes, where recruitment came from different sources (Moss & Oliver, 2008). The support group supports people internationally and has a range of ages and nationalities on its database. It is likely that the sample collated is more diverse than those recruited in clinical environments.

The participants in the study spanned a large age range, whilst this may have been advantageous (for example in considering the changes that appear to be present in people with a 9q34 deletion), it is also likely that there are other age related differences that the sample was too small to clarify, as there are very few people within each age range.

The measures used within this study are questionnaires, which are clearly not as robust as

observational techniques or detailed interviews with parents or carers. However, by using pre-established well validated measures a greater number of people were able to participate; this may allow future more in-depth interviews or observations to focus on specific areas. It also allows future non-behavioural studies to be able to add questionnaires to their clinical interviews that will add to the evidence base in an informative way.

The nature of rare genetic deletions is that there are very few people who have them, this is likely to have a detrimental effect on statistical analysis in limiting power, and making it more likely that some results will appear statistically significant that may not be replicated. Caution should be applied when applying weight to the results. However, despite the limited power, this study has provided a robust backdrop from which to conduct further research.

#### **2.5.4 Future Research**

This research has set a solid foundation for future research within the area. The findings within this study that indicate changes in executive functioning over time in people with a 9q34 deletion are an area which warrant further exploration. Longitudinally the people who participated in this study could be followed up and their results compared over time. A different angle may be to conduct MRI scans on some of the people with a 9q34 deletion to see if there are any apparent changes within the brain. Also, longer more focussed observations or interviews could be conducted to look at these effects.

This study found a lot of differences between the Autism Spectrum Disorder group and people with an 8p23 deletion, and highlighted similarities with people with Down Syndrome. This would appear to be somewhat contradictory to the literature, therefore exploration of 'hyperactivity' in people with an 8p23 deletion may help to shed further light on this.

Overall, it would also be useful if clinicians seeing children with rare genetic deletions could use standardised measures to record behaviours, so that research can be easily compared and behaviours which are not considered problematic can also be documented.

## 2.6 References

- Achenbach, T. M. & Edelbrock, C. S. (1983). *Manual for the Child Behavior Checklist and Revised Child Behavior Profile*. Burlington, VT University of Vermont, Department of Psychiatry.
- Arron, K., Oliver, C., Moss, J., Berg, K. & Burbidge, C. (2011). The Prevalence and Phenomenology of Self-Injurious and Aggressive Behaviour in Genetic Syndromes. *Journal of Intellectual Disability Research*, 55, 109-120.
- Arron, F. & Oliver, C. (unpublished). *The Health Questionnaire for People with an Intellectual Disability*. Birmingham, Uk: University of Birmingham.
- Ayyash, H., Mueller, R., Maltby, E., Horsfield, P., Telford, N. & Tyler, R. (1997). A Report of a Child with a Deletion (9) (q34.3): a Recognisable Phenotype? *Journal of Medical Genetics*, 34, 610-612.
- Babovic-Vuksanovic, D., Jenkins, S. C., Ensenuer, R., Newman, D. C. & Jalal, S. M: (2004). Subtelomeric Deletion of 18p in an Adult with Paranoid Schizophrenia and Mental Retardation. *American Journal of Medical Genetics*, 124, 318-322.
- Barnard, L., Pearson, J., Rippon, L. & O'Brien, G. (2002). Behavioural Phenotypes of Genetic Syndromes: Summaries Including Notes on Management and Therapy. Chapter in: O'Brien, G. (2002). *Behavioural Phenotypes in Clinical Practice*. London: Mac Keith Press.
- Baynam, G., Goldblatt, J. & Walpole, I. (2008). Deletion of 8p23.1 with Features of Cornelia de Lange Syndrome and Congenital Diaphragmatic Hernia and a Review of Deletions of 8p23.1 to 8pter? A Further Locus for Cornelia de Lange Syndrome. *American Journal of Medical Genetics*, 146A(12), 1565-70.
- Berument, A. K., Rutter, M., Lord, C., Pickles, A. & Bailey, A. (1999). Autism Screening Questionnaire: Diagnostic Validity. *British Journal of Psychiatry*, 175, 444-451.
- Breau, L. M., McGrath, P. J., Camfield, C., Rosmus, C. & Finley, G.A. (2000). Preliminary Validation of an Observational Pain Checklist for Persons with Cognitive Impairments and Inability to Communicate Verbally. *Developmental Medicine and Child Neurology*, 42, 609-616.
- Breau, L. M., McGrath, P. J., Camfield, C., Rosmus, C. & Finley, G.A. (2002). Psychometric Properties of the Non-Communicating Children's Pain Checklist-Revised. *Pain*, 99, (1-2), 349-357.
- Burbidge, C., & Oliver, C. (2008). The Activity Questionnaire. *Manual for administration and score*

*interpretation*. Birmingham, UK: University of Birmingham.

- Burbidge, C., Oliver, C., Moss, J., Arron, K., Berg, K., Hill, L., Trusler, K., Furniss, F. & Woodcock, K. A. (2010). The Association between Repetitive Behaviours, Impulsivity and Hyperactivity in People with Intellectual Disability. *Journal of Intellectual Disability Research*, 54, 1078-1092.
- Claeys, I., Holvoet, M., Eyskens, B., Adriansens, P., Gewillig, M., Fryns, J. & Devriendt, K. (1997). A Recognisable Behavioural Phenotype Associated with Terminal Deletions of the Short Arm of Chromosome 8. *American Journal of Medical Genetics*, 74, 515-520.
- Collis, L., Oliver, C. & Moss, J (unpublished). The Sociability Questionnaire for People with Intellectual Disability. Birmingham, UK: University of Birmingham.
- Cornish, K., Turk, J. & Hagerman, R. (2008). The Fragile X Continuum: New Advances and Perspectives. *Journal of Intellectual Disability Research*, 52, 469-482.
- de Vries, B. B., Lees, M., Knight, S. J., Regan, R., Corney, D., Flint, J., . . . Winter, R. M. (2001). Submicroscopic 8pter Deletion, Mild Mental Retardation, and Behavioral Problems Caused by a Familial t(8;20)(p23;p13). *American Journal of Medical Genetics*, 99, 314-319.
- Devriendt, K., Matthijs, G., Van Dael, R., Gewillig, M., Eyskens, B., Hjalgrim, H., . . . Marynen, P. (1999). Delineation of the Critical Deletion Region for Congenital Heart Defects, on Chromosome 8p23.1. *The American Journal of Human Genetics*, 64, 1119-1126.
- Dykens, E. M. (1995). Measuring Behavioral Phenotypes: Provocations from the 'New Genetics'. *American Journal on Mental Retardation*, 99, 522-532.
- Ekas, N. & Whitman, T. L. (2010). Autism Symptom Topography and Maternal Socioemotional Functioning. *American Journal on Intellectual and Developmental Disabilities*. 115(3), 234-249.
- Elison, S., Sinton, C. & Howlin, P. (2010). Health and Social Outcomes in Adults with Williams Syndrome: Findings from Cross-Sectional and Longitudinal Cohorts. *Research in Developmental Disabilities*, 31, 587-599.
- Fryns, J. P., Kleczkowska, A., Vogels, A. & Van Den Berghe H. (1989). Normal Phenotype and Slight Mental Retardation in De Novo Distal 8p Deletion (8pter-.8p23. 1:). *Annales de Genetique*. 32, 171-3.
- Gioia, G.A., Espy, K.A. & Isquith. P.K. (2003). The Behavior Rating Inventory of Executive Function: Preschool Version. *Psychological Assessment Resources*, FL.

- Hall, S., Arron, K., Sloneem, J. & Oliver, C. (2008). Health and sleep problems in Cornelia de Lange Syndrome: A case control study. *Journal of Intellectual Disability Research*, 52, 458-468.
- Howlin, P. & Karpf, J. (2004). Using the Social Communication Questionnaire to Identify 'Autistic Spectrum' Disorders Associated with Other Genetic Conditions: Findings From a Study of Individuals with Cohen Syndrome. *Autism*, 8, 175-182.
- Hyman, P., Oliver, C. & Hall, S. (2002). Self-Injurious Behavior, Self-Restraint, and Compulsive Behaviors in Cornelia de Lange Syndrome. *American Journal on Mental Retardation*, 107(2), 146-154.
- Iwakoshi, M., Okamoto, N., Harada, N., Nakamura, T., Yamamori, Y., Fujita, H., . . . Matsumoto, N. (2004). 9q34.3 Deletion Syndrome in Three Unrelated Children. *American Journal of Medical Genetics*, 126A, 278-283.
- Kannu, P., Winship, I. & Aftimos, S. (2005). Further Case Report of a Child with a 9q34 Deletion and a Review of the Reported Cases – Research Letter. *American Journal of Medical Genetics*, 133A, 219-221.
- Kent, L., Evans, J., Paul, M. & Sharp, M. (1999). Comorbidity of Autistic Spectrum Disorders in Children with Down Syndrome. *Developmental Medicine & Child Neurology*, 41, 153-158.
- Kushlick, A., Blunden, R., & Cox, G. (1973). A Method for Rating Behavior Characteristics for use in Large Scale Studies of Mental Handicap. *Psychological Medicine*, 3, 466-478.
- Lecavalier, L., Leone, S., & Wiltz, J. (2006). The Impact of Behaviour Problems on Care-Giver Stress in Young People with Autism Spectrum Disorders. *Journal of Intellectual Disability Research*, 50(3), 172-183.
- Moss, J. & Howlin, P. (2009). Invited Annotation - Autism Spectrum Disorders in Genetic Syndromes: Implications for Diagnosis, Intervention and Understanding the Wider ASD Population. *Journal of Intellectual Disability Research*, 53, 852-872.
- Moss, J., & Oliver, C. (2008). Repetitive Behaviour Questionnaire: *Manual for Administration and Scorer Interpretation*. Birmingham, UK: University of Birmingham.
- Moss, J., Oliver C., Arron, K., Burbidge, C. & Berg, K. (2009). The Prevalence and Phenomenology of Repetitive Behaviour in Genetic Syndromes. *Journal of Autism and Developmental Disorders*, 39, 572-588.
- Moss, J., Oliver, C., Berg, K., Burbidge, C., Caley, A., Duffay, S., & Hooker, M. (2005). The

- Phenomenology of Repetitive Behaviour in Genetic Syndromes. *Genetic Counseling*, 13, 363–381.
- Moss, J., Oliver, C., Wilkie, L., Berg, K., Kaur, G. & Cornish, K. (2008). Prevalence of Autism Spectrum Phenomenology in Cornelia de Lange and Cri du Chat Syndromes. *American Journal of Mental Retardation*, 113, 278-291.
- Mount, R. H., Charman, T., Hastings, R. P., Reilly, S. & Cass, H. (2003). Features of Autism in Rett Syndrome and Severe Mental Retardation. *Journal of Autism and Developmental Disorders*, 33, 435-442.
- Nelson, L. K. (2010) Mood and Sociability in Cornelia de Lange Syndrome. Ph.D. thesis, University of Birmingham.
- O'Brien, G. (2006). Behavioural Phenotypes: Causes and Clinical Implications. *Advances in Psychiatric Treatment*, 12, 338-348.
- Oliver, C., Berg, K., Moss, J., Arron, K. & Burbidge, C. (2010; in press). Delineation of Behavioral Phenotypes in Genetic Syndromes: Characteristics of Autism Spectrum Disorder, Affect and Hyperactivity. *Journal of Autism and Developmental Disorders*.
- Oliver, C. & Wilkie, A. (unpublished). *Gastroesophageal Reflux Questionnaire*. Birmingham, UK: University of Birmingham.
- Páez, M.T., Yamamoto, T., Hayashi, K., Yasuda, T., Harada, N., Matsumoto, N., . . . Matsuoka, R. (2008). Two Patients with Atypical Interstitial Deletions of 8p23.1: Mapping of Phenotypical Traits. *American Journal of Medical Genetics*, 146A(9), 1158-1165.
- Palmer, J. & Jenkins, J. (1982). The 'Wessex' Behaviour Rating System for Mentally Handicapped People: Reliability Study. *British Journal of Mental Subnormality*, 28, 88-96.
- Papadopoulou, E., Sismani, C., Christodoulou, C., Ioannides, M., Kalmanti, M. & Patsalis, P. (2010). Phenotype-Genotype Correlation of a Patient with a "Balanced" Trans Location 9;15 and Cryptic 9q34 Duplication and 15q21q25 Deletion. *American Journal of Medical Genetics Part A*, 152A(6), 1515-1522.
- Ross, E. & Oliver, C. (2003). Preliminary Analysis of the Psychometric Properties of the Mood, Interest and Pleasure Questionnaire (MIPQ) for Adults with Severe and Profound Learning Disabilities. *British Journal of Clinical Psychology*, 42, 81-93.
- Ross, E., Arron, K. & Oliver, C. (2008). The Mood Interest and Pleasure Questionnaire: Manual for

Administration and Scoring. Birmingham, UK: University of Birmingham.

- Russell, H. & Oliver, C. (2003). The Assessment of Food-Related Problems in Individuals with Prader-Willi Syndrome. *British Journal of Clinical Psychology*, 42, 379–392
- Rutter, M., Bailey, A., & Lord, C. (2003). *Social Communication Questionnaire*. Los Angeles, CA: Western Psychological Services.
- Sanger, T. M., Olney, A.H., Zaleski, D., Pickering, D., Nelson, M., Sanger, W.G. & Bhavana, B.J. (2005). Cryptic Duplication and Deletion of 9Q34.3 → qter in a Family with a t(9;22)(q34.3;p11.2). *American Journal of Medical Genetics*, 138A, 51-55.
- Shaw-Smith, C., Redon, R., Rickman, L., Rio, M., Willatt, L., Fiegler, H., . . . Carter, N. P: (2004). Microarray Based Comparative Genomic Hybridisation (Array-CGH) Detects Submicroscopic Chromosomal Deletions and Duplications in Patients with Learning Disability/Mental Retardation and Dysmorphic Features. *Journal of Medical Genetics*, 41, 241-248.
- Skuse, D. H. (2002). Behavioural Phenotypes. *Psychiatry*, 1(7), 98-102.
- Tunnicliffe, P. & Oliver C. (2011). Phenotype-Environment Interactions in Genetic Syndromes Associated with Severe or Profound Intellectual Disability. *Research in Developmental Disabilities*. 32, 404-418.
- Unique (2009). 8p23 Deletions. *Rare Chromosome Disorder Support Group Publication*. Retrieved February 10<sup>th</sup>, 2009 from <http://www.rarechromo.org/information/Chromosome%20%208/8p23%20Deletions%20FTNW.pdf>
- Unique (2009b). 9q34.3 Deletion Syndrome. *Rare Chromosome Disorder Support Group Publication*. Retrieved February 10<sup>th</sup>, 2009 from <http://www.rarechromo.org/information/Chromosome%20%209/9q34.3%20Deletion%20FTNW.pdf>
- Wat, M.J., Shchelochkov, O.A., Holder, A.M., Breman, A.M., Dagli, A., Bacino, C., . . . Kang, S.H. (2009). Chromosome 8p23.1 Deletions as a Cause of Complex Congenital Heart Defects and Diaphragmatic Hernia. *American Journal of Medical Genetics*, 149A(8), 1661-1677.
- White, S. J., Sterrenburg, E., van Ommen, G-J. B., den Dunnen, J. T. & Breuning, M. H. (2003). An Alternative to FISH: Detecting Deletion and Duplication Carriers within 24 Hours. *Journal of Medical Genetics*, 40, 113.

Wilde, H. & Oliver, C. (unpublished). The Social Motivation Questionnaire. Birmingham, Uk: University of Birmingham.

Yatsenko, S.A., Cheung, S.W., Scott, D.A., Nowaczy, M.J.M., Tarnopolsky, M., Naidu, S., . . . Lupski, J.R. (2005). Deletion 9q34.3 Syndrome: Genotype-Phenotype Correlations and an Extended Deletion in a Patient with Features of Opitz C Trigenocephaly. *Journal of Medical Genetics*, 42, 328-335.

**PUBLIC DOMAIN BRIEFING PAPER**

## **Toward a Behavioural Phenotype for 8p23 and 9q34 Deletion Syndromes**

### **Outline**

The research outlined below was conducted by Tracey Grandfield, Trainee Clinical Psychologist at the University of Birmingham. This research was submitted as partial fulfilment for the degree of Doctorate in Clinical Psychology.

### **Genetic Deletions**

Deoxyribonucleic acid (DNA) is made up of 23 chromosomes. A genetic deletion is where part of the DNA or chromosome is missing. Microdeletions are extremely small missing sections; until recently it has been very difficult to identify them, because traditional microscopes fail to see them. However, these deletions can have profound effects upon the person, affecting their development, physical appearance and health, and may also have psychological effects such as an increased likelihood of displaying certain behaviours. If specific behaviours are more commonly associated with a group of people with the same genetic disorder than would be expected (given their level of development and age) these are called a behavioural phenotype.

Parents and carers of people with a rare genetic deletion often report high levels of stress. Research has shown that stress levels are often associated with particular behaviours, particularly challenging behaviours and those associated with Autism Spectrum Disorder (ASD).

The review looked at the published literature to gain an understanding of where the focus of current research was. The subsequent research began to define which behaviours were most associated with two rare genetic deletions.

### Literature review

This review looked at five rare genetic deletions (18p, 1p36, 2q37, 8p23 and 9q34). Three hundred papers were found published since 1967 that had discussed these genetic deletions. Categorising the papers revealed that initially and predominantly most of the focus was on molecular analysis (techniques involved in identifying genetic deletions). This is understandable as molecular analysis is essential to the identification of the genetic deletion. The next largest category focussed on physical aspects of the deletion, for example, exploring health complaints associated with the deletion or physical characteristic. Only ten percent of the papers mentioned psychological or behavioural elements, and only one of these papers had it as the sole focus. The papers that did discuss psychological components largely failed to do so in a way that would allow other people to replicate the findings, and they may have missed many important factors.

Given the importance of psychological components to family stress levels and health care resources, it was recommended that a number of well tested questionnaires were used routinely by researchers in future studies.

### Research Component

Considering the limited amount of research looking at the behavioural phenotype of rare genetic deletions, this research aimed to describe behaviours within two genetic deletion groups (8p23 and 9q34) using robust and reliable questionnaires. The second aim was to compare and contrast these results with well known genetic syndromes with established behavioural phenotypes.

Participants were recruited via Unique, a charity which supports parents and carers of

people with rare genetic deletions. All participants were asked to complete a set of questionnaires assessing behaviours associated with Autism Spectrum Disorder, Attention Deficit Hyperactivity Disorder, challenging behaviours, and sociability. Eleven participants in the 9q34 deletion group were compared with an equal number of participants from Cornelia de Lange Syndrome, Autism Spectrum Disorder, Cri du Chat Syndrome and Down Syndrome (already held on a database) making a total of 55 participants. Similarly 26 participants in the 8p23 deletion group were compared with 26 participants from each of Cornelia de Lange Syndrome, Rubinstein Taybi Syndrome, Fragile X Syndrome, Autism Spectrum Disorder and Down Syndrome groups making a total of 144 participants. In both sets participants were matched for self help skills, mobility, verbal ability and age.

### *Overall*

There were high levels of challenging behaviours within both of the groups, these included self injury, aggression and damage to property. These are behaviours that parents or carers may find difficult to cope with.

### *9q34*

People with 9q34 deletions had a number of similarities with people with Autism Spectrum Disorder. They had high levels of stereotyped and restricted behaviours, these include doing things like repeating the same body movements, liking things to be kept in particular ways and becoming attached to particular objects or people. Unlike people with Autism Spectrum Disorder, people with 9q34 deletions had higher ratings of mood and interest and pleasure, indicating a higher likelihood of smiling, laughing and general interest. People with 9p34 deletions were also more sociable than people with Autism Spectrum Disorder, being likely

to interact with both people they know and those that they do not know. This trait was similar to that seen in people with Down Syndrome.

Changes as people with 9q34 deletions got older were also examined, there was an initial very tentative suggestion that some people with a 9q34 deletion may experience a decline in their executive functioning. Executive functioning is necessary for humans to complete higher level tasks such as organising, planning and thinking before doing something. There was also a small indication that people with a 9q34 deletion may find it more difficult to acquire self help skills. As children got older, however, they were increasingly likely to be sociable with unfamiliar adults, this may be related to the decrease in executive functioning. These results are tentative especially as participants were only measured at one time point, in order to explore this further people with a 9q34 deletion need to be followed up over a number of years.

### *8p23*

People with an 8p23 deletion were most different to people with Autism Spectrum Disorder. People with an 8p23 deletion had much lower levels of overactivity and stereotyped behaviour than people with Autism and were much more likely to be sociable with unfamiliar people. In contrast, people with 8p23 deletions were reported to have high levels of repetitive speech were similar to those seen in people with Autism Spectrum Disorder, suggesting that they may say phrases or words repetitively. In terms of comparisons, people with 8p23 deletions had most similarities with people with Down Syndrome, with similar high levels of mood and interest and pleasure levels.

### **Clinical Implications**

In both groups there was a high prevalence of challenging behaviour, these behaviours have an impact on carer stress levels. Tailored interventions that support children and their families in managing these challenging behaviours would be invaluable.

Levels of sociability were high in both groups, this may have a positive and a negative impact. On the positive side it may be that people with 9q34 and 8p23 deletions are perceived as likeable, but a tendency to be friendly with people they do not know could put them at risk.

In the current study there were a high proportion of people with 9q34 deletions who showed behaviours akin to Autism Spectrum Disorder. There are many published studies with suggestions of how to help carers with these.

## **APPENDICES**

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## Appendix 1: Post Hoc Analysis; 9q34 Deletion Comparisons

Gender; Tukeys HSD

9q34	$\bar{x}d (\sigma_{\bar{x}})$	CDCS	$\bar{x}d (\sigma_{\bar{x}})$	CDLS	$\bar{x}d (\sigma_{\bar{x}})$	DS	$\bar{x}d (\sigma_{\bar{x}})$	ASD	$\bar{x}d (\sigma_{\bar{x}})$
CDCS	-0.18(0.2)	CDLS	0.09(0.2)	CDCS	-0.09(0.2)	CDCS	-0.27(0.2)	CDCS	-0.64(0.2)*
CDLS	-0.09(0.2)	DS	0.27(0.2)	DS	0.18(0.2)	CDLS	-0.18(0.2)	CDLS	-0.55(0.2)
DS	0.09(0.2)	ASD	0.64(0.2)*	ASD	0.55(0.2)	ASD	0.36(0.2)	DS	-0.36(0.2)
ASD	0.45(0.2)	9q34	0.18(0.2)	9q34	0.09(0.2)	9q34	-0.09(0.2)	9q34	-0.45(0.2)

\*p <.05 \*\* p <.01

Age; Tukeys HSD

9q34	$\bar{x}d (\sigma_{\bar{x}})$	CDCS	$\bar{x}d (\sigma_{\bar{x}})$	CDLS	$\bar{x}d (\sigma_{\bar{x}})$	DS	$\bar{x}d (\sigma_{\bar{x}})$	ASD	$\bar{x}d (\sigma_{\bar{x}})$
CDCS	-0.38(4.55)	CDLS	-0.66(4.55)	CDCS	0.66(4.55)	CDCS	-1.04(4.55)	CDCS	-0.73(4.55)
CDLS	-1.04(4.55)	DS	1.04(4.55)	DS	1.69(4.55)	CDLS	-1.69(4.55)	CDLS	-1.39(4.55)
DS	0.65(4.55)	ASD	0.73(4.55)	ASD	1.39(4.55)	ASD	-0.31(4.55)	DS	0.31(4.55)
ASD	0.34(4.55)	9q34	0.38(4.55)	9q34	1.04(4.55)	9q34	-0.65(4.55)	9q34	-0.34(4.55)

\*p <.05 \*\* p <.01

Wessex Self Help; Tukeys HSD

9q34	$\bar{x}d (\sigma_{\bar{x}})$	CDCS	$\bar{x}d (\sigma_{\bar{x}})$	CDLS	$\bar{x}d (\sigma_{\bar{x}})$	DS	$\bar{x}d (\sigma_{\bar{x}})$	ASD	$\bar{x}d (\sigma_{\bar{x}})$
CDCS	0.09(0.27)	CDLS	-0.09(0.27)	CDCS	0.09(0.27)	CDCS	0.36(0.27)	CDCS	0.27(0.27)
CDLS	0(0.27)	DS	-0.36(0.27)	DS	-0.27(0.27)	CDLS	0.27(0.27)	CDLS	0.18(0.27)
DS	-0.27(0.27)	ASD	-0.27(0.27)	ASD	-0.18(0.27)	ASD	0.09(0.27)	DS	-0.09(0.27)
ASD	-0.18(0.27)	9q34	-0.09(0.27)	9q34	0(0.27)	9q34	0.27(0.27)	9q34	0.18(0.27)

\*p <.05 \*\* p <.01

Wessex Speech; Tukeys HSD

9q34	$\bar{x}d (\sigma_{\bar{x}})$	CDCS	$\bar{x}d (\sigma_{\bar{x}})$	CDLS	$\bar{x}d (\sigma_{\bar{x}})$	DS	$\bar{x}d (\sigma_{\bar{x}})$	ASD	$\bar{x}d (\sigma_{\bar{x}})$
CDCS	0.09(0.1)	CDLS	-0.09(0.1)	CDCS	0.09(0.1)	CDCS	-0.09(0.1)	CDCS	0.09(0.1)
CDLS	0(0.1)	DS	0.09(0.1)	DS	0.18(0.1)	CDLS	-0.18(0.1)	CDLS	0(0.1)
DS	0.18(0.1)	ASD	-0.09(0.1)	ASD	0(0.1)	ASD	-0.18(0.1)	DS	0.18(0.1)
ASD	0(0.1)	9q34	-0.09(0.1)	9q34	0(0.1)	9q34	-0.18(0.1)	9q34	0(0.1)

\*p <.05 \*\* p <.01

Wessex Mobility; Tukeys HSD

9q34	$\bar{x}d (\sigma_{\bar{x}})$	CDCS	$\bar{x}d (\sigma_{\bar{x}})$	CDLS	$\bar{x}d (\sigma_{\bar{x}})$	DS	$\bar{x}d (\sigma_{\bar{x}})$	ASD	$\bar{x}d (\sigma_{\bar{x}})$
CDCS	0(0.29)	CDLS	0(0.29)	CDCS	0(0.29)	CDCS	0.27(0.29)	CDCS	0.45(0.29)
CDLS	0(0.29)	DS	-0.27(0.29)	DS	-0.27(0.29)	CDLS	0.27(0.29)	CDLS	0.45(0.29)
DS	-0.27(0.29)	ASD	-0.45(0.29)	ASD	-0.45(0.29)	ASD	-0.18(0.29)	DS	0.18(0.29)
ASD	-0.45(0.29)	9q34	0(0.29)	9q34	0(0.29)	9q34	0.27(0.29)	9q34	0.45(0.29)

\*p <.05 \*\* p <.01

## Appendix 2: Post Hoc Analysis; 8p23 Deletion Comparisons

Gender; Tukeys HSD

8p23	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )	CdLS	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )	FXS	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )	DS	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )	RTS	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )	ASD	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )
	-0.04 (0.12)		0.38 (0.12)*	CDL	-0.38 (0.12)*	CDL	-0.08 (0.12)	CDL	-0.04 (0.12)	CDL	-0.25 (0.12)
CdLS	0.33 (0.12)	FXS	0.08 (0.12)	S	-0.29 (0.12)	S	0.29 (0.12)	S	0.33 (0.12)	S	0.13 (0.12)
FXS	0.04 (0.12)	DS	0.04 (0.12)	DS	-0.33 (0.12)	FXS	-0.04 (0.12)	FXS	0.04 (0.12)	FXS	-0.17 (0.12)
DS	0.25 (0.12)	RTS	0.25 (0.12)	RTS	-0.13 (0.12)	RTS	0.17 (0.12)	DS	0.21 (0.12)	DS	-0.21 (0.12)
RTS	0 (0.12)	ASD	0 (0.12)	ASD	-0.33 (0.12)	ASD	-0.04 (0.12)	ASD	0 (0.12)	RTS	-0.21 (0.12)
ASD	0.21 (0.12)	8p2	0.04 (0.12)	8p2	-0.33 (0.12)	8p2	-0.04 (0.12)	8p2	0 (0.12)	8p2	-0.21 (0.12)
		3		3		3		3		3	

\*p < .05 \*\*p < .01

Age; Tukeys HSD

8p23	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )	CdLS	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )	FXS	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )	DS	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )	RTS	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )	ASD	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )
	-1.19 (1.82)		0.32 (1.82)	CDL	-0.32 (1.82)	CDL	-0.99 (1.82)	CDL	-0.98 (1.82)	CDL	-1.56 (1.82)
CdLS	-0.87 (1.82)	FXS	0.99 (1.82)	S	0.67 (1.82)	S	-0.67 (1.82)	S	-0.66 (1.82)	S	-1.24 (1.82)
FXS	-0.2 (1.82)	DS	0.98 (1.82)	DS	0.66 (1.82)	FXS	-0.01 (1.82)	FXS	0.01 (1.82)	FXS	-0.57 (1.82)
DS	-0.21 (1.82)	RTS	1.56 (1.82)	RTS	1.24 (1.82)	RTS	0.57 (1.82)	DS	0.58 (1.82)	DS	-0.58 (1.82)
RTS	0.37 (1.82)	ASD	1.19 (1.82)	ASD	0.87 (1.82)	ASD	0.21 (1.82)	ASD	0.21 (1.82)	RTS	-0.37 (1.82)
ASD		8p23		8p2		8p2		8p2		8p2	
				3		3	0.2 (1.82)	3		3	

\*p < .05 \*\*p < .01

Wessex Self Help; Tukeys HSD

8p23	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )	CdLS	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )	FXS	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )	DS	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )	RTS	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )	ASD	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )
	0 (0.24)		-0.04 (0.24)	CDL	0.04 (0.24)	CDL	0.21 (0.24)	CDL	0.04 (0.24)	CDL	0.04 (0.24)
CdLS	-0.04 (0.24)	FXS	-0.21 (0.24)	S	-0.17 (0.24)	S	0.17 (0.24)	S	-0.17 (0.24)	S	-0.17 (0.24)
FXS	-0.21 (0.24)	DS	-0.04 (0.24)	DS	0 (0.24)	FXS	0.17 (0.24)	FXS	0 (0.24)	FXS	0 (0.24)
DS	-0.04 (0.24)	RTS	-0.04 (0.24)	RTS	0 (0.24)	RTS	0.17 (0.24)	DS	-0.17 (0.24)	DS	-0.17 (0.24)
RTS	-0.04 (0.24)	ASD	-0.04 (0.24)	ASD	0 (0.24)	ASD	0.21 (0.24)	ASD	0 (0.24)	ASD	0 (0.24)
ASD	-0.04 (0.24)	8p23	0 (0.24)	8p2	0.04 (0.24)	8p2	0.21 (0.24)	8p2	0.04 (0.24)	8p2	0.04 (0.24)
				3		3		3		3	

\*p < .05 \*\*p < .01

## Appendix 2: (continued)

Wessex Speech; Tukeys HSD

8p23	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )	CdLS	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )	FXS	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )	DS	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )	RTS	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )	ASD	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )
CdLS	0 (0.08)	FXS	-0.04 (0.08)	CDL	0.04 (0.08)	CDL	-0.04 (0.08)	CDL	0 (0.08)	CDL	0 (0.08)
FXS	-0.04 (0.08)	DS	0.04 (0.08)	S	0.08 (0.08)	S	-0.08 (0.08)	S	-0.04 (0.08)	S	-0.04 (0.08)
DS	0.04 (0.08)	RTS	0 (0.08)	DS	0.04 (0.08)	FXS	-0.04 (0.08)	FXS	0.04 (0.08)	FXS	0.04 (0.08)
RTS	0 (0.08)	ASD	0 (0.08)	RTS	0.04 (0.08)	RTS	-0.04 (0.08)	DS	0 (0.08)	DS	0 (0.08)
ASD	0 (0.08)	8p23	0 (0.08)	ASD	0.04 (0.08)	ASD	-0.04 (0.08)	ASD	0 (0.08)	RTS	0 (0.08)
				8p2	0.04 (0.08)	8p2	-0.04 (0.08)	8p2	0 (0.08)	8p2	0 (0.08)
				3	0.04 (0.08)	3	-0.04 (0.08)	3	0 (0.08)	3	0 (0.08)

\*p < .05 \*\*p < .01

Wessex Mobility; Tukeys HSD

8p23	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )	CdLS	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )	FXS	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )	DS	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )	RTS	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )	ASD	$\bar{x}d$ ( $\sigma_{\bar{x}}$ )
CdLS	-0.13 (0.16)	FXS	-0.04 (0.16)	CDL	0.04 (0.16)	CDL	0.17 (0.16)	CDL	0 (0.16)	CDL	0.13 (0.16)
FXS	-0.17 (0.16)	DS	-0.17 (0.16)	S	-0.13 (0.16)	S	0.13 (0.16)	S	-0.04 (0.16)	S	0.08 (0.16)
DS	-0.29 (0.16)	RTS	0 (0.16)	DS	0.04 (0.16)	FXS	0.17 (0.16)	FXS	-0.17 (0.16)	FXS	-0.04 (0.16)
RTS	-0.13 (0.16)	ASD	-0.13 (0.16)	RTS	-0.08 (0.16)	RTS	0.04 (0.16)	DS	-0.13 (0.16)	DS	0.13 (0.16)
ASD	-0.25 (0.16)	8p23	0.13 (0.16)	ASD	0.17 (0.16)	ASD	0.29 (0.16)	ASD	0.13 (0.16)	RTS	0.13 (0.16)
				8p2	0.17 (0.16)	8p2	0.29 (0.16)	8p2	0.13 (0.16)	8p2	0.25 (0.16)
				3	0.17 (0.16)	3	0.29 (0.16)	3	0.13 (0.16)	3	0.25 (0.16)

\*p < .05 \*\*p < .01