CHALLENGING BEHAVIOUR IN PHELAN-MCDERMID SYNDROME

by

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OVERVIEW

This thesis is submitted by Laurie Anne Powis for the Degree of Doctor of Clinical Psychology at The University of Birmingham. The thesis is comprised of two volumes.

Volume I of the thesis comprises the research component of the degree and includes three papers. The first paper is a review of the research literature examining aggression in genetic syndromes. The second paper is an empirical study examining challenging behaviour in Phelan-McDermid syndrome. Both of these papers are prepared for submission to Research in Developmental Disabilities. The third paper is an executive summary that aims to provide an accessible overview of the work. This paper will be used to disseminate the main findings to research participants and health professionals.

Volume II of the thesis comprises five clinical practice reports that were completed during the three years of clinical training. The first report regards a 20 year old female with borderline learning disability and depressive symptoms. This report formulates her difficulties using two different psychological perspectives. The second report presents a small scale service evaluation conducted for a local learning disability service. The evaluation was conducted to assist with the development of services for people with profound and multiple learning disabilities. The third report presents a single case experimental design to evaluate the effectiveness of an intervention package for a twelve year old female with school anxiety. The fourth report presents a case study for a thirty-eight year old female with severe obsessive compulsive disorder. Finally, the fifth report is an abstract of an oral presentation reporting the results of a service evaluation that was carried out to evaluate two consultation clinics run by a local older-adult learning disability service.

DEDICATION

For David

ACKNOWLEDGEMENTS

First and foremost I wish to thank all the families who took part in this research, and all the clients who kindly consented to be part of my clinical practice reports. I feel truly privileged to have worked with so many inspirational people.

I would like to extend a thank you to my supervisor Professor Chris Oliver for his continued guidance, patience, and support (and for putting up with my endless rambling emails!). I am also extremely grateful to Jo Moss for her help with my empirical paper, particularly during the 'dreaded cross syndrome analysis'. My thanks also go to the course team and my clinical supervisors who have taught me so much.

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Finally, I would like to thank my favourite people - my wonderful family, Kathryn, Rachael, the Hobsons, the Flints, Fred, and Ida for their unwavering encouragement, love, and support. Without them the last three years wouldn't have been half as fun. A very special thank you needs to go to David, for *always* being there, and for teaching me the true meaning of containment.

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VOLUME I

CHAPTER ONE

LITERATURE REVIEW: AGGRESSION IN GENETIC SYNDROMES

Abstract

Evidence from the operant and behavioural phenotype literatures suggests both environmental and organic factors may play a role in the manifestation of aggression in genetic syndromes. However, there is a paucity of research that directly compares aggression across syndromes and this contrasts with the literature on self-injury. Identification of increased risk for aggression would enable the implementation of early intervention strategies. Consequently, the aim of the review is to examine the extent to which aggression is associated with specific genetic syndromes by analysis of studies that report prevalence of aggression in these groups. The review also aims to examine the literature outlining the form of the behaviour, and the influence of environmental factors.

Results of prevalence studies imply that certain syndrome groups may show a stronger association with aggression than others. However, accurately determining the strength of association is limited due to methodological differences between studies. Further research that moves towards a more consistent approach to examining prevalence and includes group comparison designs is warranted. Together with the results from prevalence studies, the results from studies examining form and environmental influences point towards the importance of phenotype-environment interactions in the development of aggression in genetic syndromes. It is proposed that future work on the assessment and intervention of aggression in genetic syndromes should consider the importance of these phenotype-environment interactions. Finally, attention should be paid to possible reasons why aggression has received comparatively less attention to the examination of self-injurious behaviour in genetic syndromes.

1.1. Aggression in Genetic Syndromes

Aggression is a widely recognised problem for individuals with intellectual disability (ID) and can impinge on quality of life and carer well being and contribute to the breakdown of residential placements (Hastings, 2002; Tausig, 1985). Prevalence estimates for aggression vary widely, in part because of methodological differences (Borthwick-Duffy, 1994; Harris & Russell, 1989; Quine, 1986; Sigafoos, Elkins, Kerr & Atwood, 1994). A recent review of prevalence studies that limited inclusion to those reporting 'physical aggression' suggested rates of physical aggression in ID are likely to lie at the upper end of the widely cited 2% to 20% estimate (Davies & Oliver, 2013). For example, Tyrer et al., (2006) and Crocker, Mercier, Lachapelle, Brunet, Morin and Roy (2006) examined prevalence in over 3000 individuals with ID and reported overall rates of 14% and 24.4% respectively. Similarly, Smith, Branford, Collacott, Cooper and McGother (1996) reported a prevalence of 22% in 2202 adults with ID. Relative risk analyses of studies reporting prevalence across age groups indicated that aggression increased with age until mid-adulthood.

There is a robust research literature that highlights the importance of environmental factors and operant theory in the development and maintenance of aggression. It has been demonstrated repeatedly that such behaviours can be sensitive to, and maintained by socially, and non-socially mediated forms of reinforcement such as attention or the presentation of tangible items from carers (Carr & Durand, 1985) and removal of task demands (Iwata, Pace, Kalsher, Cowdery, & Cataldo, 1990). In a review of functional analytic studies, Hanley, Iwata and McCord (2003) demonstrated that in 50 of 52 studies, aggression was mediated by an operant reinforcement process.

Although operant theory has significant empirical support, there is a broad consensus that biological factors also play a role in behaviours such as self-injury and

aggression (e.g. Arron, Oliver, Moss, Berg, & Burbridge, 2011; Langthorne & McGill, 2012; May et al., 2009). Certain syndrome groups evidence a comparatively higher prevalence of self-injury, aggression and destructive behaviour than others (Arron et al., 2011). Furthermore, forms of behaviour also differ across genetic syndromes. For example, Cri du Chat syndrome is said to be associated with heightened levels of aggression (Collins & Cornish, 2002); self-injurious behaviours such as eye pressing, head slapping and hand biting are more common in Cornelia de Lange syndrome (Berney, Ireland, & Burn, 1999) and Prader–Willi syndrome is characterised by temper tantrums (Clarke, Boar, & Chung, 1996).

In addition to syndrome related associations, certain person characteristics are known to be associated with aggression. McClintock, Hall, and Oliver (2003) found that Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD), being male, and reduced communication skills were all associated with aggression. In a study examining the correlates of challenging behaviour in several genetic syndromes, Arron et al., (2011) found that impulsivity and over-activity were significantly higher in participants showing aggression than in those who did not show aggression. Furthermore, in studies examining risk factors for aggression in ASD, lower IQ, poorer expressive and receptive language, and repetitive behaviours have been identified as associated with aggression (Dominick, Davis, Lainhart, Tager-Flusberg, & Folstein, 2007; Kanne & Mazurek, 2011).

Evidence from the operant and behavioural phenotype literatures suggest that both environmental and organic factors may play a role in the manifestation of aggression in genetic syndromes (see Tunnicliffe & Oliver, 2011). However, there is a paucity of research that directly compares aggression across syndromes and this contrasts with the literature on self-injury. This lack of research is surprising when it is considered that many of the risk

factors known to be associated with aggression (i.e. impulsivity, over-activity, repetitive behaviours , ASD, and reduced communication abilities) are frequently described in certain genetic syndromes (e.g. Clarke & Boer, 1998; Finucane, Konar, Haas-Givler, Kurtz & Scott, 1994; Hagerman, 2002). Identification of increased risk for aggression would enable the implementation of early intervention strategies to reduce or replace behaviours before they become established. Furthermore, as it has been suggested that successful interventions require knowledge of underlying operant influences (Harvey, Boer, Meyer, & Evans, 2009) it is necessary to investigate the role of environmental influences on aggression across syndromes.

This review will examine the extent to which aggression is associated with specific genetic syndromes by analysis of studies that report the prevalence of aggression in these groups. This will ascertain whether certain syndromes show a heightened association with aggression in comparison to others. The review will then examine the literature outlining the form of the behaviour in these groups and literature that examines the influence of environmental factors on aggression.

1.2. Selecting Syndromes for Inclusion.

1.2.1. Search strategy.

Due to the number of syndromes that might potentially be investigated, an initial screening was undertaken to identify which syndrome groups had research papers relevant to the review. A search using Ovid PsychInfo was conducted on papers between 1967 – December Week 3 2012. A wide range was used to gather as many relevant papers as possible. The search strategy, including inclusion criteria, is presented in Figure 1. The keywords ‘syndrome’ and ‘aggress*’ were used as it was deemed that these would identify any syndromes that had papers relevant to the review. As expected, results included a

number of syndromes that did not have a genetic basis or were not associated with intellectual disability (e.g. restless leg syndrome, Tourette's syndrome). Consequently only syndrome groups with a known genetic basis that were associated with intellectual disability were included in the initial screening list.

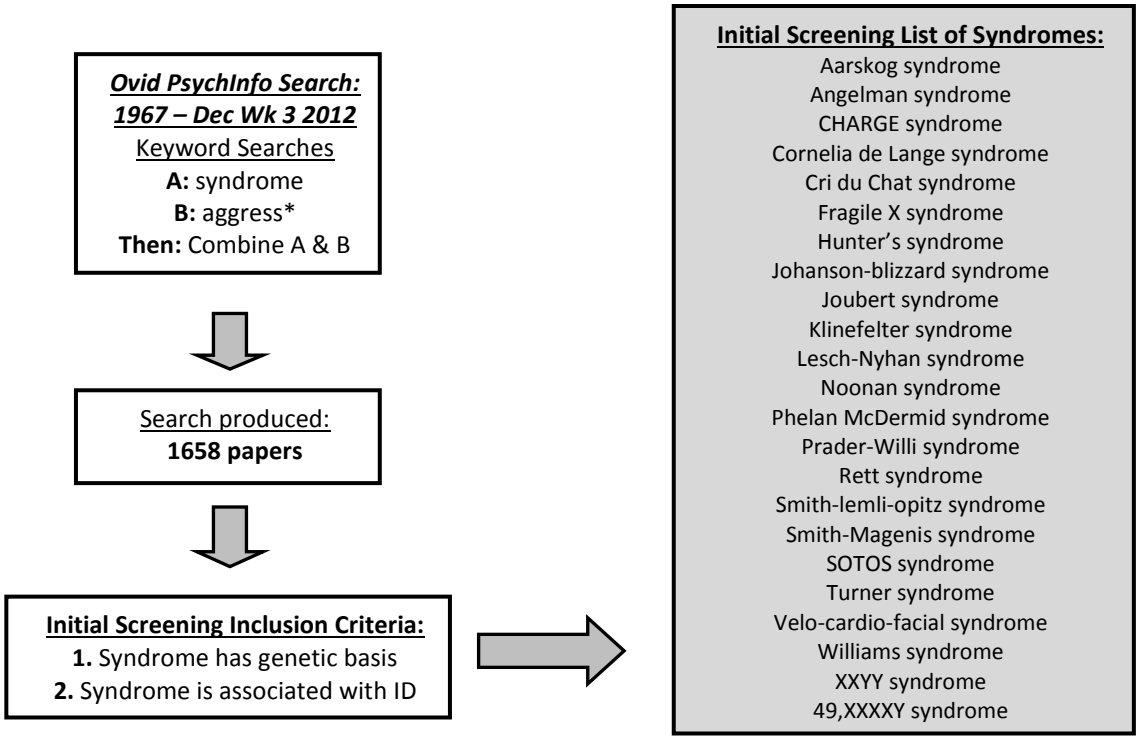

Figure 1: Initial Screening Search

The search was then broadened by combining each syndrome name with the word 'behavio*' to identify any papers documenting specific topographies of aggression (e.g. hit, kick) that would be missed if the search was restricted to aggress*. Syndromes were then selected by examining the number of papers reporting prevalence figures for a sample of 20 participants or more. As there is no single definition of aggression used consistently, any paper that reported a prevalence of 'aggress*' or a particular topography of aggression, was included. Finally, syndromes were included only if there was more than one paper estimating prevalence. Consequently, seven syndromes were selected for review: Fragile X

(FXS), Prader-Willi (PWS), Smith-Magenis (SMS), Williams (WS), Angelmans (AS), Cri du Chat (CdCS), and Cornelia de Lange (CdLS). In addition to the papers identified by Ovid PsychInfo, an additional hand search was conducted for each syndrome to locate papers that were not highlighted by the electronic review. The search strategy, including inclusion criteria, is presented in Figure 2.

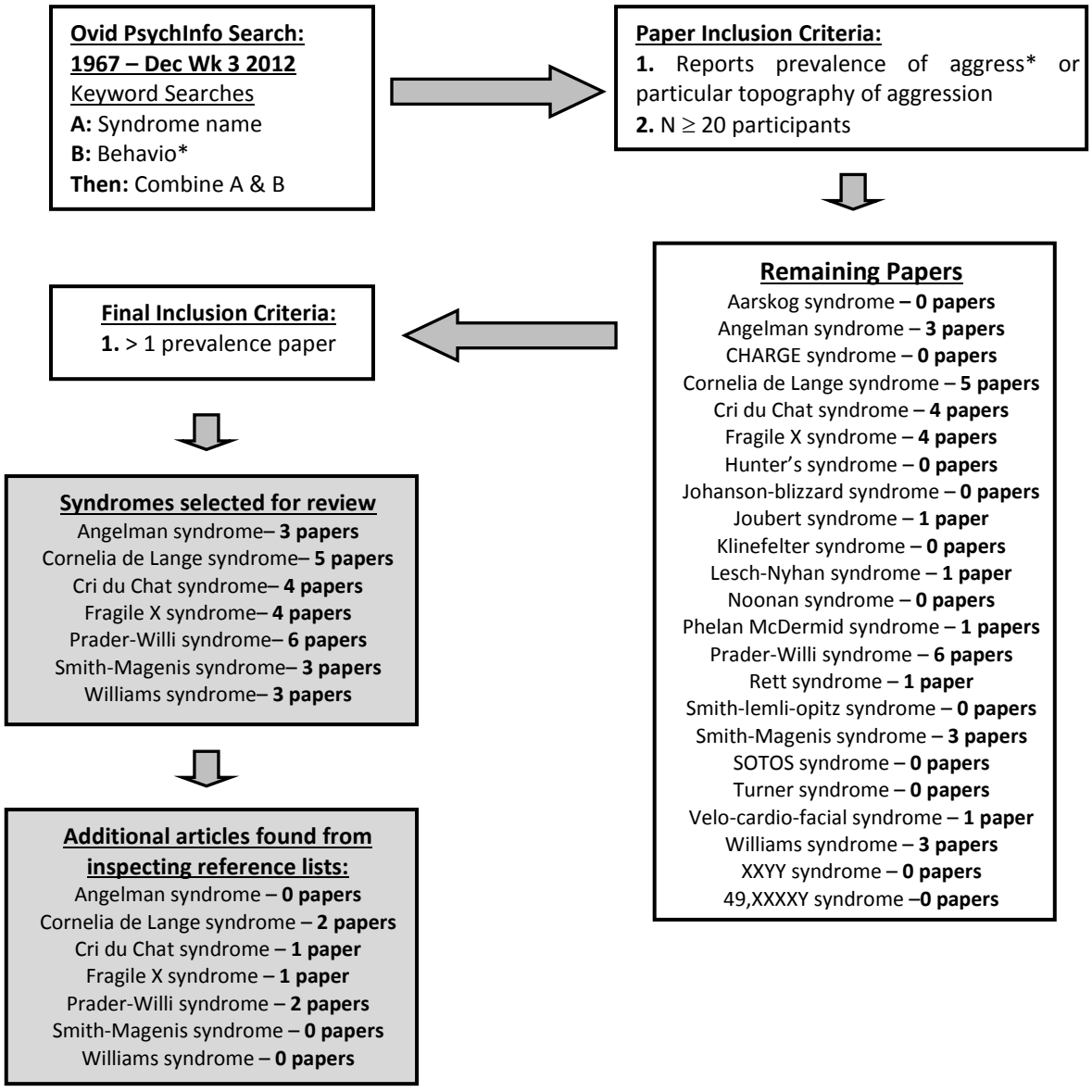

Figure 2: Search Strategy

Down syndrome (DS) was not included as part of the systematic review. DS is a well documented genetic syndrome with a comparatively clearly defined behavioural phenotype including a low rate of challenging behaviours such as aggression (Chapman & Hesketh, 2000). Therefore, due to the large variation in studies outlining the prevalence of aggression in intellectual disabilities, it was decided that DS would be used as a contrast group with which to compare prevalence rates across other genetic syndromes. Due to the extensive literature available for DS, a different search strategy was adopted to identify papers. The search strategy, including inclusion criteria, is presented in Figure 3.

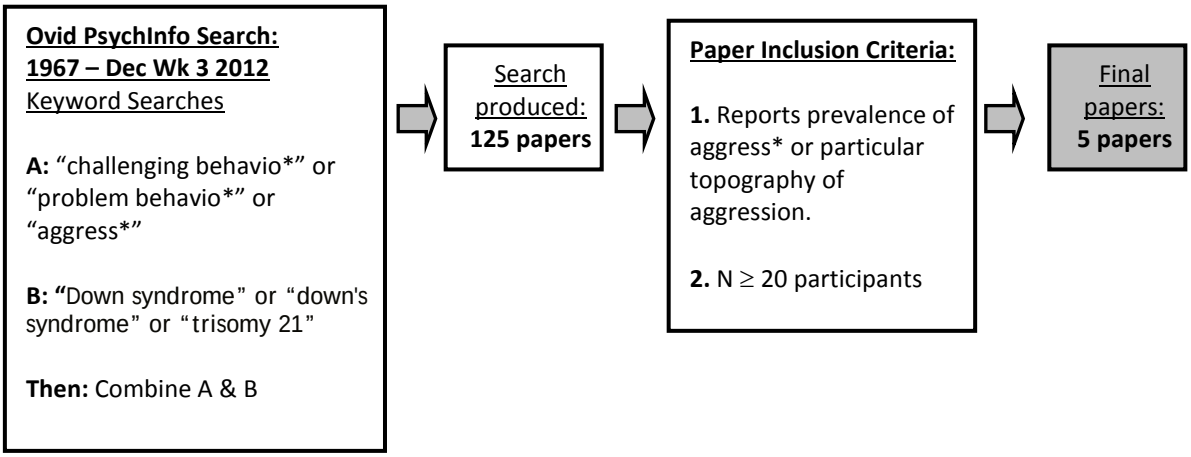

Figure 3: Search Strategy for Down syndrome (DS)

1.3. Syndromes Included for Review

1.3.1. Cri du Chat syndrome.

Cri du Chat syndrome (CdCS) has an estimated prevalence of around 1 in 50,000 live births (Niebuhr, 1978) and is predominately caused by a deletion on the tip of the short arm of chromosome 5, with a critical region of 5p15 (Wu, Niebuhr, Yang, & Hanson, 2005). A de novo deletion is present in 85% of cases and 10-15% of cases are familial (Van Buggenhout et al., 2000). Behaviours noted to occur in CdCS include self-injurious behaviour, repetitive behaviour, obsessive attachment to objects, sleep problems,

hypersensitivity to sensory stimuli and aggressive and destructive behaviour (Clarke & Boer, 1998; Collins & Cornish, 2002; Van Buggenhout et al., 2000).

1.3.2. Smith-Magenis syndrome.

Smith-Magenis syndrome (SMS) has a reported prevalence of between 1 in 25,000 live births (Greenberg et al., 1996) and 1 in 15,000 (Laje et al., 2010). Typically, the syndrome results from a de novo deletion on chromosome 17 (17p11.2) (Girirajan et al., 2006) but for approximately 10% of cases, a mutation of the retinoic acid-induced 1 (RAI1) gene on the same chromosome has been implicated (Elsea & Girirajan, 2008). Self-injurious behaviour has been frequently noted (e.g. Smith et al., 1986), along with sleep difficulties, aggressive behaviour, restlessness, distractibility, hyperactivity, autistic features, and a unique 'self hug' (Finucane et al., 1994).

1.3.3. Fragile X syndrome.

Fragile X syndrome (FXS) is the most common inherited form of intellectual disability with a prevalence of approximately 1 in 3,600 males and 1 in 8,000 females (Turner, Webb, Wake, & Robinson, 1996). Genetic basis involves the expansion of a trinucleotide repeat sequence, cytosine-guanine-guanine (CGG), in the promoter region of the FMR1 gene located at Xq27.3 of the long arm of the X chromosome (Sansone et al., 2012). In addition to ID, research suggests a specific behavioural phenotype characterised by aggression, inattention, hyperactivity, and autism spectrum disorder (ASD) behaviours (Hagerman, 2002; Hatton et al., 2002; Sullivan et al., 2006).

1.3.4. Angelman syndrome.

Angelman syndrome (AS) has a reported prevalence of approximately 1 in 52,000 live births (Oiglane-Shilk et al., 2006). AS results from the absence of maternally derived genetic material on chromosome 15 in the region of 15q11-q13 but there are several different genetic mechanisms. In a small proportion of cases, AS results from either a paternal uniparental disomy (UPD; 4-7% of cases), a UBE3A gene mutation (10% of cases), or imprinting centre deficits (3-4% of cases). However, in the majority of cases (approximately 70%), AS is caused by maternal deletions of chromosome 15q11-q13 (Dagli, Buiting & Williams, 2012; Ludwig et al., 2005). The behavioural phenotype of AS is said to be characterised by a strong drive for adult attention and high levels of laughing and smiling behaviours (e.g. Horsler & Oliver, 2006; Oliver, Demetriades & Hall, 2002). Other notable behaviours include sleep difficulties (Bruni et al., 2004); hyperactivity, and inattentive behaviour (Clark & Marston, 2000; Summers & Feldman, 1999).

1.3.5. Cornelia de Lange syndrome.

Cornelia de Lange syndrome (CdLS) has a reported prevalence of between 1 in 10,000 and 1 in 50,000 live births (Beck & Fenger, 1985; Opitz, 1985). Approximately 60% of cases result from a mutation on the NIP-BL gene (5p13.1), but other mechanisms including mutations on chromosome 10 (SMC3 gene) and X-linked SMC1A and HDAC8 genes have been implicated (Deardorff et al., 2012; Musio et al., 2006). The behavioural phenotype is said to include self-injurious behaviours, hyperactivity, and repetitive behaviours (Arron et al., 2011). A heightened prevalence of autistic-like characteristics has been suggested (Moss, Howlin & Oliver, 2011), and anxiety, social impairments and low mood have been described in adolescents and young adults (Nelson, 2010).

1.3.6. Prader-Willi syndrome.

Prader-Willi syndrome (PWS) has a reported prevalence of approximately 1 in 52,000 live births (Whittington et al., 2001) and is caused by either a paternal deletion (e.g. larger Type I versus smaller Type II deletions) within the 15q11-q15 region (approx. 70%), or by maternal uniparental disomy (UPD) of chromosome 15 (Cassidy & Driscoll, 2009). Characteristic behaviours include hyperphagia, temper tantrums, impulsivity, skin picking, repetitive speech, stubbornness, and aggression (Dykens & Cassidy, 1995; Dykens & Kasari, 1997; Einfield, Smith, Durvasula, Florio & Tonge, 1999; Greenswag, 1987).

1.3.7. Williams syndrome.

Williams syndrome (WS), has a reported prevalence of 1 in 7,500 live births (Stromme, Bjornstad, & Ramstad, 2002) and is caused by the microdeletion of approximately 25 genes on the long arm of chromosome 7 (Donnai & Karmiloff-Smith, 2000). The most widely documented behaviours associated with the WS phenotype include heightened sociability, increased empathy, and anxiety (Dykens, 2003; Udwin & Yule, 1991). Challenging behaviours such as aggression do not typically form part of the behavioural phenotype and thus have not been widely examined.

1.3.8. Down syndrome.

Down Syndrome (DS) is the most common cause of intellectual disability associated with a chromosomal anomaly, with an estimated prevalence of 1 in every 732 live births when averaged across maternal ages (Canfield et al., 2006). In the vast majority of cases, the syndrome results from non-disjunction involving chromosome 21 during meiosis, but a small proportion of cases are mosaic in nature or caused by a translocation of genetic material between chromosome 21 and another chromosome (Connor & Ferguson-Smith,

1997). Research has indicated that typically, individuals with DS display fewer behavioural problems than individuals with other intellectual disabilities (Dykens, 2007).

1.4. Prevalence of Aggression in Selected Syndromes

The studies outlining prevalence data for each syndrome group are presented in Table 1 together with information regarding the studies' aims, recruitment strategy, methodology, definition, time period, age of sample and sample size. The review identified 39 papers reporting the prevalence of aggression. For CdCS, five papers were identified with estimates ranging from 18.5% to 88%; SMS, three papers (57% to 87.5%); FXS, five papers (14% to 75%); AS, three papers (10% to 73%); CdLS, seven papers (7.4% to 75%); PWS, eight papers (10.4% to73%); WS, three papers (6.7% to 15%) and finally, for DS, five papers (3.7% to 12%).

Table 1 – *The prevalence of aggression in genetic syndromes*

	Author	Study Aims	Recruitment	Method	Definition used to report prevalence of aggression	Time period	Mean Age (Range)	N	Prevalence
CdCS									
CdCS	Cornish & Pigram (1996)	To assess the developmental and behavioural characteristics of 27 children with CdCS	UK Syndrome support group	Parents completed The Society for the Study of Behavioural Phenotypes Postal Questionnaire	1.'Physically aggressive to family members' 2.'Physically aggressive to non family members'	Not given	8.3 years (4-16)	27	1. **33.3%** 2. **18.5%**
CdCS	Dykens & Clarke (1997)	To examine the range, distinctiveness and correlates of maladaptive behaviour in individuals with CdCS	US & UK Syndrome support groups	Parents completed The Aberrant Behavior Checklist-Community	'Aggressive to others' (verbally or physically)	1 month	12.0 years (2-40)	146	**70%**
CdCS	Cornish et al., (1998)	To extend knowledge of the behavioural phenotype of CdCS to include a profile of a young cohort's adaptive and maladaptive functioning	UK Syndrome support group	Parents were interviewed using The Vineland Adaptive Behavior Scales, Interview Edition. (includes a 'maladaptive behaviour' section)	'Too physically aggressive'	'Current'	7.6 Years (4-16)	49	**30%**
CdCS	Collins & Cornish (2002)	To determine the prevalence and frequency of stereotypy, self-injurious behaviour, and aggression in children and adults with CdCS.	UK Syndrome support group	Parents completed The Behavior Problems Inventory (BPI)	Prevalence reported based on 'informant responded to at least one item on this subscale'. Items on the aggressive/destructive subscale included: Hitting others with hand or body part; hitting others with objects; meanness or cruelty; biting others; scratching others; pinching others; & destructive behaviour.	Rated between 'less than monthly to 'hourly'.	14.75 years (6-37)	66	**88%**

Table 1 – *The prevalence of aggression in genetic syndromes*

	Author	Study Aims	Recruitment	Method	Definition used to report prevalence of aggression	Time period	Mean Age (Range)	N	Prevalence
CdCS	Arron et al.,(2011)	To examine the prevalence and associated characteristics of self injurious and aggressive behaviour in seven genetic syndromes.	Syndrome support group	Parents completed The Challenging Behaviour Questionnaire (CBQ)	'Physical aggression' (e.g. punching, pushing, kicking, pulling hair, grabbing other's clothing).	1 month	17.20 years	58	**70.2%**
SMS									
SMS	Dykens & Smith (1998)	To examine the distinctiveness and correlates of maladaptive behaviour in 35 children with SMS	Syndrome support group & Syndrome conference	Parents completed The Child Behavior Checklist (CBCL)	Prevalence reported as 'Physical aggression' but exact CBCL items used were not specified.	6 months	9.00 years	105	**57%**
SMS	Arron et al.,(2011)	To examine the prevalence and associated characteristics of self injurious and aggressive behaviour in seven genetic syndromes.	Syndrome support group	Parents completed The Challenging Behaviour Questionnaire (CBQ)	'Physical aggression' (e.g. punching, pushing, kicking, pulling hair, grabbing other's clothing).	1 month	15.45 years	42	**73.8%**
SMS	Sloneem et al., (2011)	To investigate the prevalence and phenomenology of aggressive behaviour in SMS	UK Syndrome support group	Parents were interviewed using the Challenging Behaviour Interview (CBI)	'A non-accidental, physical act involving physical contact with another person likely to result in pain or distress. Examples: Punching, pushing, kicking, tripping, pulling hair, scratching, throwing objects, using objects as weapons, and grabbing clothing.'	1 month	15.09 years (6-39)	32	**87.5%**

Table 1 – *The prevalence of aggression in genetic syndromes*

	Author	Study Aims	Recruitment	Method	Definition used to report prevalence of aggression	Time period	Mean Age (Range)	N	Prevalence
FXS									
FXS	Sarimski (1997a)	To explore the behavioural phenotypes of three genetic syndromes.	German Syndrome support group	Parents completed the Society for the Study of Behavioural Phenotypes Postal Questionnaire (SSBPQ)	Prevalence reported as 'Physically aggressive' but exact SSBPQ items used were not specified.	Not given	84.3 months	30 males	**40%**
FXS	Hatton et al., (2002)	To examine the problem behaviour over time in boys with FXS	Genetic clinics, developmental evaluation centres, and early intervention programs.	Parents completed the Child Behavior Checklist (CBCL)	Prevalence reported based on 'Aggressive behaviour' domain score being in the 'borderline or clinical range'. The CBCL Aggressive Behaviour domain includes various constructs including: arguing, meanness, destruction of property and jealousy.	6 months	86.60 months (48-152)	59 males	**17%**
FXS	Bailey et al., (2008)	To report the frequency of selected co-occurring conditions in individuals with variations in the FMR1 gene.	Three FXS Foundations	Informant report via telephone or web-based questionnaire.	"Has this child ever been diagnosed with or treated by a medical professional for any of the following conditions?" 'Aggressiveness towards others' was listed.	'ever'	Not specified	976 males 259 females	**38%** **14%**
FXS	Hessl et al., (2008)	To examine whether the 5-HTTLRP and MAOA-VNTR polymorphisms are associated with severity of behavioural problems in FXS	Two referred due to concerns about aggression. All others were sequential clinic referrals.	Parents completed The Behavior Problems Inventory (BPI)	Prevalence reported based on 'aggression towards others' but exact BP1-01 items used were not specified.	2 months	15.6 years (8-24)	50 males	**75%**

Table 1 – *The prevalence of aggression in genetic syndromes*

	Author	Study Aims	Recruitment	Method	Definition used to report prevalence of aggression	Time period	Mean Age (Range)	N	Prevalence
FXS	Arron et al.,(2011)	To examine the prevalence and associated characteristics of self injurious and aggressive behaviour in seven genetic syndromes.	Syndrome support group	Parents completed The Challenging Behaviour Questionnaire (CBQ)	'Physical aggression' (e.g. punching, pushing, kicking, pulling hair, grabbing other's clothing).	1 month	16.57 years	191 males	**52%.**
AS									
AS	Zori et al., (1992)	To further delineate the clinical and developmental features of Angelman syndrome.	UK Syndrome Support Group and USA Research Group	Parents completed 'a general developmental questionnaire'.	Prevalence reported based on 'Aggressive Behaviour' but further definition not provided.	Not given	Not given	66	**10.6 %**
AS	Summers et al., (1995)	To examine the nature and prevalence of behaviour problems among clients with Angelman syndrome.	Medline literature search of case reports from 1965 – 1992	Review of 34 case reports	Prevalence reported based on 'Aggression' but further definition not provided.	Not given	Not given	108	**10%**
AS	Arron et al.,(2011)	To examine the prevalence and associated characteristics of self injurious and aggressive behaviour in seven genetic syndromes.	Syndrome support group	Parents completed The Challenging Behaviour Questionnaire (CBQ)	'Physical aggression' (e.g. punching, pushing, kicking, pulling hair, grabbing other's clothing).	1 month	13.40 years	104	**73%**

Table 1 – *The prevalence of aggression in genetic syndromes*

	Author	Study Aims	Recruitment	Method	Definition used to report prevalence of aggression	Time period	Mean Age (Range)	N	Prevalence
CdLS									
CdLS	Gualtieri (1991)	Investigation into behaviour in the CdLS.	USA Syndrome support group	Parents completed a questionnaire about medical background, family history, drug treatment, and abnormal behaviours	Prevalence reported based on 'been aggressive at one time or another' but further definition not provided.	'at one time or another'	10.4 years (1-39)	78	**73%**
CdLS	Sarimski (1997b)	To survey the social-communicative abilities and behavioural abnormalities in CdLS	German Syndrome support group and from an existing database from previous assessment.	Parents completed The Behavior Problems Inventory (BPI) & The Society for the Study of Behavioural Phenotypes Postal Questionnaire (SSBPQ)	1.BPI prevalence reported based on informant endorsing 'biting, hair pulling or beating others' as 'a problem'	Rated between 'monthly' to 'hourly'.	7.1 years (1-16)	27	**7.4%**
					2.SSBPQ prevalence reported on informant endorsing 'attacking other people'	Not given			**7.4%**
CdLS	Berney et al., (1999)	To further delineate the behavioural phenotype of CdLS	UK Paediatrics, clinical genetics, child psychiatry & Syndrome support group.	Parents completed The Society for the Study of Behavioural Phenotypes Postal Questionnaire (SSBPQ)	Prevalence reported as 'aggression' but exact SSBPQ items used were not specified.	1. At least occasionally	Not given	49	1. **75%**
						2. At least daily			2. **49%**
CdLS	Hyman et al., (2002)	To examine the range of challenging behaviours in CdLS, with a focus on SIB and self restraint.	UK Syndrome support group	Caregivers were asked via a questionnaire whether the individual 'had shown physical aggression in the last month'	Physical Aggression was defined as any punching, pushing, kicking, pulling hair, throwing objects, or grabbing other's clothing.	1 month	12.89 years (1-38)	88	**43.2%**

Table 1 – *The prevalence of aggression in genetic syndromes*

	Author	Study Aims	Recruitment	Method	Definition used to report prevalence of aggression	Time period	Mean Age (Range)	N	Prevalence
CdLS	Basille et al., (2007)	To provide greater insight into the clinical, behavioural and cognitive characteristics associated with CdLS.	Clinic referrals and Italian Syndrome support group	Parents completed The Developmental Behaviour Checklist – Primary Carer Version (DBC-P).	Prevalence reported as 'aggressiveness' but exact DBC-P items used were not specified.	6 months	10.58 years (1-31)	56	**20%**
CdLS	Arron et al.,(2011)	To examine the prevalence and associated characteristics of self injurious and aggressive behaviour in seven genetic syndromes.	Research database	Parents completed The Challenging Behaviour Questionnaire (CBQ)	'Physical aggression' (e.g. punching, pushing, kicking, pulling hair, grabbing other's clothing).	1 month	17.49 years	101	**40.2%**
CdLS	Rojahn et al., (2012)	To validate the Behavior Problem Inventory-01 in a population of individuals with CdLS	USA Syndrome support group	Parents completed The Behavior Problems Inventory (BPI)	Prevalence based on 'informant responded to at least 1 item on aggressive/destructive subscale'. Items included: Hitting, kicking, pushing, biting, and scratching others; grabbing and pulling, bring verbally abusive, destroying things, and being mean or cruel.	Rated between 'monthly' to 'hourly'.	16.8 Years (1.5-61.4)	180	**70.5%**
PWS									
PWS	Sarimski (1997a)	To explore the behavioural phenotypes of three genetic syndromes.	German Syndrome support group	Parents completed The Society for the Study of Behavioural Phenotypes Postal Questionnaire.	Prevalence reported as 'physically aggressive' but exact SSBPQ items used were not specified.	Not given	80.2 months	35	**11.4%**
PWS	Boer & Clarke (1999)	To describe the developmental and behavioural aspects of PWS	UK Syndrome support group	Parents completed The Society for the Study of Behavioural Phenotypes Postal Questionnaire	'Aggressive towards' 1. Children 2. Adults	Not given	**(**3-51) years	205	1. **10.7%** 2. **14%**

Table 1 – *The prevalence of aggression in genetic syndromes*

	Author	Study Aims	Recruitment	Method	Definition used to report prevalence of aggression	Time period	Mean Age (Range)	N	Prevalence
PWS	Einfeld et al., (1999)	To determine PWS has increased psychopathology compared to controls.	Australian Hospital Genetics Register	Parents completed The Developmental Behaviour Checklist – Primary Carer Version (DBC-P)	Prevalence reported based on number of informants who endorsed 'kicks, hits others' on the DBC-P	6 months	17.7 years	75	**41%**
PWS	Wigren & Heimann (2001)	To relate differences in patterns of skin picking to prevalence of compulsive and impulsive-aggressive behaviours	Swedish Syndrome support group	Parents completed a questionnaire 'designed for the purpose of capturing specific features relevant to PWS.'	Prevalence reported based on 'tantrums including violent acts against persons, for example, hitting, kicking, spitting or pinching'.	Rated between 'once a year' to ''once a week"	20.6 years (12-30)	37	**49%**
PWS	Holland et al., (2003)	To report the behavioural differences between PWS and learning disabilities, and the prevalence of these behaviours.	Research database and Syndrome support group	Informant based interviews utilising a diagnostic checklist to establish the presence/absence of clinical characteristics	Prevalence reported based on 'definite or some violent or aggressive outbursts'	Not given	20.8 years	91	**73%**
PWS	Hartley et al., (2005)	To further define significant differences in maladaptive behaviours among the typical deletion and UPD subtypes of PWS, and determine if subject characteristics are significant correlates.	Not given	Parents completed The Reiss Screen for Maladaptive Behaviour (RSMB)	Prevalence reported based on 'Aggressive behaviour' subscale score being above the clinically significant range.	3 months	23.81 years (12-45)	1. 65 (total) 2. 41 (deletion) 3. 23 (UPD)	1. **39.7%** 2. **47.5%** 3. **26%**

Table 1 – *The prevalence of aggression in genetic syndromes*

	Author	Study Aims	Recruitment	Method	Definition used to report prevalence of aggression	Time period	Mean Age (Range)	N	Prevalence
PWS	Hiraiwa et al., (2007)	To test whether behavioural and psychiatric disorders intensified with age in PWS	Japanese Syndrome support group	Parents completed a questionnaire asking whether their child had showed a number of behavioural problems	Prevalence reported based on the number of informants answering 'yes' to "Has your child shown aggressive behaviour in the last five years"?	5 years	**(**2-31) years	165	**32%**
PWS	Arron et al.,(2011)	To examine the prevalence and associated characteristics of self injurious and aggressive behaviour in seven genetic syndromes.	Syndrome support group	Parents completed The Challenging Behaviour Questionnaire (CBQ)	'Physical aggression' (e.g. punching, pushing, kicking, pulling hair, grabbing other's clothing).	1 month	17.04 years	571	**43 %**
WS									
WS	Gosch & Pankau (1997)	To determine whether individuals with WS show differences in aspects of personality and rates of behavioural problems at different ages.	Syndrome Association National Conference and German Syndrome support group	Parents completed the Child Behavior Checklist (CBCL)	Prevalence reported based on number of informants who endorsed 'hits others'	6 months	169.7 months (27-424)	105	**6.7%**
WS	Sarimski (1997a)	To explore the behavioural phenotypes of three genetic syndromes	German Syndrome support group	Parents completed The Society for the Study of Behavioural Phenotypes Postal Questionnaire	Prevalence reported as 'physically aggressive' but exact SSBPQ items used were not specified.	Not given	74.4 months	35	**8.6%**

Table 1 – *The prevalence of aggression in genetic syndromes*

	Author	Study Aims	Recruitment	Method	Definition used to report prevalence of aggression	Time period	Mean Age (Range)	N	Prevalence
WS	Papaeliou et al., (2011)	To provide a comprehensive account of the behavioural profile of Greek young children with WS	Not given	Parents completed the Child Behavior Checklist (CBCL)	Prevalence reported based on the 'Aggressive behaviour' domain score being in the 'borderline or clinical range'. The CBCL Aggressive Behaviour domain includes various constructs including: arguing, meanness, destruction of property and jealousy.	6 months	61.5 months	20	**15%**
DS									
DS	Collacott et al., (1998)	To examine the behavioural characteristics of a substantial and unselected cohort of adults with DS.	National Health Service Records, Social Services, & Care Homes	Parents responded to the Disability Assessment Schedule (DAS) Interview.	Prevalence reported as 'aggression' but exact DAS items used were not specified.	Not given	37.14 years	360	**8.6%**
DS	Tyrer et al., (2006)	To report on the prevalence of physical aggression towards other people in adults with LD living in Leicestershire	Leicestershire LD Register	Parents responded to the Disability Assessment Schedule (DAS) Interview.	Prevalence reported based on if respondent reported aggression was 'severe & occurred frequently (> 3 times a week)' or was 'severe in nature but occurred less frequently'; or considered to be 'less severe but occurred frequently (> three times a week)'.	12 months	Not given as DS included as part of larger study	502	**6.0%**
DS	Dykens et al., (2002)	To examine age-related changes in the maladaptive behaviour of children and adolescents with DS.	Syndrome support group & clinic for people with DS.	Parents completed the Child Behavior Checklist (CBCL)	Prevalence reported as 'engaging in physically aggressive acts' but exact CBCL items used were not specified.	6 months	9.74 years	211	**12%**

Table 1 – *The prevalence of aggression in genetic syndromes*

	Author	Study Aims	Recruitment	Method	Definition used to report prevalence of aggression	Time period	Mean Age (Range)	N	Prevalence
DS	Van Gameren-Oosterom et al., (2011)	To investigate the development, problem behaviour, & health-related quality of life in a sample of Dutch children with DS at the age of 8 years old.	Dutch Syndrome support group	Parents completed the Child Behavior Checklist (CBCL)	Based on the 'Aggressive behaviour' domain being in the 'clinical range'. The Aggressive Behaviour domain includes various constructs including: arguing, meanness, destruction of property and jealousy.	6 months	8.14 Years (7.8-9.1)	325	**4.4%**
DS	Hattier et al., (2012)	To investigate the effects of diagnostic group and gender on challenging behaviours in infants and toddlers with cerebal palsy, DS, or seizures	Via an early intervention project	Parents responded to the Baby and Infant Screen for Children with Autism Traits- Part 2 (BISCUIT)	Prevalence reported based on number of informants who endorsed 'physically cruel to people or animals'	Not given	Not given as DS included as part of larger study	27	**3.7%**

1.4.1. Comparison of prevalence across genetic syndromes.

Figure 4 presents a visual representation of the prevalence rates reported for each syndrome group. Median values and number of studies per group are also displayed. The highest prevalence rate was reported for CdCS at 88% and the lowest rate was for DS at 3.7%.

The prevalence rates for aggression in DS and WS are consistently low. For these two groups, prevalence estimates cluster closely together and all lie below 15%, with median values of 8.6% and 6% for WS and DS respectively. These results are perhaps unsurprising given that the research literature for these two groups suggests that challenging behaviour does not constitute part of the behavioural phenotype (Dykens, 2003; Dykens, 2007). However, when compared to the prevalence rates for total population studies of around 20% noted in the introduction, it seems that there may be something that protects these groups against aggression. In contrast, the prevalence rates reported for the other syndrome groups include very high estimates. Although the highest estimate of 88% is reported in CdCS; the SMS, FXS, AS, CdLS, and PWS groups all have high end estimates above 70%. When these high end estimates are compared to the estimates reported for DS and WS and the generally accepted estimate of 20% in total population studies, it seems that the prevalence of aggression is higher in these groups. However, the range of estimates for these groups is very large. Not only does this variability make it difficult to ascertain the degree to which aggression is associated with each group, it also makes drawing comparisons between groups difficult. Such variation may result from the wide range of methodological differences that exist between studies.

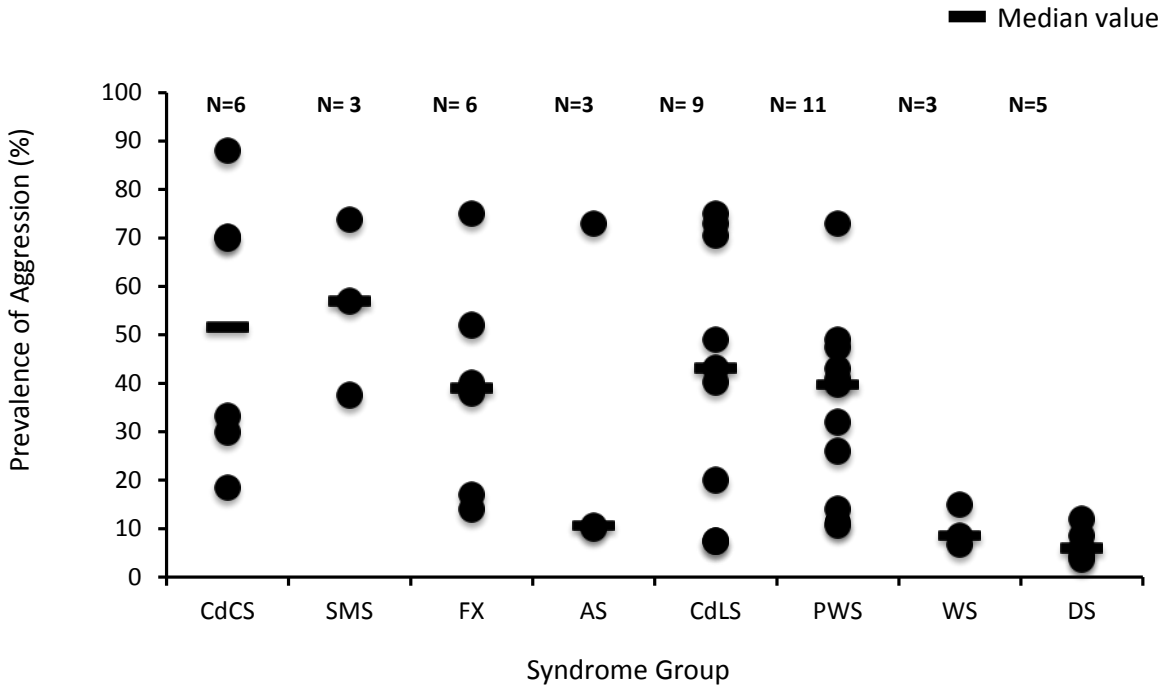

Figure 4: Percentage prevalence rates of aggression across genetic syndromes.

1.4.2. Methodological influences on prevalence estimates.

One of the main methodological issues to consider when evaluating variability in estimates both within and between syndrome groups is 'case' ascertainment. Methods include: a review of case studies, standardised informant questionnaires and interviews, and non standardised questionnaire measures. It is possible that certain methods, such as the Challenging Behaviour Interview (CBI; Oliver et al., 2003) as used by Sloneem et al., (2011) for SMS, may yield larger estimates because it does not constrain parents to report on a predetermined set of behaviours. In contrast, other methods such as a review of case studies as used by Summers et al., (1995) may yield lower estimates. Although case studies can offer important information, it has been suggested that they are often based on global impressions rather than systematic measurement (Dykens, 1995). Summers et al., (1995)

drew attention to this limitation and concluded that behavioural problems may have been under reported due to case studies focussing predominately on diagnostic and management issues.

The definition and time period used for case ascertainment also varies. Across studies, the time periods used vary from 'ever' to 'daily'. The impact of such variation can be demonstrated by considering four of the studies reporting prevalence for CdLS. Both Gualteri (1991) and Berney, Ireland and Burn (1999) used a broad time period when asking about aggression in CdLS ('at any time in the past' and 'at least occasionally' respectively) and produce estimates above 70%. In contrast, Arron et al., (2011) and Hyman, Oliver and Hall (2002) asked whether aggression occurred 'in the last month', and produce estimates below 45%. From these figures, it is easy to see one reason for the variance in prevalence estimates. The use of a broad time period means that less frequent behaviours are also included resulting in higher estimates. Indeed, when Berney et al., (1999) reduced the time period from 'at least occasionally' to 'at least daily', prevalence rates dropped from 75% to 49%.

The definitions used across studies vary widely between structured and clear behavioural descriptions as used by Sloneem et al (2011) for SMS; to the use of subjective statements such as "too physically aggressive" as used by Cornish, Munir and Bramble (1998) for CdCS; or the use of subscales that combine two separate constructs such as the 'aggressive/destructive subscale' used by Collins and Cornish (2002) for CdCS. The use of different definitions has a significant effect on the spread of prevalence rates reported. For example, it could be that some individuals with CdCS in the Cornish et al., (1998) study *did* show aggression but subjectively were not considered as 'too aggressive' and consequently this could yield a comparatively lower prevalence rate. This possibility seems likely given that the same author conducted a similar study four years later (recruiting via the same UK

parent support group) yet reported a much higher prevalence rate when the prevalence was derived from a subscale that combined two separate constructs – aggression and destruction. The issue of subjectivity is also important to consider when interpreting the prevalence rates for AS. The prevalence rate reported by Arron et al., (2011) is approximately seven times higher than the rates reported by the other two studies. This difference is striking but when considered alongside the terms and definitions used by the three studies, highlights an important point. When parents are asked about aggression, it is likely that they typically interpret the term as it is used in common usage, where an intent to harm is implicit. This is particularly relevant in AS where the behavioural phenotype is characterised by a strong desire for adult interaction (e.g. Horsler & Oliver, 2006). Even though forms of aggressive behaviour may be present, parents may often feel that the person they care for does not intend to harm and so do not label these behaviours as aggressive. Such subjectivity does not arise when individual forms of behaviour are specified. Therefore, it is possible that the much higher prevalence rate reported by Arron et al., (2011) results because the Challenging Behaviour Questionnaire (CBQ; Hyman, Oliver & Hall, 2002) defines aggression using specific behaviours and so is not as influenced by inferring intent.

The effect of age, gender and genetic-subtype differences on prevalence estimates within and between studies also requires attention. Evidence suggests that these factors are related to the prevalence of aggression and therefore should be considered when interpreting the estimates provided in this review. More specifically, care should be taken when generalising from the prevalence rates reported in Table 1.

The studies in the review differ widely with regard to the age range of recruited participants. Some studies recruit children only whereas others recruit across the lifespan. This is relevant as it been suggested that aggression increases with age until mid-adulthood in people with ID (Davies & Oliver 2013). Similarly, evidence suggests aggression may

differ across ages within syndrome groups. Arron et al., (2011) found aggression was more likely to occur in younger individuals with CdCS, FXS, and PWS but not in other syndromes. Furthermore, the paper by Hartley, MacLean, Butler, Zarcone and Thompson (2005) suggests that young adults with PWS in their twenties were more likely to show aggressive behaviour than adolescents and older adults, and Hiraiwa, Maegaki, Oka and Ohno (2007) suggest a trend towards more problem behaviours in PWS with age.

Although gender differences for aggression in ID have previously been described (McClintock et al., 2003), the majority of estimates reported in this review are based on mixed gender samples and potential gender differences are not considered. However, the study by Bailey, Raspa, Olmsted and Holiday (2008) for FXS can be used to highlight the importance of considering gender differences. Studies have shown that males and females with FXS can vary widely in the extent of intellectual impairment, with females typically being less severely affected than males (Loesch, Huggins & Hagerman, 2004). Such male-female differences are thought to be due to cellular mosaicism and X inactivation (Migeon, 2006). Although there are no studies with which to compare, the results by Bailey et al (2008) suggest lower rates of aggression in females.

Consideration of the potential impact of within syndrome genetic-subtype differences on aggression is lacking. Although some syndromes in the review arise from various different genetic mechanisms, rates are reported for the entire syndrome group rather than for each genetic-subtype. This is important when considering that phenotypic presentations may differ between genetic-subtypes. For example in AS, emerging evidence suggests that individuals with the paternal UPD may have a milder phenotypic presentation (Bottani et al., 1994). It is currently unclear whether a milder phenotypic presentation might be associated with higher or lower levels of aggression. However, one possibility might be

that higher ability levels could enable an individual to be more physically capable of instrumental aggression.

Another important methodological consideration to note relates to the recruitment methodology used across studies. The vast majority of studies recruit participants via syndrome support groups. It is possible that families and carers are more likely to access support groups and clinics if they care for a person showing challenging behaviour. Therefore, it is possible that the estimates reported in these studies may be elevated and unrepresentative of the wider population of individuals with genetic syndromes. Also, a number of the studies included in the review recruited via the same support groups and therefore the different studies may contain the same participants. This is especially likely in the studies outlining prevalence of aggression in CdCS as all five studies recruited via the same UK syndrome support group.

1.4.3. Comparison of prevalence across syndrome groups.

Implementing a group comparison design can overcome some of the difficulties listed above. At present, only a few studies utilise such a design. Of the 39 studies listed above, only three compared aggression prevalence figures across groups. These studies are listed in Table 2, and provide some insight into which syndrome groups may display comparatively more aggression. Both the studies by Sloneem et al., (2011) and Arron et al., (2011) found aggression was significantly more prevalent in SMS than individuals with mixed aetiological intellectual disabilities (HID). However, some of the results of these studies are inconsistent and without similar studies it remains difficult to draw strong conclusions about the association between aggression and genetic syndromes.

Table 2 - *Studies reporting comparisons of prevalence rates of aggression across syndrome groups.*

Authors	Syndrome specific differences in the prevalence of aggression
Sarimski (1997a)	FXS > PWS, WS
Sloneem et al., (2011)	SMS > HID
Arron et al., (2011)	AS, SMS > HID = CdCS, CdLS, FXS, PWS

1.5. Interim summary

Results of prevalence studies imply that certain syndromes may show a stronger association with aggression than others. However, the review has highlighted how limited the existing literature is for accurately determining the strength of association. Given the importance of the early identification of individuals at increased risk of developing aggression, it is necessary that research moves towards a more consistent approach to examining prevalence. More specifically, as well as the increased use of group contrast designs, it is important to develop consensus on the methodology, definition and time period used when assessing prevalence. Furthermore, it is important to move beyond broad syndrome group descriptions and towards a consideration of age, gender and genetic-subtype differences within groups.

1.6. Form of Aggression and the Influence of Environmental Factors

To identify papers that provided information on the *form* of aggression and\or on the influence of environmental factors in the selected syndromes the initial electronic search was repeated. Any paper that outlined form and/or implicated or discussed the role of environmental factors in the development and/or maintenance of aggression in the syndrome groups was included. Table 3 displays the number of papers that were identified for each syndrome group to investigate these factors.

Table 3 - *The number of papers considered, and the number of papers identified to investigate the form of aggression, and the role of environmental influences for each syndrome group.*

Syndrome (number of papers considered)	Number of papers reporting on the form of aggressive behaviour.	Number of papers reporting the role of environmental influences.
Cri du Chat syndrome (33)	1	0
Smith Magenis syndrome (53)	1	3
Fragile X syndrome (592)	1	1
Angelman syndrome (105)	1	3
Cornelia de Lange syndrome (45)	1	0
Prader-Willi syndrome (315)	0	2
Williams syndrome (325)	0	0

1.6.1. Form.

Additional information regarding form was found for five of the seven syndrome groups reviewed. For AS, Summers et al., (1995) used the Child Behavior Checklist (CBCL; Achenbach & Edelbrock, 1983) and outlined that children were more likely to 'grab at people and things' than they were to 'hit, kick, bite or scratch others'. The Behavior Problems Inventory (BPI; Rojahn, Matson, Lott, Esbensen, & Smalls, 2001) was used in three separate studies to examine the frequency of different forms of aggressive behaviour in FXS, CdLS, and CdCS. Hessl et al., (2008) reported that the most common forms of aggressive behaviour in FXS were hitting others (49%) and kicking others (30%). Rojahn et al., (2012) found that the most frequently endorsed behaviours for CdLS were hitting others (44.4%), and grabbing and pulling others (40.0%); and Collins and Cornish (2002) reported that the most frequent behaviours for CdCS were hitting others (65%) and pulling other's hair (65%). For SMS, Sloneem et al., (2011) used The Checklist for Challenging Behaviour (CCB; Harris, Humphreys & Thomson, 1994) and found that the most prevalent forms of aggression were hitting and grabbing (>80% of participants) as well as biting, kicking and pinching (>50% of participants). Where available, further breakdown of the prevalence for different forms of aggression in these syndromes are shown in Appendix A.

1.6.2. Summary and considerations.

The findings of these papers appear to indicate that for FXS, CdLS, CdCS and SMS, 'hitting others' is a shared common form of aggression, but that these behaviours may be less common in individuals with AS. However, drawing conclusions regarding the form of aggression within syndromes, and making comparisons between syndromes is virtually impossible given the very small number of papers in this area. Furthermore, many of the methodological concerns discussed previously remain. It is clear from this review that further studies, particularly those utilising a group comparison design, are required. In addition to the methodological considerations discussed previously in this review, future work outlining the form of aggressive behaviour in genetic syndromes should consider that the use of standardised measures, such as those used above, may result in idiosyncratic forms of aggression being missed.

1.6.3. Environmental influences.

Despite evidence suggesting that the most successful interventions for challenging behaviour seek to define the cause or function of the behaviour before intervening (Harvey et al., 2009), papers examining the role of environmental factors in the development and/or maintenance of aggression were found for four of the syndrome groups only. An overview of these papers is presented in Table 4.

Table 4 – *Environmental influences on aggression in genetic syndromes*

	Authors	N	Study Aim	Method	Main findings
AS					
AS	Strachen et al., (2009)	12	To examine the hypothesis that aggression in children with AS would occur at a higher rate when social contact is withheld due to an increased propensity to seek out, and interact with others.	Experimental functional analysis	Aggression was shown by 10 children; 1 child showed aggression maintained by attention, 3 children showed aggression during social interaction, and 2 children showed escape motivated aggression. The pattern of results, particularly aggression during social interaction, did not confirm the initial hypothesis. However, the authors argued that evidence of positive affect alongside aggression during the social interaction condition might suggest that aggression serves to both maintain *and* initiate social contact in AS.
AS	Didden et al., (2009)	79	To examine the function of communicative behaviours in 79 individuals with AS.	Indirect functional analysis methodology: The Inventory of Potential Communicative Acts Questionnaire (IPCA; Sigafoos et al., 2000)	Findings indicated that aggression functioned most commonly to 'reject/protest' (28%) and to 'comment' (33%). Based on their findings, the authors suggested that aggression in AS may be maintained by negative reinforcement.
AS	Radstaake et al., (2012)	4	To examine the function of challenging behaviour in 4 children with AS and assess the effects of functional communication training	Experimental functional analysis	All 4 children exhibited aggressive behaviour. Although the specific function varied for each child, the frequency of this behaviour was influenced by environmental variables such as level of attention, access to tangibles, and demand.
FXS					
FXS	Langthorne & McGill (2012)	34	To examine between-syndrome differences in the function of problem behaviour for FXS and SMS.	Indirect functional analysis methodology: The Questions about Behavioral Function Scale (QABF; Matson & Vollmer, 1995)	Findings for FXS showed 6.2% displayed attention-maintained aggression, 46.9% tangible maintained, 59.4% escape maintained, 21.9% discomfort related, and 3.2% self stimulatory. Together with findings for the function of self-injurious behaviour and destructive behaviour, the authors concluded that children with FXS may be more likely to display 'escape' or 'tangible maintained' problem behaviours than 'attention maintained' behaviours.

Table 4 – *Environmental influences on aggression in genetic syndromes*

	Authors	N	Study Aim	Method	Main findings
SMS					
SMS	Taylor & Oliver (2008)	5	To examine the association between problem behaviour in SMS and environmental events indicative of social reinforcement processes.	Sequential analysis of observational data	All participants exhibited aggressive/disruptive behaviour. Results indicated that for 2 (out of 4 participants for whom analysis was possible) aggressive/disruptive was significantly associated with low levels of adult attention. Together with results for self-injury the authors concluded that preference for adult contact and challenging behaviour in SMS, may illustrate a potential phenotype-environment interaction.
SMS	Sloneem et al., (2011)	28	To investigate the prevalence and phenomenology of aggressive behaviour in SMS. Also, as previous studies have suggested that people with SMS may have a propensity to seek adult contact, to examine the association of aggression with environmental events.	Indirect functional analysis methodology: The Questions about Behavioral Function Scale (QABF; Matson & Vollmer, 1995)	Findings indicated that, for the whole group, the 'attention' subscale of the QABF yielded the highest mean score for physical aggression. The authors consequently argued that it is likely that operant factors play a role in the development of aggression in SMS. Furthermore, the authors discuss that results of 'attention maintained' aggression are consistent with reports that people with SMS have a preference for adult contact. Findings replicate and extend the study by Taylor & Oliver (2008).
SMS	Langthorne & McGill (2012)	25	To examine between-syndrome differences in the function of problem behaviour for FXS and SMS.	Indirect functional analysis methodology: The Questions about Behavioral Function Scale (QABF; Matson & Vollmer, 1995)	Results indicated that 62.5% of participants with SMS met criteria for attention-maintained aggression and 70.8% also met criteria for physical-discomfort related aggression. Taken together with findings for the function of self-injurious behaviour and destructive behaviour, the authors concluded that problem behaviours in SMS may serve multiple functions.
PWS					
PWS	Woodcock et al., (2009a)	46	To investigate the context of specific profiles of repetitive behaviour associated with PWS and FXS.	Semi-structured interviews that focussed on behavioural and environmental contexts.	Findings indicated that anger/aggression was seen in 71.1% of individuals with PWS following changes to routines or expectations. The authors argued that a decrease in predictability is aversive to children with PWS and thus may trigger aggressive outbursts.
PWS	Woodcock et al., (2009b)	28	To extend previous findings (Woodcock et al., 2009a) by examining the relationship between preference for predictability and executive dysfunction in individuals with PWS and FXS.	Cognitive assessments of executive functioning and informant questionnaires.	Findings indicated an attention switching deficit. Furthermore, switch cost was found to be associated with scores on questionnaire items relating to preference for routine and predictability. Together with previous findings the authors hypothesised that changes to routine may trigger aggressive outbursts in PWS because a decrease in predictability is aversive due to an underlying deficit in attention switching.

1.6.4. Summary and considerations.

Surprisingly few papers were found that examined the influence of environmental factors on aggression. However, findings from the papers listed in Table 4 all implicate the importance of environmental factors and suggest that aggression may be mediated by different environmental influences for different groups. Furthermore, some findings point towards an interaction between phenotypic characteristics and environmental influences. For example, it was found that a desire for adult attention in SMS and AS (Sloneem et al., 2011; Strachen et al., 2009; Taylor & Oliver, 2008) and a preference for predictability in PWS (Woodcock et al., 2009a; Woodcock et al., 2009b) may influence the occurrence of aggressive behaviour in these groups.

Despite these findings, a number of methodological limitations relating to the assessment of behaviour need to be taken into consideration before drawing conclusions. Different methods of analysis were used in the studies listed above. Some of the studies examined naturally occurring antecedents and consequences through observational data, rating scales, or interviews, whereas others used experimental methods of functional analysis. These different methods give rise to different constraints.

One of the main advantages of experimental functional analysis over other methods is that by experimentally manipulating the antecedents or consequences of behaviours, greater control over environmental variables is possible. Conventional experimental functional analysis, as used by Strachan et al., (2009) and Radstaake et al., (2012) in their studies with AS, test the effects of a specific set of establishing operations: levels of social attention, demand, and access to tangibles. However, it is possible that these methods may not provide the scope to identify idiosyncratic or unusual functions. The same difficulty regarding the identification of idiosyncratic or unusual functions arises in the studies by Sloneem et al., (2011) and Langthorne and McGill (2012) who use the Questions about

Behavioral Function Scale (QABF; Matson & Vollmer, 1995) to examine behavioural function indirectly. The QABF is restricted to five predetermined functions and therefore, it is possible that parental responses may not map onto the contingencies that influence the person's behaviour. Therefore, although these studies provide an insight into the behavioural functions of aggression in these groups, a finer grained analysis may be beneficial.

In contrast, the assessments used by Woodcock et al., (2009a) for PWS, and by Taylor and Oliver (2008) for SMS, have the potential of being able to identify such idiosyncratic variables associated with aggression. However, as the authors point out, such assessments are only correlational in nature and do not appraise causality. In these cases, it is important that further studies that experimentally manipulate the antecedents or consequences of behaviours are conducted to validate any conclusions drawn.

1.7. Discussion

The first aim of this review was to examine the extent to which aggression was associated with genetic syndromes. As expected, the prevalence rates for aggression in DS were consistently low (8.6%. 6.0%, 12.0%, 4.4%, and 3.7%). Low prevalence rates were also reported consistently for WS (6.7%, 8.6% and 15.0%). Moreover, when compared against the prevalence rates for aggression in ID reported in the review by Davies and Oliver (2013), it would appear that these groups show less aggression than expected, a phenotypic characteristic that warrants comment and explanation. In contrast, the prevalence rates reported for the other syndrome groups included some very high estimates. The highest estimate of 88% was reported for CdCS, but the SMS, FXS, AS, CdLS, and PWS groups all had high end estimates above 70% suggesting that aggression may feature more prominently in these groups compared to DS and WS.

The prevalence of known correlates of aggression within these syndromes is of interest. Correlates of aggression include characteristics of ASD, reduced communication skills, impulsivity, over-activity, and repetitive behaviour (Arron et al., 2011; Dominick et al., 2007; Kanne & Mazurek, 2011; McClintock et al., 2003). Typically, these behaviours are not frequently noted in DS and WS (Dykens, 2003; Dykens, 2007; Udwin & Yule, 1991) but have been described in the other groups (Arron et al., 2011; Clarke & Boer, 1998; Clark & Marston, 2000; Collins & Cornish, 2002; Dykens & Cassidy, 1995; Dykens & Kasari, 1997; Einfield, et al., 1999; Finucane et al., 1994; Hagerman, 2002; Hatton et al., 2002; Moss et al., 2011; Sullivan et al., 2006; Summers & Feldman, 1999; Van Buggenhout et al., 2000). Consequently, it might be that these groups share common characteristics that increase their risk of developing aggression.

The review drew attention to the impact that methodological differences between studies may have had on the variation of prevalence rates. Many of the studies utilised different assessment methodologies which in turn, resulted in a number of different definitions and time periods being used to derive estimates. One way to overcome some of these difficulties, and allow for comparisons to be drawn between syndrome groups, is through the implementation of group comparison designs. However, the current review highlighted that, at present, very few studies that document aggression in genetic syndromes have utilised such a design. Consequently, the results of this review demonstrate that future research that assesses the prevalence of aggression in genetic syndromes should be conducted in a more consistent way with group contrast designs. This is particularly important given that although estimates did vary widely, high rates of aggression were reported for CdCS, SMS, FXS, AS, CdLS and PWS. Accurate identification of individuals at increased risk of developing aggressive behaviours requires that these prevalence rates, and hence relative risk, are established more accurately.

The second aim was to further delineate aggression by examining the form of aggression in the groups and the influence of environmental factors. Examination of the literature indicated that very few studies had moved beyond broad prevalence estimates of aggression to examine the behaviour in more detail. For the studies that had, drawing strong conclusions was made difficult by a number of methodological limitations and the lack of comparable studies that replicated results.

One overarching difficulty that was demonstrated both in studies exploring prevalence, and those exploring form and environmental influences, was the lack of emphasis many studies placed on examining gender, genetic-subtype or age differences. Studies have demonstrated that, in at least some groups, age, gender and subtype factors are important to consider when examining aggression (Arron et al., 2011; Bailey et al., 2008; Bottani et al., 1994; Hartley et al., 2005; Loesch et al., 2004). Accurate identification of individuals at increased risk of developing aggressive behaviours requires that any potential differences relating to age, gender or genetic-subtype are explored further.

Although methodological limitations clearly impact on the strength of the conclusions that can be drawn from the existing literature in this area, this review has highlighted a number of important points. A substantial research literature highlights the importance of environmental factors and operant learning in the development and maintenance of challenging behaviours such as aggression (e.g. Marcus, Vollmer, Swanson, Roane, & Ringdahl, 2001). However, there is also evidence that biological and genetic factors play an important role (e.g. Arron, et al., 2011; Langthorne & McGill, 2012; May et al, 2009). The current review points towards the necessity to integrate these two models. More specifically, biological models and genetic factors alone are insufficient to account for aggression in genetic syndromes as this would predict no within syndrome variability and no effect of operant processes on behaviour. Yet, methodological limitations aside, the

current review has highlighted within syndrome variability and has also outlined a number of papers demonstrating the effect of operant processes on aggression in genetic syndromes (e.g. Langthorne & McGill., 2012; Sloneem et al., 2011; Strachan et al., 2009). Similarly, environmental factors and operant theory alone are insufficient to account for aggression in genetic syndromes as this would predict that prevalence rates would be equal across groups (because environmental influences are consistent across groups). Yet, prevalence estimates and group comparison designs suggest that some syndrome groups may display comparatively more aggression than others (e.g. Arron et al., 2011; Sarimski, 1997; Sloneem et al., 2011).

Instead, this review points towards the importance of phenotype-environment interactions in the development of aggression in genetic syndromes. More specifically, the review reports papers that begin to describe phenotype-specific characteristics which lead to an increased motivation or predisposition, which is then sensitive to environmental factors and operant processes. For example, in the study by Strachan et al., (2009) examining aggression in AS, it was suggested that a genetic predisposition to seek out and interact with adults, may underpin aggression if attention is presented contingent on this behaviour. Similarly, the studies examining the function of aggression in SMS, suggest that aggression may function to elicit attention as a result of an accentuated preference for adult contact (Langthorne & McGill, 2012; Taylor & Oliver, 2008; Sloneem et al., 2011). Furthermore, the review has highlighted papers that begin to describe syndrome-specific cognitive characteristics which may lead to a predisposition to find particular situations aversive. For example, the studies examining aggression in PWS suggest that changes to routine may trigger aggressive outbursts because a decrease in predictability is aversive. It is hypothesised that such difficulties are underpinned by an underlying executive function deficit in task switching/mental flexibility (Woodcock et al., 2009a, 2009b). Overall, these

papers emphasise the importance of building causal models of aggression that take into consideration the interaction between person characteristics and environmental factors (see Oliver et al., 2013, for further discussion)

With phenotype-environment interactions in mind, a comparison of the form of aggression across groups warrants further attention. Closer examination of the form of aggression may provide insight into the underlying predisposition or motivation for the behaviour. Given findings from papers examining function, it is interesting that the most common forms of aggression in FXS were 'hitting and kicking others' whereas, in AS the most common forms were 'grabbing and pulling'. More specifically, papers examining function demonstrated that children with FXS were more likely to display 'escape' or 'tangible maintained' aggression (Langthorne & McGill, 2012) whereas for AS, it has been hypothesised that aggression may function to maintain social contact (Strachan et al., 2009). It could be considered that 'grabbing and pulling' would be more effective to prolong social contact whereas 'hitting and kicking' would be more effective to 'escape'. Although it is important to stress that findings of the current review are limited due to the extremely small number of studies conducted that outline both form and function, the findings highlight the importance of looking beyond broad behavioural phenomenology and towards a more detailed study of behavioural characteristics.

Such findings relating to the role of phenotype-environment interactions have important clinical implications. Intervention strategies to reduce aggression in individuals with genetic syndromes may be enhanced by shifting focus away from the behaviour, and towards the underlying motivation or predisposition that is sensitive to operant reinforcement. For instance, for PWS, cognitive training, or interventions that make change less unexpected, may be beneficial. Furthermore, methodologies used in the assessment of aggression, should incorporate designs that not only determine environmental influences but

also investigate whether a specific motivation of predisposition is driving the behaviour. For example, an additional assessment of social motivation for individuals with AS, may provide important additional information to inform intervention.

An interesting observation that arose from this review, was the striking lack of information regarding aggression in ID and genetic syndromes when compared to the parallel literature documenting self-injurious behaviour. In the self-injury literature there are numerous reviews, papers outlining the early development of self-injury, predicted persistence, assessment and intervention, and models (e.g. Carr, 1977; Deb, 1998; Emerson, 1991; Emerson et al, 2001; King, 1993; Oliver, 1995; Oliver, Hall & Murphy, 2005; Rojahn, Schroader & Hoch, 2007). Furthermore, it has been noted that aggression *is* present in other syndromes such as Rett Syndrome (RS) (Naidu et al., 1990) and Lesch-Nyhan syndrome (LNS) (Schretlen et al., 2005) but studies have yet to delineate this aggression or document the extent to which it is associated with these groups. One explanation for this disparity is that aggression is overlooked in some syndromes because other, more prominent features take precedence. For LNS, this might be the extremely high rate of very severe self-injury, or in RS, the characteristic hand stereotypies. However, this would not explain why generally, there is a smaller body of research outlining aggression in ID and genetic syndromes. Another explanation could be that aggression might be perceived as a more 'understandable' or typical behaviour than self-injury and thus has not prompted the same level of interest or enquiry. For example, it is perhaps easier to see the potential reasons for why a person with an ID might be aggressive, than to see the reasons for self-injury. Although a body of research has investigated causal attributions about challenging behaviour in people with ID (e.g. Hastings, Reed & Watts, 1997), it would be informative to examine whether people's attributions or understanding of challenging behaviours differ for the different types of behaviour.

In summary, this paper has highlighted important directions for future research. Accurate identification of individuals at risk of developing aggression requires that research is conducted in a more consistent and robust way, comparing directly across groups. The impact of age, gender and genetic-subtype differences on aggression should also be explored. Future work on the assessment and intervention of aggression, should consider the importance of phenotype-environment interactions and finally, attention should be paid to the possible reasons why aggression has received comparatively less attention to the examination of self-injurious behaviour in genetic syndromes.

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Running Head: Challenging Behaviour in PMS

VOLUME I

CHAPTER TWO

EMPIRICAL PAPER: CHALLENGING BEHAVIOUR IN PHELAN-MCDERMID SYNDROME

Abstract

To date, no research has examined the presence of challenging behaviour in Phelan-McDermid syndrome (PMS). However, characteristics noted in the syndrome include known risk markers for challenging behaviour. In this paper, study one adopts a questionnaire methodology to delineate the prevalence and aetiology of challenging behaviour in thirty participants with PMS. Study two adopts an interview methodology to examine the form, frequency, severity, and function of this behaviour in eighteen participants.

Responses to the Challenging Behaviour Questionnaire indicated that, thirteen (43.3%) participants with PMS showed self-injurious behaviour, thirteen (43.3%) showed physical aggression, and twenty (66.7%) showed destruction of property. Examination of associated characteristics indicated that self-injury was associated with impulsivity; aggression was associated with younger age and compulsive behaviour; and destruction of property was associated impulsivity and stereotyped behaviour. Between group comparisons indicated that the presence of challenging behaviour in PMS is broadly comparable to other groups of known genetic aetiology with similar levels of ability.

In study two, responses to the Challenging Behaviour Interview highlighted multiple topographies of challenging behaviour. The behaviour of most concern typically occurred every fifteen minutes. Examination of behavioural function showed that self-stimulation was the predominant function for self-injury and destruction of property. However, many behaviours were found to serve multiple functions.

The results of this paper emphasise the importance of building causal models of challenging behaviour that incorporates both person characteristics and environmental factors. Limitations and areas for future research are discussed.

2.1 Challenging Behaviour in Phelan-McDermid Syndrome.

There is a robust literature that highlights the importance of environmental factors and operant learning in the development and maintenance of challenging behaviour (e.g. Marcus, Vollmer, Swanson, Roane, & Ringdahl, 2001). It has been demonstrated repeatedly that such behaviours can be sensitive to, and maintained by socially, and non-socially mediated forms of reinforcement such as attention or the presentation of tangible items from carers (Carr & Durand, 1985); removal of task demands (Iwata, Pace, Kalsher, Cowdery, & Cataldo, 1990); pain (Courtemanche, Shroder, Sheldon, Sherman & Fowler, 2012) or sensory stimulation (Lovass, Newsome, & Hickman, 1987; Rincover, 1978). Functional analytic methodologies have been widely adopted to identify the contingencies that maintain challenging behaviour. Hanley, Iwata and McCord (2003) found that 514 out of 536 datasets depicting the results of functional analyses evidenced mediation by operant reinforcement. Additionally, it has been argued that the most successful interventions aim to examine the function of behaviour, before intervening (Harvey, Boer, Meyer, & Evans, 2009).

Despite a large body of supporting literature, the operant model alone cannot fully account for all empirical observations of the development and maintenance of challenging behaviour. Research in the field of behavioural phenotypes has implicated a role for biological factors in challenging behaviour. Studies have demonstrated that certain syndrome groups have a higher prevalence of challenging behaviours than other groups. Arron, Oliver, Moss, Berg and Burbridge (2011) demonstrated that self-injury was more prevalent in Cornelia de Lange, Cri du Chat, Fragile X, Prader Willi, Lowe and Smith Magenis syndromes than a comparison group of individuals with intellectual disability of heterogeneous aetiology. Furthermore, the prevalence of aggression was found to be heightened in individuals with Angelman and Smith-Magenis syndromes. Other studies in

this area have demonstrated that specific profiles of challenging behaviour differ across genetic syndromes. For example, the behavioural phenotype of Prader-Willi syndrome includes an increased propensity towards temper outbursts (Clarke, Boar, Chung, 1996) and skin picking (Dykens & Kasari, 1997; Greenswag, 1987; Whitman & Accardo, 1987).

Research has also indicated that some person characteristics are associated with challenging behaviour. More specifically, challenging behaviours are associated with degree of disability, gender, autism spectrum disorder (ASD), stereotyped and repetitive behaviours, and the presence of ADHD or ADHD-type behaviours such as over activity and impulsivity and more transient characteristics such as low mood (Arron et al., 2011; Bodfish et al., 1995; Cooper et al., 2009a,b; McClintock, Hall & Oliver, 2003; Powell, Bodfish, Parker, Crawford & Lewis, 1996; Rojahn, Matson, Naglieri, & Mayville, 2004; Hayes, McGuire, O'Neill, Oliver & Morrison, 2011; Hill & Furniss, 2006).

A synthesis of these bodies of literature suggests that both environmental and organic factors play a role in the development and manifestation of challenging behaviour with research into genetic disorders indicating phenotype-environment interactions. For example, Taylor and Oliver (2008) outlined how a genetic predisposition in Smith-Magenis syndrome to interact with adults may underpin aggression if attention is presented contingent on this behaviour (see Tunnicliffe and Oliver, 2011 for a review of phenotype-environment interactions).

Further examination of environmental determinants, person characteristics, and the identification of individuals at increased risk of developing challenging behaviours is important. The presence of challenging behaviour can impact significantly on the wellbeing of individuals and their carers, contribute to the breakdown of residential placements, lead to exclusion and the need for costly services (Hastings, 2002; Olsson & Hwang, 2001; Schwartz, 2003; Tausig, 1985;). Identifying individuals at risk for challenging behaviour,

for example by establishing relative risk within syndromes, will enable the implementation of early intervention strategies. Furthermore, research in this area will add to the understanding of the aetiology of challenging behaviours within genetic syndromes and extend existing generic models. Although the list of genetic syndrome groups known to be associated with challenging behaviour is growing (e.g. Arron et al., 2011), no studies have specifically examined the presence or phenomenology of challenging behaviour in Phelan-McDermid syndrome.

2.1.1. Phelan-McDermid Syndrome.

Phelan-McDermid syndrome (PMS; 22q13 deletion syndrome), is a rare genetic syndrome caused by disruption of chromosome region 22q13.3 (Phelan et al., 2001). Approximately 80% of cases result from an interstitial or terminal deletion involving 22q13.3, and approximately 20% result from unbalanced chromosomal translocations or other structural rearrangements (Phelan, Stapleton & Rogers, 2010). These abnormalities predominately involve haploinsufficiency of the *SHANK3* gene (Phelan & McDermid, 2011).

The syndrome is characterised by neonatal hypotonia, moderate to profound intellectual disability, absent or severely delayed speech, and normal to accelerated growth (Phelan et al., 2001; Phelan & McDermid, 2011). Behavioural characteristics have not been studied extensively but autistic-like behaviour, sleep difficulties, decreased pain perception, and stereotyped behaviours such as hand flapping and rocking have been noted (Havens, Visootsak, Phelan & Graham, 2004; Luciani et al., 2013; Phelan, 2008; Phelan et al., 2001; Philippe et al., 2008). Chewing and mouthing of non-food items has been described repeatedly and are reported to occur in approximately 70% of individuals (Havens et al., 2004; Phelan, 2008; Phelan et al., 2001; Philippe et al., 2008). To date, there has been no

research that specifically examines the presence of challenging behaviours in PMS. However, aggression has been described briefly (Luciani et al., 2003) and Shaw, Rahman, & Sharma (2011), using the Children's Interview for Psychiatric Symptoms (ChIPS; Weller, Weller, Fristad, Rooney & Schecter, 2000), reported that 45.7 % of 35 parents/carers endorsed the item 'is irritable or aggressive'.

Given that the syndrome is associated with known risk markers for challenging behaviour (i.e. presence of intellectual disability, stereotyped behaviour, autism spectrum disorder) it is important to examine further the challenging behaviour in this group. The first aim of this paper is to delineate the prevalence, phenomenology, and associated characteristics of challenging behaviour in PMS using both within and between group analyses (Study One). The second aim of the paper is to further delineate challenging behaviour in PMS through closer examination of the form, frequency and severity of the behaviour (Study Two). Finally, drawing from the operant literature, the third aim of the paper is to examine the potential role of environmental influences on these behaviours (Study Two).

2.2. Study One

2.3 Overview

This study employs a matched group design and questionnaire methodology to examine the prevalence, phenomenology and associated characteristics of challenging behaviour in PMS.

2.4. Method

2.4.1. Recruitment.

Parents and carers of individuals with PMS were contacted for participation via the syndrome support group, UNIQUE. 85 individuals were contacted, and 36 participants responded (return rate of 42.4%).

2.4.2. Participants

All participants had received a diagnosis from a Clinical Geneticist, Paediatrician, Neurologist or General Practitioner. Data on participants were excluded from the study if more than 25% of information was missing from any questionnaire. Individuals under the age of four were also excluded as one measure was not appropriate for young children. Following exclusion, 30 participants with PMS were included in the study.

Matched groups of individuals with Angelman syndrome (AS; N=30), Cornelia de Lange syndrome (CdLS; N=30) and Autism Spectrum Disorder (ASD; N=30) were drawn from the existing database of an ongoing study investigating behavioural difference in rare genetic syndromes and neurodevelopmental disorders (Burbidge et al., 2010; Moss, Oliver, Arron, Burbidge, & Berg, 2009; Oliver, Berg, Moss, Arron & Burbidge, 2011). These comparison groups were selected as the degree of intellectual disability in these groups is broadly comparable to that of PMS[1]. Participants were matched for chronological age (+/- 2 years), and self-help score (+/- 2 scores; derived from the Wessex Scale: Kuschlick et al., 1973). Self-help scores were employed as an indicator of degree of disability. The demographic characteristics of the matched groups are displayed in Table 5. Of the 120 participants included in the study, 60 (50.0%) were male; 33 (27.5%) were able or partly able[2]; 68 (56.7%) were fully mobile; and 58 (48.3%) were verbal. 86 (71.1%) of the group had normal vision; and 99 (82.5) had normal hearing[3]. The mean age of the group was 12.17 years (SD: 12.17; Range; 4.02-45.33).

[1] Full details regarding the recruitment methodology and response rate for these groups can be found in: Burbidge et al., (2010); Moss, Oliver, Arron, Burbidge, & Berg (2009); and Oliver, Berg, Moss, Arron & Burbidge (2011).

[2] Scoring six or above on the self help subscale of the Wessex Scale (Kuschlick et al. 1973). The self-help score is derived from summing three items regarding independent feeding, washing and dressing. Items are scored from one to three resulting in a total score ranging between three and nine.

[3]Information regarding mobility, verbal ability, vision, and hearing was derived from the Wessex Scale (Kuschlick et al. 1973)

Table 5: *Participant characteristics. Mean age (standard deviation) and range, percentage of males, and percentage of participants who were able, mobile, and verbal in each group. Percentage of participants with normal sight and hearing, and mean SCQ total score (standard deviation) and range.*

		Syndrome group				Chi –square / Kruskal-Wallis*			Post Hoc <.05
		PMS	**AS**	**ASD**	**CdLS**	**df**	X^2	**P value**	
N		30	30	30	30				
Age[a]	Mean (SD)	12.11 (8.23)	12.32 (9.31)	11.91 (8.12)	12.27 (8.24)	3	0.127*	.988	-
	Range	4.34-37.77	4.05-45.33	4.08-39.67	4.02-38.64				
Gender	Male	13	11	24	13	3	13.97	.003	ASD>PMS,AS,CdLS
	(%)	(43.3)	(36.7)	(80.0)	(43.3)				
Self help[b]	Partly able/able[c]	8	6	10	9	3	1.46	.691	-
	(%)	(26.7)	(20.0)	(33.3)	(30.0)				
Mobility[b]	Fully mobile	22	12	23	13	3	12.50	.006	ASD,PMS>AS,CdLS
	(%)	(73.3)	(40.0)	(76.7)	(43.3)				
Vision[b]	Normal	23	24	27	12	3	21.91	p<.001	ASD,AS,PMS>CdLS
	(%)	(76.7)	(80.0)	(90.0)	(40.0)				
Hearing[b]	Normal	27	30	27	15	3	30.65	p<.001	ASD,AS,PMS>CdLS
	(%)	(90.0)	(100.0)	(90.0)	(50.0)				
Speech[b]	Partly verbal/verbal	11	12	23	13	3	12.37	.006	ASD>AS,PMS,CdLS
	(%)	(36.7)	(40.0)	(76.7)	(43.3)				
SCQ Total Score[d]	Mean (SD)	22.39 (6.52)	16.74 (5.46)	26.78 (4.69)	22.33 (6.23)	3	35.92*	p<.001	ASD>AS,CdLS,PMS
	Range	2.00-35.00	6.00-30.00	18.00-34.00	6.00-31.00				CdLS,PMS>AS

Groups: PMS = Phelan McDermid syndrome; AS = Angelman syndrome; ASD = Autism Spectrum Disorder; CdLS = Cornelia de Lange syndrome.

[a] In years (decimal)

[b] data derived from the Wessex Scale (Kushlick et al. 1973)

[c] Those scoring six or above on the self help subscale. Self-help score is derived from summing three items regarding independent feeding, washing and dressing. Items are scored between one and three resulting in a total score ranging between three and nine.

[d] data derived from the Social Communication Questionnaire (SCQ; Berument, Rutter, Lord, Pickles & Bailey 1999).

2.4.3. Measures.

Questionnaires included measures developed for use with individuals with intellectual disabilities. These included[4] a demographic questionnaire, the Wessex Scale (Kuschlick et al., 1973), the Challenging Behaviour Questionnaire (CBQ; Hyman, Oliver & Hall, 2002); the Social Communication Questionnaire[5] (SCQ; Rutter, Bailey, Lord, & Berument, 2003), the Mood Interest and Pleasure Questionnaire – Short form (MIPQ-S; Ross, Oliver & Arron, 2008), The Activity Questionnaire (TAQ; Burbidge & Oliver, 2008; Burbidge et al., 2010), and the Repetitive Behaviour Questionnaire (RBQ; Moss & Oliver, 2008; Moss, Oliver, Arron, Burbidge & Berg, 2009).

2.4.3.1. Demographic questionnaire.

The demographic questionnaire obtains information regarding date of birth, gender, mobility, verbal ability and diagnosis.

2.4.3.2. Wessex Scale (Kuschlick et al., 1973.)

The Wessex Scale is used to assess ability in children and adults with intellectual disabilities. Five subscales measure continence, mobility, self help skills, speech and literacy. In this study, the scale was used to establish the degree of disability of participants. The scale has good inter-rater reliability at subscale level for both children and adults (Kushlick et al., 1973; Palmer & Jenkins, 1982).

[4] As this paper is part of a wider study examining behaviour in PMS, other questionnaire measures were also included but will be described elsewhere.

[5] The CdLS and AS groups completed an earlier version of the SCQ (Autism Screening Questionnaire; Berument, Rutter, Lord, Pickles & Bailey, 1999). However, one item (item 20: social chat) differs for non verbal individuals between the ASQ and the SCQ. Consequently, to ensure consistency, this item was treated as a missing item and prorated for all nonverbal participants. A mean item score was calculated based on the other completed items of the communication domain. This method has been used previously (Moss, Oliver, Nelson, Richards & Hall, 2013) and current analysis indicated that the use of this prorated item did not impact on the between group differences in SCQ scores.

2.4.3.3. The Challenging Behaviour Questionnaire (CBQ; Hyman et al., 2002).

The CBQ determines the presence or absence of self-injury, physical aggression, destruction of property and stereotyped behaviour over the preceding month. The measure, adapted from Bodfish et al., (1995) also examines eight topographies of self-injury. The psychometric properties of the measure indicate good inter-rater reliability (Kappa value=.92; Hyman et al., 2002).

2.4.3.4. Social Communication Questionnaire (SCQ; Rutter, Bailey, Lord, & Berument, 2003).

Based on the Autism Diagnostic Interview, the SCQ was developed as a tool for screening for ASD in children and adults. The measure contains 40 items grouped into three subscales: Communication; Social Interaction; and Repetitive and Stereotyped patterns of behaviour. The SCQ shows good concurrent validity with the Autism Diagnostic Interview and the Autism Diagnostic Observation Schedule (Howlin & Karpf, 2004). Internal consistency is good (α = .90 for the total scale; Berument, Rutter, Lord, Pickles & Bailey, 1999)

2.4.3.5. Mood, Interest and Pleasure Questionnaire Short-form (MIPQ-S; Ross, Oliver & Arron, 2008).

The MIPQ-S is used to assess affect. Informants rate 12 items on five point Likert scales based on their observations over the previous two weeks. The MIPQ-S yields an overall score and two subscale scores – 'Mood' and 'Interest and Pleasure'. Low scores correspond to low mood, interest and pleasure. The measure has good internal consistency (Cronbach's alpha coefficients: total = .88, Mood = .79, Interest and Pleasure = .87) and good test-retest and inter-rater reliability, with Kappa values of .97 and .85 respectively.

2.4.3.6. The Activity Questionnaire (TAQ; Burbidge & Oliver, 2008; Burbidge et al., 2010).

The Activity Questionnaire (TAQ) assesses overactive and impulsive behaviours. The measure contains eighteen items that comprise three subscales: Overactivity, Impulsivity and Impulsive Speech. Inter-rater reliability for verbal and non verbal participants is .74 and .78 respectively. Test-retest scores for verbal and non verbal participants are .88 and .94 respectively. Overall internal consistency is .94.

2.4.3.7. The Repetitive Behaviour Questionnaire (RBQ; Moss & Oliver, 2008; Moss et al., 2009).

The Repetitive Behaviour Questionnaire (RBQ) assesses repetitive behaviour. Five subscales are formed from 19 items rated on a four point Likert scale ranging from 'never' to 'more than once a day'. Subscales measure compulsive behaviour, insistence on sameness, restricted references, stereotyped behaviour, and repetitive speech. Examination of the psychometric properties of the RBQ has indicated good inter-rater and test-retest reliability (Moss et al., 2009).

2.4.4. Procedure

Participants were sent a covering letter, consent form, information sheet, and questionnaire pack (see Appendix B-E). To avoid priming, the study was entitled 'Understanding behaviour in people with neurodevelopmental disorders'. Participants returned their completed consent forms and questionnaires in prepaid envelopes. Ethical approval to conduct this study was obtained from the University of Birmingham's Science, Technology, Engineering and Mathematics Ethical Review Committee (see Appendix M).

2.4.5. Data Analysis

Data were inspected for normality using Kolmogorov-Smirnov tests. Where data were not normally distributed ($p<.05$), non parametric tests were used. To examine differences in demographic characteristics between groups, Kruskal-Wallis tests were employed for ordinal data and Chi-square statistics for categorical data. To compare the prevalence of challenging behaviours in PMS to the comparison groups, the percentage of each group showing self-injury, physical aggression and destruction of property was obtained from the CBQ. Chi square statistics were employed to examine differences in prevalence. To examine variables associated with challenging behaviour in PMS, participants with PMS who showed self-injury, aggression and/or destruction of property were compared with participants with PMS who did not show these behaviours. Mann-Whitney U tests were employed for ordinal data and Chi-square for categorical data. Due to the clinical significance of identifying risk and risk markers appropriately, p levels of less than .05 were adopted to avoid making Type 2 errors.

2.5. Results

2.5.1. Demographic characteristics

Table 5 displays the demographic characteristics for each group. Between group analyses indicated that participants in all four groups were matched for age and ability. However, significant group differences were found for gender, mobility, hearing, speech and SCQ total score. Post-hoc comparisons revealed that, as expected, the ASD group contained a higher proportion of male participants (Fombonne, 2003). Individuals with CdLS evidenced poorer hearing and vision than all other groups; and the ASD group showed greater levels of speech than all other groups. Individuals with CdLS and AS were

less mobile than individuals with PMS and ASD. With regard to SCQ total score, the ASD group had higher scores than all other groups, and the CdLS and PMS groups had higher scores than the AS group.

2.5.2. Prevalence of challenging behaviour

Analysis of the total sample indicated that 68 (56.7%) participants showed self-injury, 65 (54.2%) showed physical aggression; and 75 (62.5%) showed destruction of property. The proportions of participants showing these behaviours within each group are displayed in Table 6. Chi-square comparisons showed significant differences between groups for physical aggression [X^2 (3) = 15.94, p=.001], but not for self injury [X^2 (3) = 5.70, p=.127], or destruction of property [X^2 (3) = .68, p=.879]. Post hoc comparisons for physical aggression indicated that AS and ASD groups showed significantly more physical aggression than the PMS and CdLS groups.

Table 6: *The percentage of self-injurious behaviour, physical aggression and destruction of property shown by each group.*

	Self-injurious behaviour	Physical aggression	Destruction of property
Syndrome Group	Frequency (%)	Frequency (%)	Frequency (%)
PMS (n = 30)	13 (43.3)	13 (43.3)	20 (66.7)
AS (n = 30)	16 (53.3)	22 (73.3)	17 (56.7)
ASD (n = 30)	17 (56.7)	21 (70.0)	19 (63.3)
CdLS (n = 30)	22 (73.3)	9 (30)	19 (63.3)

Groups: PMS = Phelan-McDermid syndrome; AS = Angelman syndrome; ASD = Autism Spectrum Disorder; CdLS = Cornelia de Lange syndrome

Different topographies of self-injury were examined and prevalence rates are presented in Table 7. For individuals with PMS who showed self-injury, the most common topographies were biting self (46.2%) and rubbing/scratching self (38.5%). Chi-square comparisons between groups revealed a significant difference for the topography 'hit self with body' [X^2 (3) = 11.89, p=.008]. Post hoc comparisons (p<0.05) indicated that the ASD group were more likely to show this topography than the CdLS, AS and PMS groups. No significant differences between groups were found for the other topographies of self-injury.

Table 7: *Topographies of self-injury shown by each group*

	Topography Frequency (%)						
Syndrome Group	Hits self with body	Hits self against object	Hits self with object	Bites self	Pulls self	Rubs/ scratches self	Inserts
PMS (n = 30)	3 (23.1%)	3 (23.1%)	3 (23.1%)	6 (46.2%)	4 (30.8%)	5 (38.5%)	4 (30.8%)
AS (n = 30)	6 (37.5%)	5 (31.3%)	2 (43.8%)	7 (43.8%)	3 (18.8%)	3 (18.8%)	2 (6.7%)
ASD (n = 30)	14 (82.4%)	4 (23.5%)	5 (29.4%)	5 (29.4%)	7 (41.2%)	5 (29.4%)	2 (11.8%)
CdLS (n = 30)	11 (50.0%)	10 (45.5%)	4 (18.2%)	11 (50.0%)	9 (42.9%)	6 (27.3%)	8 (36.4%)

Groups: PMS = Phelan-McDermid syndrome; AS = Angelman syndrome; ASD = Autism Spectrum Disorder; CdLS = Cornelia de Lange syndrome

2.5.3. Predictors of challenging behaviour in Phelan-McDermid syndrome

To detect possible predictors of challenging behaviour in PMS, comparisons were made between PMS participants who showed self-injury, aggression and destructive behaviour and those that did not. Results are displayed in Table 8. Participants with PMS who showed self-injury had significantly higher Impulsivity scores (z = -2.26; p=.022) than

participants who did not show self-injury. Participants who showed physical aggression were younger (z=-2.07; *p*=0.39) and had significantly higher Compulsive behaviour scores (z=-2.52; *p*=0.02) than those who did not show physical aggression. Finally, participants who showed destruction of property had significantly higher Impulsivity scores (z=-2.60; *p*=.008) and significantly higher Stereotyped behaviour scores (z=-2.08; *p*=0.39).

Table 8: *Differences in demographic characteristics, hyperactivity, affect, repetitive behaviours, and autism spectrum characteristics shown by participants with PMS showing and not showing self-injury/physical aggression/destruction of property.*

Measure	Subscale	Self-injurious behaviour	Physical Aggression	Destruction of Property
DQ	Age	--	+	--
	Gender	--	--	--
WESSEX	Self help	--	--	--
	Mobility	--	--	--
	Vision	--	--	--
	Hearing	--	--	--
	Speech	--	--	--
TAQ	Impulsive	+	--	++
	Overactive	--	--	--
MIPQ	Mood	--	--	--
	Interest & Pleasure	--	--	--
RBQ	Stereotyped behaviour	--	--	+
	Compulsive behaviour	--	+	--
	Insistence on sameness	--	--	--
SCQ	Communication	--	--	--
	Repetitive behaviour	--	--	--
	Socialisation	--	--	--

-- no significant differences between scores for individuals with PMS showing/not showing self-injury/physical aggression/destruction of property
+ ,++ significantly higher scores for individuals with PMS showing self-injury/physical aggression/destruction of property : + at the $p<.05$ level; ++ at the $p<.01$ level.
For age, + significantly younger at the $p<.05$ level
DQ= The Demographic Questionnaire ; WESSEX = The Wessex Scale ; TAQ = The Activity Questionnaire; MIPQ = Mood, Interest and Pleasure Questionnaire; RBQ = Repetitive Behaviour Questionnaire; SCQ = Social Communication Questionnaire.

2.6. Interim Summary

Study one found that self-injury, physical aggression and destruction of property was shown by 43.3%, 43.3% and 66.7% of the PMS group respectively. When compared to the other groups, PMS showed comparatively less aggression than the AS and ASD groups. The most common topographies of self-injury in PMS were 'biting self' and 'rubbing/scratching self'. Group comparisons indicated that the ASD group were more likely to show the topography 'hits self with body' than the PMS, CdLS and AS groups. Examination of predictors of challenging behaviour in PMS indicated that self-injury was associated with impulsivity; aggression was associated with younger age and compulsive behaviour; and destruction of property was associated with impulsivity and stereotyped behaviour.

2.7. Study Two

2.8. Overview

This study uses interview measures to further delineate challenging behaviour in PMS by examining the form, frequency, and severity of the behaviour and the potential role of environmental influences.

2.9. Method

2.9.1 Recruitment

In study one, 28 participants with PMS were identified as showing challenging behaviour[6] (either self-injury, physical aggression or destruction of property), 23 of these participants were contacted to participate in study two[7]. Participants were sent an invitation letter, information sheet and consent form (see Appendix F-H). Fourteen participants

[6] This includes 4 participants who were excluded from the analysis of study 1 because they were under 4 years or had more than 25% of information missing from any questionnaire.

[7] Four participants were not contacted as they were aged over 16 years. Ethical approval for study two limited participation to individuals under 16 years of age. One participant was not contacted as they had not granted permission to be contacted regarding future research.

responded yielding a return rate of 60.9%. Additional participants who showed challenging behaviour but had not participated in study one were recruited via the syndrome support group, UNIQUE. UNIQUE disseminated a recruitment flyer (Appendix I) and seven people who expressed interest in the study were sent a recruitment pack. Four of these individuals responded, yielding a return rate of 57.1%. A total of 18 participants were included in study two.

2.9.2. Procedure and Measures

Following receipt of consent forms, participants were interviewed by telephone interview. Interviews involved completion of the measures listed below and lasted approximately two hours (see Appendix J). For four participants, the interview was split into two sessions. Ethical approval was obtained from the University of Birmingham's Ethical Review Committee (see Appendix M).

2.9.2.1. The Vineland Adaptive Behavior Scale Survey Edition (VABS; Sparrow, Balla, & Cicchetti, 1984)

The VABS was utilised to describe participants' adaptive functioning. The VABS derives four subscales (communication, daily living, socialisation, and motor skills) from 383 items, scored between 0 (never) and 2 (usually). An optional maladaptive behaviour domain is included in the interview but was not used in the current study as these behaviours were assessed by other means.

2.9.2.2. Challenging Behaviour Interview (CBI; Oliver et al., 2003)

The CBI is a two-part interview that assesses the incidence and severity of challenging behaviour in people with intellectual disability. In part one, respondents

identify topographies of behaviour displayed in the last month. In part two, the severity of the behaviour is determined by totalling the responses from fourteen questions asking about certain characteristics of the behaviour such as frequency, duration, and necessary response. The authors report good inter-rater, test-retest reliability and content validity.

All topographies of behaviour that a carer deemed challenging were included. Part two of the CBI was then conducted in relation to up to four of these topographies. When children demonstrated more than four topographies of challenging behaviour, parents/carers ordered the behaviours in terms of severity and/or frequency (i.e. which behaviours they perceived as being of the most concern), then the 'top four' behaviours were selected. A breakdown of the different topographies of challenging behaviour recorded in part two of the CBI are provided in Appendix K)

2.9.2.3. Questions about Behavioral Function (QABF; Matson & Vollmer, 1995)

The QABF is a 25 item measure used to assess factors that maintain challenging behaviour. Each item is rated on a four point Likert scale from zero (never) to three (often) and summary statistics are then generated for five functional categories (attention, escape from demand, self-stimulation, physical discomfort, and tangible). The measure is reported to have good reliability predictive and convergent validity (Nicholson, Konstantinidi, & Furniss, 2006; Paclawskyj, Matson, Rush, Smalls, & Vollmer, 2000; Matson, Bamburg, Cherry & Paclawskyj, 1999; Paclawskyj, Matson, Rush, Smalls, & Vollmer 2001).

2.9.2. Participants

Table 9 presents information regarding age, gender, and adaptive functioning (calculated from the VABS II, Sparrow, Cicchetti & Balla, 2005) of the group. All eighteen

participants were classified as having a low level of adaptive functioning as calculated from the Adaptive Behavior Composite score.

Table 9: *Information regarding the age, gender and adaptive functioning of the group*

		PMS (n=18)
Age (in years)	Mean (SD)	7.52
	(SD)	(3.72)
	Range	2.67 - 14.83
Gender	Male (%)	50
Adaptive behaviour		
	Communication (SD)[1]	46.89 (9.22)
	Daily Living Skills (SD)[1]	49.11 (8.60)
	Socialisation (SD)[1]	51.78 (8.50)
	Adaptive Behavior Composite (SD)[1]	48.17 (8.01)

[1]Standard scores from VABS II (Sparrow, Cicchetti & Balla, 2005)
PMS = Phelan-McDermid syndrome

2.9.3. Data Analysis

When interpreting the QABF, Matson and Vollmer (1995) state a clear function is considered when there is an endorsement (scoring 1 or above) of at least four or five items on one QABF subscale, with no other subscales containing 'significant' endorsements. However, various approaches to the analysis of the QABF have been used (Applegate, Matson, & Cherry, 1999; Langthorne & McGill, 2012; Matson & Boisjoli, 2007). For the initial QABF analysis, the method used by Matson & Boisjoli (2007) was employed, so that multiple functions could be identified. Any subscale score greater than six (ratings of 0-3 across five items, maximum score 15) was identified as a maintaining variable. Behaviours with more than one subscale scoring greater than six were identified as having multiple

functions. To assess possible differences between the functions of each form of behaviour, total function scores for each form of behaviour were analysed using repeated measures ANOVAs with 'function' as a within subjects factor.

2.10. Results

2.10.1. Form, frequency and severity of challenging behaviour in Phelan-McDermid syndrome.

Based on responses to the CBI, of the eighteen participants, twelve (66.6%) displayed four or more topographies of challenging behaviour; five (27.8%) displayed two or three topographies and only one (5.56%) displayed only one topography of challenging behaviour. Part two of the CBI was completed on a total of 66 behaviours. Self-injurious behaviour accounted for nineteen of the behaviours (28.8%); physical aggression accounted for eighteen of the behaviours (27.3%); destruction of property accounted for fourteen of the behaviours (21.2%) and PICA accounted for four of the behaviours (6.1%). Eleven of the behaviours (16.7%) were other forms of challenging behaviour such as smearing or inappropriate vocalisations. A further breakdown of the different topographies of challenging behaviour is provided in Appendix K. As described previously, when children demonstrated more than four topographies of challenging behaviour, parents/carers were asked to order the behaviours in terms of severity and/or frequency (i.e. which behaviours they perceived as being of most concern). For the behaviour rated as of most concern, the modal frequency was five, meaning that most participants showed this behaviour at least every fifteen minutes. For the behaviours rated as second and third most concerning, the modal frequency was three, meaning most participants showed these behaviours at least daily.

To test for differences in severity between the behaviours ordered in terms of concern by parents, a repeated measures ANOVA with a single within-subjects factor (total severity score) was conducted for the twelve participants who displayed four topographies of behaviour. Findings indicated that there was a significant main effect of severity between the behaviours ($F_{2,19} = 5.873$, $p = .013$). Post Hoc, Bonferonni adjusted pairwise comparisons indicated that the behaviour rated first (of most concern) was significantly more severe than the behaviours rated as second [$t(11) = 4.75$, $p = 0.01$); third [$t(11) = 6.83$, $p = 0.007$] and fourth [$t(11) = 6.83$, $p = 0.02$]. No significant differences were found in severity for behaviours rated as second, third and fourth concern.

2.10.2. Function of challenging behaviours in Phelan-McDermid syndrome.

The QABF was completed for the 66 behaviours identified by the CBI. For these 66 behaviours, 4 (6.1%) did not meet criteria for function; 36 served a single function (54.5%), 13 served two functions (19.7%) and 13 served three or more functions (19.7%). Figure 5 shows the percentage of behaviours[8] that met criteria for each subscale score of the QABF for the three most common classes of challenging behaviour - Self-injury (SIB); Aggression (PAG); and Destruction of property (DST)[9]. This figure also shows the proportion of these behaviours that served single vs. multiple functions. For SIB and DST, the most frequently endorsed function was self stimulation. For PAG, the most frequently endorsed function was attention.

[8] Percentage of behaviours was derived rather than percentage of participants as some participants showed more than one topography of self-injury, aggression, or destruction of property.
[9] Other classes of challenging behaviour were not included due to small N.

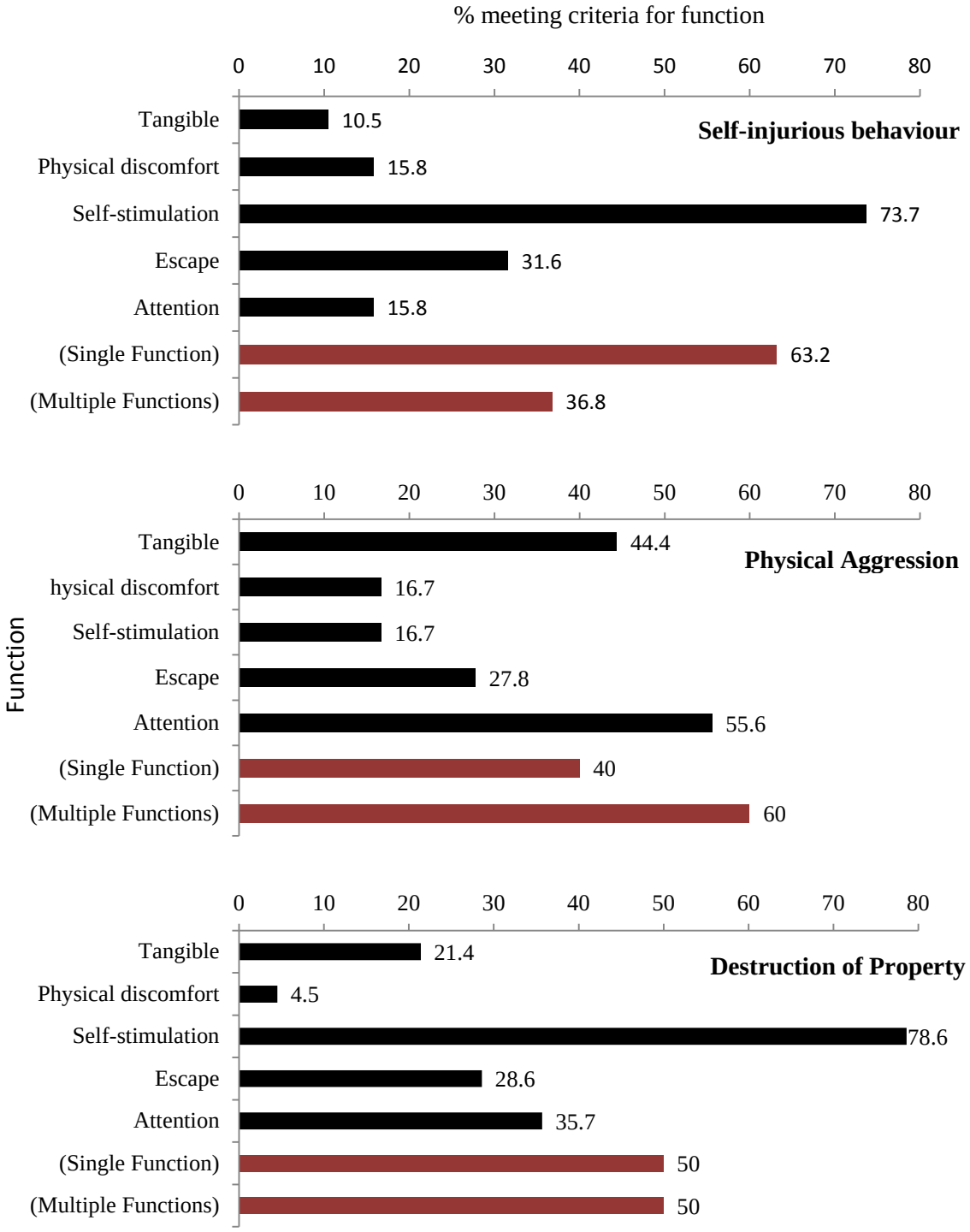

Figure 5. The percentage of behaviours that met criteria for each subscale of the QABF, and the percentage of behaviours that served single vs. multiple functions, for self-injury, aggression, and destruction of property.

Table 10 displays the mean total function scores for SIB, PAG and DST. A series of repeated measures ANOVAs with a single within-subjects factor (function sub-scale) was conducted, to test for differences between the functions of each form of behaviour. Findings indicated that there were significant main effects of function for self-injury ($F_{2,35}$ = 9.16, p=.001) and destruction of property ($F_{2,28}$ = 5.41, p=.009). There were no significant main effects of function for aggression (F2,42 = 2.80, p>.05). Post Hoc, Bonferroni adjusted pairwise comparisons indicated that significantly more self-injury was related to a self-stimulatory function than attention [t (19) = 7.58, p<0.001]; physical discomfort [t (19) = 7.37, p = 0.004]; and tangible function [t (19) = 7.00, p=0.015]. Significantly more destruction of property was related to a self-stimulatory function than physical discomfort [t (13) = 7.36, p=0.02].

Table 10: *Mean total function scores derived for the three most common classes of behaviour.*

	Subscale				
	Attention	Escape	Self-stimulation	Physical Discomfort	Tangible
SIB (n= 19)	2.32 (3.13)	4.37 (5.73)	9.89 (5.12)	2.53 (3.37)	2.89 (4.34)
PAG (n=18)	6.78 (4.80)	4.17 (5.33)	3.94 (2.80)	2.44 (3.31)	5.28 (5.22)
DST (n=14)	4.36 (5.53)	4.00 (5.66)	10.07 (4.90)	2.17 (3.97)	3.14 (4.87)

Data presented as mean (standard deviation)
SIB = Self-injurious behaviour; PAG = Physical Aggression; DST = Destruction of Property

2.11. Interim Summary

Virtually all participants showed multiple topographies of challenging behaviour with the most common forms being self-injury and aggression. The behaviour rated as being of most concern to carers typically occurred at least every 15 minutes. This behaviour was also rated as significantly more severe than other behaviours. Behaviours rated as second and third most concerning typically occurred at least daily. Examination of function indicated that more self-injury was related to a self-stimulatory function than an attention, physical discomfort or tangible function. Similarly, more destruction of property was related to a self-stimulatory function than a physical discomfort function. Although the most frequently endorsed function for aggression was attention, statistical analysis did not indicate any differences between the different possible functions.

2.12. Discussion

Study one examined the prevalence, phenomenology, and associated characteristics in the group using both within and between group analyses. A strength of the study is that the use of standardised, valid measures along with the inclusion of comparable contrast groups enabled the consideration of the specificity of findings to those with PMS. Study two further delineated challenging behaviour by using standardised measures to assess frequency and severity of behaviour and the potential role of environmental influences on these behaviours.

Prevalence findings indicated that 43.3% of the PMS group showed self-injurious behaviour; 43.3% showed aggression; and 66.7% showed destruction of property. The most common topographies of self-injurious behaviour in the group were biting self (46.2%) and rubbing/scratching self (38.5%). Although no prevalence estimates of self-injurious behaviour or destruction of property have been previously reported in the literature, the

prevalence of aggression is comparable to the 45.7% reported by Shaw et al., (2011). Furthermore, although not previously described with reference to self-injurious behaviour, the finding that the most common topography of self-injury was 'biting self' is consistent with the numerous reports of frequent mouthing and chewing behaviours in the group (Havens et al., 2004; Phelan et al., 2001; Phelan & McDermid, 2011).

Between group comparisons indicated that the PMS and CdLS groups showed comparatively lower rates of aggression than the AS and ASD groups, but no group differences were found for self-injurious behaviour and destruction of property. Such findings are informative as they suggest that the presence of challenging behaviour in PMS is broadly comparable to other groups of known genetic aetiology with similar levels of ability. Despite a small sample size, examination of associated characteristics in PMS indicated that self-injury in the group was associated with higher impulsivity scores; aggression was associated with younger age and higher compulsive behaviour scores; and destruction of property was associated with higher impulsivity and stereotyped behaviour scores. These findings support previous literature that has demonstrated links between challenging behaviour and these factors (Arron et al., 2011; Bodfish et al., 1996; McClintock et al., 2003; Rojahn et al., 2004). It also suggests that challenging behaviour in PMS may share common aetiological pathways with other groups showing similar behaviours.

In study two, findings from the CBI indicated that virtually all children showed multiple topographies of challenging behaviour, with the majority of these behaviours falling within the categories of self-injury, aggression and destruction of property. The behaviour rated as being of most concern to carers typically occurred at least every 15 minutes. This behaviour was also rated by carers as significantly more severe than behaviours rated as second, third and fourth most concerning. Behaviours rated as second

and third most concerning typically occurred at least daily. These findings are clinically relevant as they provide an insight into the degree of difficulty that these behaviours are likely to pose to carers.

The QABF examined the functions that these behaviours served for children with PMS. For both self-injury and destruction of property, the most frequently endorsed function was self stimulation. Analysis of total function scores for these behaviours revealed that significantly more self-injury was related to a self-stimulatory function than an attention, physical discomfort or tangible function; and significantly more destruction of property was related to a self-stimulatory function than a physical discomfort function. Although the most frequently endorsed function for aggression was attention, statistical analysis revealed no significant differences between total function scores. The finding that self-stimulation was the most frequently endorsed function for self-injury and destruction of property implies that these forms of challenging behaviour may be maintained by sensory reinforcement rather than operant functions. However, it is important to note that for these behaviours, significant total score differences were not found between *all* functions. For self-injurious behaviours, 31.6% also reached criteria for an 'escape' function and for destruction of property, 21.4%, 28.6% and 35.7% also reached criteria for 'tangible', 'escape' and 'attention' functions respectively. Therefore, it is possible that these behaviours may additionally serve communicative functions in people with PMS. The finer details of this are worth further consideration and exploration. It is noticeable that a number of the self-injurious and destructive behaviours in children with PMS serve multiple functions. Given the high endorsement of the self-stimulatory function, one possibility is that behaviours may initially enter the children's behavioural repertoires for self-stimulatory purposes but then become sensitive to operant reinforcement processes. Similar pathways have been described in the literature to account for the early development of challenging

behaviours such as self-injury (e.g. Lovaas, Newsome & Hickman, 1987; Murphy & Wilson, 1985; Carr & McDowell, 1980; Guess and Carr, 1991). Consequently, it would be of interest to conduct longitudinal research that examines the developmental pathways of these behaviours in more detail.

The QABF has been used to identify environmental functions for challenging behaviour in other genetic syndrome groups. Langthorne and McGill (2012) used the QABF to examine the function of challenging behaviour in Fragile X (FXS) and Smith Magenis syndromes (SMS), and Didden, Korzilius and Curfs (2007) used the measure to examine skin picking in Prader-Willi syndrome (PWS). The findings from these studies indicate that the function of challenging behaviour differs across groups. Children with FXS were more likely to display escape or tangible maintained challenging behaviours, children with SMS showed more behaviour related to physical discomfort, and for PWS, skin picking was predominately maintained by the non-social functions - sensory stimulation and physical discomfort. Consequently, the findings of the current paper add to this literature and provide further evidence for the importance of examining environmental factors in the development and maintenance of challenging behaviour within genetic syndromes.

2.12.1. Limitations

The findings of the current paper need to be considered alongside methodological limitations. Throughout the paper, alpha values of .05 were adopted to indicate significance. The use of a less conservative p-value increases the chance of making a Type 1 error and therefore it is possible that some of the associations noted may have arisen by chance alone. However, given the clinical significance of identifying risk, risk markers and functions appropriately it was deemed that this was preferable to adopting a more conservative p-value (i.e. .01) where important associations may have been missed as a result of Type 2 errors. Given that the main rationale for examining challenging behaviour in PMS is to

identify increased risk, and subsequently to reduce carer burden, it is of ethical importance to ensure that associations of clinical significance are not missed.

Participants with PMS were recruited via a syndrome support group. It has been suggested that families and carers may be more likely to access support groups if they care for a person showing challenging behaviour. Therefore it is possible that the prevalence rates reported in this paper may be elevated and not representative of the wider population of individuals with PMS as a whole. However, group comparisons remain valid as the matched groups used in this paper were recruited in the same way, resulting in any potential bias being consistent across groups.

Limitations relating to the use of the QABF should also be noted. The QABF is an indirect measure of behavioural function which is restricted to five predetermined functions. It is possible that parental responses may not have mapped onto the exact contingencies that influence the children's behaviours. Consequently other, perhaps more idiosyncratic functions may have been missed. Therefore, although the current paper has provided a useful insight into the environmental determinants of behaviour in PMS, future research is required that adopts more rigorous experimental functional analysis methods and direct observations of function. By experimentally manipulating the antecedents and consequences of behaviours, experimental functional analysis exerts greater control over environmental variables and therefore stronger conclusions regarding function can be made.

2.12.2. Conclusions

Overall, the current paper has emphasised the importance of building causal models of challenging behaviour that take into consideration both person characteristics and environmental factors. The findings of this paper suggest that both these factors may play a role in the development and maintenance of challenging behaviour in Phelan-McDermid

syndrome. However, more research is required to obtain more robust findings and to further tease out the potential intricacies of phenotype-environment interactions for this group.

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Running Head: Executive Summary

VOLUME I

CHAPTER THREE

EXECUTIVE SUMMARY

3.1. Executive Summary

3.2. Overview

Volume I of this thesis was prepared by Laurie Powis for the degree of Doctor of Clinical Psychology at the University of Birmingham. This volume includes two main chapters; a review of the research literature examining aggression in genetic syndromes, and an empirical study investigating challenging behaviour in a rare genetic syndrome called Phelan-McDermid syndrome. This executive summary aims to provide an accessible overview of these two chapters.

3.3. Literature Review

3.3.1. Background

Aggression is a widely recognised problem for individuals with intellectual disability, their families and the services supporting them. However, at the moment there is very little research that compares aggression across genetic syndrome groups. This is important because research suggests that certain syndrome groups may be more likely to show aggression than others. Identifying which groups are at increased risk of developing aggression is necessary because it means that interventions can be introduced early for these groups, before behaviours become established. Therefore, the first aim of the review was to examine the extent to which aggression is associated with genetic syndromes by looking at all the studies that report how common aggression is in these groups. The second aim was to find out more about aggression in these groups by looking at studies that examined the form of behaviour, and impact of environmental influences.

3.3.2. What did the review find?

The review found that certain genetic syndrome groups may be more likely to show aggression than others. However, making accurate comparisons between groups was made difficult by methodological differences across research studies. This means that more research is required before strong conclusions can be made. The review suggests that future research should be conducted in a more consistent and robust way, with an emphasis on group contrast designs. Furthermore, future research needs to take into consideration what impact gender, age, and genetic-subtype differences might have on aggression rates in genetic syndromes.

Although methodological differences between research studies made it difficult to draw strong conclusions regarding the association between aggression and genetic syndromes, the review did highlight some important points. The review showed that both person characteristics and environmental influences play an important role in the development and maintenance of aggression in genetic syndromes. Consequently, it emphasised the importance for researchers and clinicians to consider both of these factors in the assessment and intervention of aggression.

3.4. Empirical Paper

3.4.1. Background

Phelan-McDermid syndrome (PMS) is a rare genetic syndrome, which occurs because a small amount of genetic material on chromosome 22 is missing or damaged. This missing piece of chromosome means that people with PMS have difficulties with their health, behaviour and learning. At the moment, no research has looked at the presence of challenging behaviours such as self-injury, aggression and destruction of property in PMS. This is particularly important because other studies examining PMS have reported

characteristics that we know can increase the risk of a person developing challenging behaviour (e.g. the presence of intellectual disability, autism spectrum disorder, and stereotyped behaviours). Challenging behaviour can have a major impact on the wellbeing of individuals and their families. Therefore, we carried out the current study to find out more about challenging behaviour in PMS. We wanted to see how common challenging behaviour was in PMS, and whether there were particular characteristics that might increase the likelihood that someone with PMS will develop challenging behaviour. Also, for people with PMS who did show challenging behaviour we wanted to find out whether there were any common underlying causes or triggers for these behaviours. We hope that this type information will help professionals develop more timely, and more effective interventions.

3.4.2. What did we do?

We carried out two separate studies. In the first study we contacted the families of 85 people with PMS and asked them to fill out a questionnaire pack. Questionnaires asked about lots of different behaviours including: challenging behaviour, mood, repetitive behaviour (doing things over and over), hyperactivity (always being 'on the go') and autism spectrum disorder-type behaviours. In the second study, we interviewed the families who had reported that the person they cared for showed challenging behaviour. We asked them to tell us more about what the challenging behaviour looked like, how frequently it occurred, and how severe it was. To see whether there were any common underlying triggers for these behaviours we also asked whether the behaviours occurred in particular situations and contexts.

3.4.3. What did the studies find?

In the first study, we collected data for 30 participants with PMS. The average age of these participants was 12.11 years. Results from the questionnaire asking about challenging behaviour showed that thirteen (43.3%) of the participants showed self-injurious behaviour, thirteen (43.3%) showed physical aggression, and twenty (66.7%) showed destruction of property. The most common types of self-injurious behaviour shown by the group were 'biting self' and 'rubbing and scratching self'. We then compared all the different behaviours that were shown by people *with* challenging behaviour to those shown by people *without* challenging behaviour. This comparison indicated that people with PMS who showed self-injurious behaviour were more likely to be impulsive (act without thinking); people with PMS who showed physical aggression were younger, and more likely to show compulsive behaviour ('have to' behaviours); and people with PMS who showed destruction of property were more likely to be impulsive and show stereotyped behaviour (repetitive mannerisms and movements). Finally, we found that the number of people with PMS showing challenging behaviour was similar to other groups of people with similar levels of disability.

In the second study, we collected data for 18 children with PMS. The average age of these children was 7.52 years. Results indicated that virtually all the children in the study showed more than one type of challenging behaviour. The majority of these behaviours fell into the categories of self-injurious behaviour, physical aggression, and destruction of property. However, other behaviours such as PICA (eating inedible objects), smearing of faeces, and inappropriate vocalisations (e.g. screaming) were also described. The behaviours rated by parents 'as of most concern' typically occurred 'at least every fifteen minutes'. When we asked about the situations and contexts that behaviours occurred in, our findings showed that there were many different reasons why someone with PMS might

show challenging behaviour. However, the most common of these reasons was 'self-stimulation' (i.e. because the person enjoys the behaviour or likes the sensation that the behaviour brings.)

3.4.4. What do these findings really mean?

These findings tell us that challenging behaviour is relatively common in people with PMS. This means that we should be aware that people with PMS may benefit from early intervention strategies that aim to reduce behaviours before they become established. As findings showed that self-stimulation was an important factor in the challenging behaviour for many people with PMS, intervention strategies that take this into consideration may be more effective. However, as findings also showed other reasons why someone with PMS might show challenging behaviour, it is important that clinicians undertake a full 'functional assessment' before intervening.

3.4.5. What's next?

As this is the first study to investigate challenging behaviour in PMS it important that further work is conducted to gather more information. Although this study has provided an initial insight, it would be helpful to examine people's challenging behaviour using more robust experimental methods (i.e. observing a person's behaviour directly rather than using interviews).

Appendix A

Prevalence rates of aggressive behaviours in Cornelia de Lange syndrome reported by Rojahn et al. (2013)

Aggressive Behaviour	%
Hitting others	44.4
Kicking others	29.4
Pushing others	31.1
Biting others	26.7
Grabbing and pulling	40.0
Scratching others	22.8
Pinching others	26.7
Spitting on others	9.4

Prevalence rates of aggressive behaviours in Cri du Chat syndrome reported by Collins & Cornish (2013).

Aggressive behaviour	Occurrence (%)	Frequency (%)				
		Less than monthly	Monthly	Weekly	Daily	Hourly
Hitting others with hand or body part	65.2	18.6	6.9	27.9	37.1	9.2
Hitting others with objects	36.4	29.1	16.7	16.7	29.1	8.4
Biting others	45.5	43.5	9.9	36.7	6.6	3.3
Pulling others hair	65.2	20.9	11.7	23.3	37.1	6.9
Scratching others	36.4	20.9	8.2	33.2	29.2	8.4
Pinching others	45.5	16.7	6.6	36.7	33.4	6.6

Prevalence rates of aggressive behaviours in SMS reported by Sloneem et al. (2011)

Aggressive Behaviour	%
Hitting	84
Grabbing	84
Kicking	59
Pinching	59
Biting	50
Pulling hair	41
Using objects as weapons	38
Head butting	31
Choking or throttling	25
Throwing things at people	47
Scratching	28

Appendix K

Topography		N
Self-injurious behaviour		
	Chews/bites self	**8**
	Hits self	**5**
	Scratches self	**1**
	Grinds teeth	**1**
	Pulls own hair	**1**
	Bangs head	**2**
	Hits body against object	**1**
Physical Aggression		
	Hits others	**8**
	Kicks others	**1**
	Pulls other's hair	**4**
	Pokes others	**1**
	Pushes/squeezes others	**2**
	Bites others	**2**
Destruction of Property		
	Chewing objects/clothes	**7**
	Ripping/tearing items	**3**
	Throwing items	**4**
Other		
	Pica	**4**
	Inappropriate vocalisations	**3**
	Running off	**3**
	Throwing self to floor	**2**
	Smearing faeces	**1**
	Verbal aggression	**1**
	Inappropriate removal of clothing	**1**