The assessment and presentation of Autism Spectrum Disorders in Genetic Syndromes: Implications for diagnosis, intervention and understanding the wider ASD population.

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Invited Annotation - Autism Spectrum Disorders in Genetic Syndromes: Implications for diagnosis, intervention and understanding the wider ASD population.

Key Words: autism spectrum disorder, genetic syndromes, behavioural phenotypes

Suggested Running Head: ASD in genetic syndromes

Abstract:

Background: An emerging literature on behavioural phenotypes has highlighted apparent associations between autism spectrum disorders (ASDs) or ASD related phenomenology and a number of different genetically determined syndromes.

Method: A systematic review of the current literature regarding the association with ASD and ASD characteristics was conducted in the following syndrome groups: Fragile X, Rett, Tuberous Sclerosis Complex, Down, Angelman, CHARGE and Phenylketonuria. Specific consideration was given to the role of intellectual disability in assessing the association between ASD and these syndrome groups.

Results: The review highlighted that whilst formal diagnostic assessments may indicate an association between ASD and specific syndrome groups, detailed investigation has revealed subtle but qualitative differences in the presentation of ASD like phenomenology in particular syndrome groups. The degree of intellectual disability of the individual clearly has a role to play with regard to the development and presentation of ASD like characteristics, and caution should be taken when assessing ASD symptomatology in genetically determined syndromes associated with severe intellectual disability. However, degree of intellectual disability cannot solely account for the heightened prevalence of ASD characteristics in some specific syndrome groups.

Conclusions: There is a need for caution in interpreting the significance of superficial similarities between ASD and the behavioural phenotypes of certain genetically determined syndromes.
However, recognition of ASD like characteristics (even where a true diagnosis of ASD may not be relevant) in individuals with genetic syndromes is crucial in ensuring that individuals receive appropriate behavioural management and educational placement. Further research in this field requires fine-grained investigation of behavioural phenomenology within individual syndrome groups.

**Introduction:**

Autism spectrum disorders (ASDs) are classified by DSM-IV-TR (APA, 2000) and ICD-10 (WHO, 1992) as pervasive developmental disorders (PDD) characterised by the presence of three core features: qualitative impairments in communication and in social interaction and the presence of repetitive behaviour and restricted interests. ASDs¹ occur in up to 1% of children in the general population (Baird et al., 2006) and in up to 40% of individuals with intellectual disability (ID; La Malfa et al., 2004).

The specific causes of ASD remain unknown but are largely considered to be genetically linked (Abrahams & Gershwind, 2008). However, whilst a number of chromosomes and genetic loci have been implicated, there is little evidence to suggest that any one of these is solely linked to ASD diagnosis. The large number of identified risk loci has led researchers to suggest that ASD is caused by complex multigenetic interactions rather than simple single gene mutations (Zhao et al., 2007). Recent evidence from a population based study suggests that there may be different aetiological pathways contributing to each of the different diagnostic domains of ASD (Ronald et al., 2006). Some researchers, therefore, consider it to be more helpful to conceptualise the aetiology of ASD in terms of a ‘network’ of dysfunctions that occur on a number of levels, including genetic and neuronal pathways. The underlying aetiology of ASD now appears to be a highly complex process,

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¹ For the purposes of this review the term Autism Spectrum Disorder (ASD) will be employed throughout the text to refer to all conditions classified by the DSM-IV-TR (2000) within the category of Pervasive Developmental Disorder with the exception of Rett syndrome and Child Disintegrative Disorder. When referring to particular studies, the terminology used by the authors of the study will be employed.
involving various genes that effect downstream proteins and neural substrates that subsequently lead to the behavioural manifestations of ASD (Abrahams & Gerschwind, 2008; Belmonte & Bourgeron, 2006; Persico & Bourgeron, 2006). An alternative approach to the multigenetic hypothesis is proposed by Zhao et al. (2007) who suggest that most cases of autism are due to de novo mutations in the paternal germ line which can affect any number of critical loci. It is suggested that de novo mutations may be carried by some protected and asymptomatic individuals, particularly females, who will transmit the mutation in a dominant pattern to male offspring.

There has been an increasing interest in the association between ASD and a number of genetically linked conditions. The presence of ASD or autistic characteristics has been reported in a wide variety of disorders including those with variable aetiology (e.g. anorexia nervosa, Tourette syndrome, ADHD); physical and sensory disorders (cerebral palsy, muscular dystrophy, Leber's congenital amaurosis), and syndromes with a known genetic cause (e.g. Tuberous Sclerosis Complex, Fragile X, Down, Angelman, Coffin-Lowry, Cohen Laurence-Moon-Biedel, Marinesco-Sjogren, Moebius, Rett and Williams syndromes; see Fombonne, 1999; Gillberg & Coleman, 2000 for reviews).

The apparent overlap between various syndromes with known genetic causes and ASD symptomatology clearly has implications with regard to our understanding of ASD at both the behavioural and biological level. Some researchers propose that genetic syndromes may be influential in identifying and understanding the genetic and neural pathways underlying ASD more widely (Persico & Bourgeron, 2006). One suggestion is that although each syndrome may arise from different genetic abnormalities, with multiple molecular functions, the effects of these abnormalities give rise to common effects downstream, in the biological pathway or neural circuits, that result in the presentation of ASD characteristics (Abrahams & Gerschwind, 2008). An alternative stance is proposed by Skuse (2007) who suggests that the list of genetic syndromes with
an apparent association with ASD is growing to such an extent and with such diversity, that these associations are unlikely to provide specific answers with regard to the gene loci and network pathways involved in ASD. In fact, this emergence of association across a range of genetically determined syndromes makes the interpretation and understanding of their significance more complex. Skuse argues that genetic susceptibility for ASD does not manifest in the behavioural phenotype of specific genetic syndromes. Rather, the intellectual disability associated with many genetic syndromes simply increases the risk that ASD or autistic characteristics will be revealed. Skuse suggests that this is due to the fact that impaired intellectual ability diminishes the possibility for cognitive compensation of independently inherited autistic-type traits. In this way, the presence of a genetic syndrome and the associated degree of intellectual disability may simply act as an additional risk marker for ASD characteristics, rather than playing a causal role. According to this model of association we would expect to find that genetic syndromes associated with more severe intellectual disability will be more likely to manifest ASD like symptoms. In the following review, we consider this position in a range of syndrome groups that have been reported to be associated with ASD.

The following annotation is divided into two sections. Section I presents a brief systematic review of the association between ASD and a number of different genetic syndromes. In this section we aim to provide a broad understanding of the nature of the association between ASD and these various genetic syndromes. We also consider the role of intellectual disability in the association between a given syndrome and ASD. Section II focuses on the specific clinical implications of understanding the association between ASD and genetic syndromes in terms of diagnosis and intervention and also the conceptual implications of these associations.

**Section I: The association between ASD and genetic syndromes**
For the purpose of this review a systematic search, using the Web of Science, of papers published since 1970 was conducted. All articles with the terms ‘autism’ OR ‘autistic’ AND each of the different neurodevelopmental genetic syndromes identified as having an association with ASD in the reviews of Gillberg and Coleman (2000) or Fombonne, (1999) were scrutinised. Only papers in which the title indicated an association between ASD and the syndrome concerned were considered. Series of papers involving the same participant samples were counted as a single study. Table 1 summarises the dates/number of articles identified. For some syndromes (eg Klein-Levin, Smith Magenis, Sanfilippo and Steinert’s myotonic dystrophy), although an association with ASD has been suggested, no articles with the words ‘autism’ or ‘autistic’ in the title were identified, hence these are not included in Table 1.

(Insert Table 1 about here)

Based on this search, this section of the annotation focuses first on syndromes in which the association with ASD has been most frequently reported - Fragile X and Rett syndromes and Tuberous Sclerosis Complex. We include here only studies that have employed standardised assessments with good psychometric properties /diagnostic criteria. We then consider several other genetic disorders that have received comparatively less attention in the literature, but where at least five published papers on the association with ASD are described. These include: Down, CHARGE and Angelman syndromes and Phenylketonuria.

1. Fragile X syndrome:

(Insert Table 2 about here)

Fragile X syndrome (FXS) is the most common cause of inherited intellectual disability, occurring in 1 in 3,600 males and 1 in 8,000 females (Cornish et al., 2008). It results from an excess of CGG
trinucleotide repeats on the \textit{FMR1} (Fragile X Mental Retardation-1) gene at location Xq27-3 (Dykins \textit{et al.}, 2000). In FXS males, the degree of intellectual disability is usually reported to be within the mild to severe range while FXS females usually demonstrate a mild degree of learning disability although this can be more severe in a small percentage of females (approximately 25%; Cornish \textit{et al.}, 2008).

Reported prevalence rates of ASD in FXS vary widely from 0 to 60\%, although the most recent estimates from studies conducted between 2001 to date are more consistent, ranging from 21\% to 50\%. The percentage of ASD in females with FXS is lower, between 1 and 3\% (see Table 2). The variation in estimates of ASD among the earlier studies is likely to result from the use of different methodologies and diagnostic criteria; the more consistent findings in recent years are likely to reflect an increased reliability in both ASD diagnosis and genetic testing for FXS. Recent studies report a strong correlation between the associated degree of intellectual disability and, in particular, impairments in verbal skills and the presence of ASD characteristics in FXS (Demark \textit{et al.}, 2003; Kaufmann \textit{et al.}, 2004; Lewis \textit{et al.}, 2006; Loesch \textit{et al.}, 2007). This seems to support Skuse’s suggestion that the severity of intellectual disability increases the risk of ASD symptomatology in genetic syndromes. However, ASD has also been identified in individuals with the pre-mutation FXS with mild cognitive impairments or IQ in the normal range (Hagerman \textit{et al.}, 2005). Dissanayake \textit{et al.}, (20009) report that while individuals with FXS and ASD demonstrate a similar profile of scores on the ADOS (Lord \textit{et al.}, 2000) to individuals with idiopathic ASD, individuals with FXS score significantly lower on tests of performance and verbal IQ. The authors suggest that the common pathway underlying the shared characteristics of FXS and ASD is likely to be neural rather than genetic, in which diverse biological pathways may lead to a common cognitive and behavioural outcome.
Studies that have focused on the specific phenomenology of ASD in FXS have raised doubts about the strength of association. Bailey et al. (2001) and Demark et al. (2003) suggest that severe autism is relatively rare and that a milder presentation of ASD symptomatology is more characteristic of individuals with FXS. Fine-grained analysis has identified specific areas of behaviour which, although they may appear initially to be ASD related, seem to be qualitatively different from the characteristics identified in idiopathic autism. Individuals with FXS are more likely to demonstrate social anxiety, extreme shyness and gaze avoidance alongside seemingly preserved emotion sensitivity and willingness to interact (Cornish et al., 2007; Hall et al., 2006; Lesniak-Karpiak et al., 2003; Roberts et al., 2007; Turk & Cornish, 1998). This profile is somewhat different to the social impairments that are characteristic of idiopathic autism. Moreover, the gaze avoidance and perseverative speech described in FXS are reported to be unrelated to verbal ability or age (in contrast to the autism population) and are more marked in FXS than they are in autism or ‘non-specific’ intellectual disability (Sudhalter et al., 1990). Recent research suggests that in FXS it is the impairments in social interaction that are most likely to contribute to an individual meeting criteria for ASD (Budimirovic et al., 2006; Kaufmann et al., 2004). The developmental trajectory of ASD in FXS is also reported to differ from idiopathic autism and, according to some studies, the rate of autism and social avoidance behaviours increases with age in males with full mutation FXS (Hatton et al., 2006; Roberts et al. 2007). These findings suggest that even when individuals with FXS meet criteria for ASD on autism specific assessments, they may do so for somewhat different reasons to those with idiopathic ASD.

Recent findings also suggest that in addition to subtle differences at the behavioural level regarding apparently shared ASD characteristics in FXS, differences between these two populations may be observed at the level of social-cognition (Cornish et al., 2008). For example, detailed analysis of ToM skills in individuals with FXS with and without ASD and individuals with intellectual disability indicates that, while all three groups seem to perform at a similar level on ToM tasks,
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differences in error patterns suggest that the underlying bases for these deficits are syndrome specific. Grant et al. (2007) reported that impaired false belief reasoning in FXS was downstream of a more primary impairment in working memory in those with and without ASD characteristics. In contrast to individuals with ASD, emotion perception in FXS is reported to be commensurate with overall level of ability (Turk & Cornish, 1998; Wishart et al., 2007).

It is clear that whilst the association between ASD and FXS is considered to be reasonably robust, this may only be evident at the level of overt symptomatology/diagnostic cut-off scores. When the specific profile of behaviours is considered in more detail, those characteristics that initially appear to be autism related, in fact demonstrate qualitative differences with idiopathic autism at both the behavioural and socio-cognitive level. Thus, although individuals with FXS may appear to share a number of core characteristics with individuals with ASD, the underlying aetiological pathways involved may differ between these two disorders (Cornish et al., 2008). The study of ASD characteristics in FXS provides a good example of why careful, detailed assessment and identification of ASD related characteristics is important in order to avoid erroneous conclusions concerning the association between ASD and genetic syndromes.

Summary: FXS is a genetic syndrome associated with mild to severe intellectual impairments. Current estimates suggest that ASD occurs in 21% to 50% of males with FXS, with ASD being more likely to be identified in individuals with a greater degree of intellectual disability. Studies that have considered the phenomenology of ASD in FXS in more detail have identified differences in the nature, quality and development of ASD characteristics in FXS that raise questions regarding the strength of association between these two disorders.

2. Rett syndrome:

(Insert Table 3 about here)
Rett syndrome (RS) is a neurological disorder, predominantly affecting females, occurring in between 1 in 15,000 to 22,800 live female births (Kozinetz et al., 1993). It is caused by mutations on the X-linked MECP2 gene (Amir et al., 1999). In the classic form of RS, development often appears relatively normal for the first six to eighteen months. This is followed by a period of regression resulting in a reduction in head circumference growth, onset of seizures and loss of language and motor skills, leading to severe or profound intellectual and physical disabilities (Nomura & Segawa, 2005). However, there is a range of severity of RS, and some individuals have been reported to retain and develop their language skills further (Kerr et al., 2001; Smeets et al., 2005). These milder cases of RS are more likely to be associated with a slightly different type and location of genetic mutation on the MECP2 gene than those with classic RS (Kerr et al., 2001; Neul et al., 2008; Smeets et al., 2005).

In Rett’s initial account of the syndrome (1966; cited in Van Acker, 1997) ‘autistic-like’ behaviour was noted as being characteristic of the disorder. Subsequently, estimates of rates of ASD in RS range from 25% to 40% and up to 97% in individuals with the preserved speech variant of RS (See Table 3). ASD is also the most common initial misdiagnosis in children with RS, with 18% of individuals being diagnosed with ASD prior to receiving a diagnosis of RS (Young et al., 2007).

The overlap between RS and ASD has previously been considered to be so robust that RS is currently classified as a pervasive developmental disorder alongside autism, according to both the DSM-IV-TR (APA, 2000) and the ICD-10 (WHO, 1992) diagnostic criteria. However, the inclusion of RS within the PDD category is now considered inappropriate by many (Tsai, 1992), due to distinct differences in phenomenology. For example, many (although not all) individuals with RS develop simple speech prior to regression and despite the marked deterioration in social skills, eye contact is often maintained; social impairments and autistic characteristics also tend to improve with age (Nomura & Segawa, 2005). Furthermore, the characteristic repetitive hand movements in
RS are very different to the motor stereotypies observed in individuals with ASD (Howlin, 2002). It is important to ensure that unique syndrome characteristics such as these are not misclassified in assessments of ASD symptomatology. Even when diagnostic criteria for autism are met, individuals with RS demonstrate an atypical profile of phenomenology. They manifest fewer of the core features of autism and are more likely to score on non-autism specific items, such as ‘sleeps too much’, ‘under active’ and ‘unhappy’ (Mount et al., 2003a).

The severity of intellectual disability typically associated with RS also confounds the distinction between ASD and RS. The ability reliably to identify ASD specific impairments in the areas of communication, social interaction and repetitive behaviours becomes far more difficult as the degree of intellectual disability increases (Howlin, 2000). However, Mount et al. (2003b) reported that individuals with RS scored significantly higher on the Autism Behavior Checklist (Krug et al., 1980) than individuals with a matched level of intellectual disability, indicating that ASD characteristics in RS are not solely accounted for by the degree of intellectual disability. Moreover, estimated prevalence rates of ASD characteristics are actually higher in more mildly affected individuals with RS (up to 97%; Zappella et al., 2001; Zappella et al., 1998) although other studies report that these individuals demonstrate good social interaction skills (Kerr et al., 2006).

Summary: Early studies indicated an increased prevalence of ASD in RS and led to the inclusion of RS under the PDD category within DSM and ICD criteria. Recent, more fine-grained assessments suggest that the inclusion of RS in the PDD category is inappropriate. Although the prevalence of ASD in RS is heightened when compared to individuals matched for degree of intellectual disability, and individuals with RS who are more mildly affected have been reported to demonstrate a higher prevalence of ASD characteristics, individuals with RS demonstrate an atypical profile of characteristics compared to those with idiopathic autism.
Tuberous Sclerosis Complex (TSC) occurs in 1 in 6,000 live births (O’Callaghan, 1999) and is caused by a mutation in the \textit{TSC1} (9q34) or \textit{TSC2} genes (16p13; Povey \textit{et al.}, 1994). Mutations in either gene result in dysregulated cell development, giving rise to abnormal tissue growth or benign tumours in the brain, skin, kidneys and heart (Crino \textit{et al.}, 2006). The TSC phenotype is extremely variable with some individuals having only superficial skin problems or mild seizures; others show severe physical effects and profound intellectual disability (de Vries & Howe, 2007).

Autistic-type symptoms in TSC were first noted by Critchley and Earl (1932) who described 29 individuals with impaired social contact, stereotyped behaviours, absent or abnormal speech and social withdrawal. However, it was only after Kanner’s description of autism in 1943 that the behaviours noted by Critchley and Earl were recognised as being characteristic of ASD. Despite these early descriptions, the association between ASD and TSC has only recently been systematically explored. Reported rates of ASD in TSC range from 5% to 89% although the more consistently reported prevalence figures range from 24% to 60% (see Table 4). Although it has been suggested that comorbidity of ASD in TSC is associated with the presence of temporal-lobe tubers (Bolton \textit{et al.}, 2002), not \textit{all} individuals with temporal-lobe tumours meet ASD criteria and this association has not been replicated by others (Asano \textit{et al.}, 2001).

Few studies have considered the phenomenology of ASD in TSC in detail. Smalley \textit{et al.} (1992) reported that individuals with TSC had somewhat higher (though non-significant) scores than individuals with autism on the social and communication domains of the Autism Diagnostic Interview-Revised (ADI-R; Rutter \textit{et al.}, 2003). However, TSC individuals scored significantly lower on the repetitive behaviour domain of this measure. Interestingly, Jeste \textit{et al.} (2008) reported
a global deficit in play skills (assessed by the Autism Diagnostic Observation Schedule; ADOS Lord et al., 2000) in all children with TSC regardless of ASD status, suggesting that deficits in this particular area may be syndrome specific. Moreover, the male: female ratio in TS is reported to be approximately equal (Smalley, 1998; de Vries et al., 2007), in contrast to the much higher proportion of males found in ASD (Baird et al., 2006). Such findings suggest that ASD features in TSC may differ from those identified in idiopathic ASD.

The role of intellectual disability in the association between ASD and TSC is unclear. Earlier studies suggested that the association between ASD and TSC was independent of degree of intellectual disability, with up to 25% of individuals who met autism criteria having an IQ >70. (Harrison & Bolton, 1997; Smalley, 1998). However, more recent studies have identified a greater risk of autism and ASD with increased degree of intellectual disability in TSC (de Vries et al., 2007; Jeste et al., 2008; Wong, 2006). The latter findings are consistent with Skuse’s model of overall increased risk of ASD with increased degree of intellectual disability. Nevertheless, current research indicates that up to 17% of individuals with TSC with an IQ in the normal range are reported to meet criteria for ASD (de Vries et al., 2007; Prather & de Vries, 2004). This is still a heightened rate in comparison to the prevalence of ASD in the general population, suggesting that the degree of intellectual disability associated with TSC cannot solely account for the raised prevalence of ASD in TSC.

Summary: Although research suggests a strong association between ASD and TSC at the diagnostic level, few studies have considered the precise nature of ASD phenomenology in this condition. The degree to which the associated intellectual disability contributes to the association between ASD and TSC is unclear but recent studies indicate that, as is the case with FXS, the prevalence of ASD increases with the degree of intellectual disability.
In the final part of this section, we consider four genetic disorders where the association with ASD has received comparatively less attention within the literature but where at least five published papers on the association with ASD have been identified. Since the evidence concerning their association with ASD is limited, the discussion here includes case-reports and studies that have either investigated the prevalence of ASD or have described ASD-like behaviours within the syndrome. Only studies using standardised assessments and diagnostic criteria are included within the tables.

4. **Down Syndrome:**

Down syndrome (DS) is the most common chromosomal cause of intellectual disability, occurring in approximately 10.3 in 10,000 live births (Bell *et al.*, 2003). Typically, DS is caused by the presence of a full or partial trisomy of chromosome 21, although occasionally an unbalanced translocation involving chromosome 21 has been identified (Dykens *et al.*, 2000). Intellectual disability in DS ranges from mild to severe (Capone *et al.*, 2005).

Previously, the association between ASD and DS was considered to be relatively rare; indeed, there were suggestions that DS might actually be protective against autistic like behaviours (Turk, 1992). However, several case studies have described individuals with DS who also met ASD criteria (Bregman & Volkmar, 1988; Ghaziuddin *et al.*, 1992; Howlin *et al.*, 1995; Wakabayashi, 1979) and recent research indicates that co-morbidity may be more common than previously thought with prevalence rates ranging from 5% to 39% (see Table 5). Difficulties in social-cognition, notably in areas related to ToM and emotion perception have also been reported in some children with DS (Hippolyte *et al.*, 2008; Wishart, 2007; Wishart *et al.*, 2007; Zelazo *et al.*, 1996). Higher rates of impaired social skills have also been reported in family members of individuals with DS and ASD in comparison to individuals with DS without ASD (Lowenthal *et al.*, 2007).
Individuals with DS and ASD are reported to have a greater degree of intellectual disability and higher rates of stereotyped behaviours, hyperactivity and inappropriate speech, than those with DS without ASD (Capone et al., 2005). However, it remains unclear how far the increased severity of intellectual impairment can explain the increased prevalence of ASD symptomatology in this subgroup. Further research is required to investigate the phenomenology of these characteristics in DS more carefully, in order to clarify whether these characteristics are indeed shared, are superficially similar to that of idiopathic ASD or perhaps associated with different underlying aetiologies.

 Insert Table 5 about here

5. Phenylketonuria:
Phenylketonuria (PKU) is a genetic disorder associated with defects in protein metabolism, resulting in an inability to break down the amino acid phenylalanine. PKU occurs in approximately 1 in 10,000 live births (Scriver et al., 1994). Pre/post natal screening has significantly reduced PKU in developed countries and with early diagnosis and a controlled diet the effects of PKU are minimal. However, in cases of late diagnosis, high levels of protein in the diet can produce toxic levels of phenylalanine hydroxylase (PAH) resulting in ID, seizures and many physical difficulties. The majority of individuals with PKU have an IQ within the normal range (Yalaz et al., 2006) although intellectual disability can range from mild to severe, particularly in late diagnosis cases.

Co-occurrence of autism and PKU has been described in several case reports (Chen & Hsiao, 1989; Lowe et al., 1980; Steiner et al., 2007), although the strength of the association is inconsistent and difficult to determine due to significant improvements in early identification and treatment. In a recent study of 243 individuals with PKU, Baieli et al. (2003) reported that autism was only identified (based on ADI-R and Childhood Autism Rating Scale criteria; CARS Schopler et al., 1988) in those with a late PKU diagnosis (2 cases among 35 (5%) late diagnosed individuals). This
is somewhat different to the rate reported by Reiss *et al.* (1986) who suggested that the prevalence of ASD in PKU may be as high as 20%. These discrepancies are likely to be accounted for by the increased availability of early identification methods and treatment. Dennis *et al.* (1999) reported substantial overlap in the cognitive profiles (notably good performance on Block Design and low scores on Comprehension) of individuals with autism and poorly controlled PKU, matched for age and IQ. Those with better controlled PKU did not demonstrate this profile. The link between poor control/late diagnosis PKU and ASD suggests that with improvements in diagnosis and treatment of PKU, the association with ASD will likely decrease (Gillberg & Coleman, 2000). The association between ASD in PKU has important implications for understanding possible underlying factors in the development of ASD. In the case of PKU, the toxic levels of PAH appear to play a significant role in the development of ASD symptomatology. In the wider ASD population, this is unlikely to be a common underlying factor. This suggests that the presence of ASD characteristics may be a common end state of a number of different aetiological pathways.

6. CHARGE Syndrome:

Insert Table 6 about here

CHARGE Syndrome occurs in approximately 1 in 10,000-12,000 live births (Issekutz *et al.*, 2005). The underlying genetic cause has yet to be established although recent studies have identified mutations on the *CHD7* gene (Vissers *et al.*, 2004). The syndrome’s acronym, CHARGE, refers to the characteristic physical deficits: Coloboma of the eye, Heart defects, Atresia of the choanae, Retardation of growth and/or development, Genital and/or urinary abnormalities, and Ear abnormalities and deafness. There is great variability in the presence and severity of these abnormalities. Many children with CHARGE syndrome have IQs in the normal range although intellectual disability can occur.
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The behavioural phenotype of CHARGE has not been widely studied but hyperactivity, obsessions, compulsions and tic disorders have been noted (Kuijpers et al., 2007; Wachtel & Hartshorne, 2006). Autistic like behaviours have been described in several case reports (Davenport et al., 1986; Fernell et al., 1999; Kuijpers et al., 2007; Sabaratnam et al., 2000; Wachtel & Hartshorne, 2006). Larger scale studies suggest that the prevalence of ASD ranges from 15% to 50% (see Table 6).

Information is limited regarding the degree of intellectual disability and sensory deficits associated with CHARGE-ASD co-morbidity. The two cases described by Smith et al. (2005) suggest that ASD is more likely in nonverbal individuals with severe-profound intellectual disability. In a larger study, Hartshorne et al. (2005) found some variability in the severity of autistic symptomatology in comparison to individuals with ASD but the results indicated that the presence of autism characteristics in CHARGE could not be wholly accounted for by the visual and hearing impairments typically associated with the syndrome

7. Angelman Syndrome:

Insert Table 7 about here

Angelman Syndrome (AS) occurs in approximately 1 in 12,000 to 15,000 live births (Clayton-Smith & Pembry, 1992; Kyllerman, 1995) and is caused by maternally inherited anomalies on chromosome 15. Approximately 70% of cases of AS are due to maternal deletions; between 2 and 5% are caused by paternal uni-parental disomy. Approximately 2 to 3% of cases have imprinting defects, including deletions of the imprinting centre, and a further 1% have other unusual mutations on chromosome 15. The remaining 22-25% of individuals with AS have mutations in the UBE3A critical region (Dykens et al., 2000). AS is associated with a severe to profound ID (Peters et al., 2004), poor mobility and communication skills and seizure disorder (Dykens et al., 2000).
Reported prevalence rates of ASD in AS range from 50% to 81% (see Table 7). Inherited duplications involving the chromosomal region 15q11-15q13 (the same region affected in individuals with Angelman and Prader-Willi Syndromes) are among the most commonly reported genetic abnormalities identified in individuals with ASDs and account for 1 to 2% of cases (Abrahams & Gershwind, 2008). Peters *et al.* (2004) reported a significant difference between AS individuals with and without autism, with the former group being significantly more intellectually impaired. Thus, it is possible that, in line with Skuse’s model, the presence of ASD in AS is an artefact of the profound intellectual disability associated with the syndrome. Trillingsgaard and Østergaard (2004) found that individuals with AS and autism were significantly less impaired in areas such as social smile, facial expression directed to others, shared enjoyment in interaction, response to name and unusual interests or repetitive behaviour (all of which are less reliant on developmental level) than individuals with idiopathic autism. Bonati *et al.* (2007) also reported that individuals with AS with better expressive language skills did not meet ASD or autism criteria on the ADOS or ADI-R. These findings indicate that the associated degree of intellectual disability in AS may play a significant role in the association with ASD rather than representing a syndrome specific associated between ASD and AS.

With regard to the profile of ASD behaviours in AS, Walz and Benson (2002) and Walz (2007) found that some of the characteristic features of ASD, such as finger/hand flicking, object spinning, lining up objects, looking through people and lack of affection, were rarely reported in AS. This may suggest that even when individuals with AS meet diagnostic criteria for ASD, the profile of behaviours may be somewhat different to that of idiopathic ASD.

**Summary of syndrome review:**

> Insert Table 8 about here
Table 8 provides a summary of the prevalence figures reported and associated degree of intellectual disability. It is clear that, in each of these syndromes, there is some degree of association with ASD and in many cases heightened prevalence of ASD can be accounted for, to some degree, by associated intellectual disability. In particular, Capone et al. (2005) demonstrate that individuals with DS who meet criteria for ASD have a greater degree of intellectual disability compared to those with DS without ASD. Furthermore, research findings indicate that the association between AS and ASD may be attributed to the degree of intellectual disability associated with this syndrome. Some research studies of FXS and TSC also suggest that individuals who meet criteria for ASD are more likely to be those with more severe intellectual disability (Demark et al., 2003; de Vries et al., 2007; Jeste et al., 2008; Kaufmann et al., 2004; Lewis et al., 2006; Loesch et al., 2007; Wong, 2006), although the findings in these two syndrome groups are inconsistent. However, it is also clear that in many syndromes, particularly those associated with a moderate to mild level of intellectual disability, the associated cognitive impairment cannot solely account for the raised prevalence of ASD. Of the three most commonly researched syndromes, with regard to their association with ASD, (i.e. FXS, RS and TSC) only RS is characterised by severe and profound intellectual disability. TSC and FXS are both associated with a milder degree of intellectual disability and yet the reported prevalence rate of ASD in all three groups is upwards of 15%. The role that the degree of intellectual disability plays in the manifestation of ASD in these syndrome groups is, therefore, unclear and further work is required, particularly in AS and TSC, in order to establish further the specificity of the syndrome-ASD association. It is clearly important that individuals’ degree of intellectual disability be taken into account when considering whether or not they meet diagnostic criteria. This is relevant to both research and clinical assessments of ASD.

A final point to note is that within each of the syndrome groups reviewed above, clinical diagnosis or formal, algorithm based cut off criteria have been used to determine the prevalence or rate of ASD. However, further detailed examination of the specific ASD profile in these syndromes reveals
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a range of similarities and differences in the specific behavioural pattern of ASD within each group. It seems that each syndrome group may have their own, unique, syndrome specific ‘signature’ of ASD characteristics and impairments that are different to those observed in idiopathic ASD. It is these atypical profiles that may prove to be of most importance in further understanding the aetiology of ASD and the conceptualisation of the triad of impairments and the spectrum of autism.

Section II: Diagnostic considerations of differential diagnosis in genetic syndromes and implications for intervention, conceptual and theoretical frameworks

Studies identifying ASD symptomatology in specific genetic conditions have provided valuable information on the behavioural phenotypes of the syndromes described in this review. However, research in this area has also highlighted some important diagnostic, intervention-related and conceptual issues.

**Diagnostic considerations:**

Recent research regarding the boundaries of the autism spectrum has tended to support a continuous severity gradient (Constantino *et al.*, 2004; Ring *et al.*, 2008, Spiker *et al.*, 2002), rather than a clear distinction between “affected” and “non-affected” individuals. Family genetic studies clearly show that among first-degree relatives of probands with ASD, up to 20% show difficulties associated with social functioning, communication or rigid behaviours/beliefs (Bolton *et al.*, 1994; Fombonne, *et al.*, 1997). Indeed, none of the core characteristics of ASD are unique to individuals with ASD. Most people have fixed patterns of doing certain things; sociability varies widely, and few people are fully competent in *all* aspects of verbal and non-verbal communication. In the absence of any genetic test for ASD, diagnosis is based on clinical judgement of when such problems extend beyond the normal range. However, as yet, there is no definition of where the boundaries of the
“normal range” lie and it should be remembered that even when standardised instruments such as the ADI-R or ADOS (both of which are becoming increasingly considered as the ‘gold standard’ instruments for assessment of ASD) are used, cut-off scores are determined by statistically significant group differences. This is why, for reliable diagnosis, such assessments must be used in conjunction with expert clinical judgement (Lord, 1995; Lord et al., 2006). Similarly, caution should be taken when relying on clinical judgement alone without the use of standardised measures to guide diagnosis. The nature of the ICD-10 and DSM-IV-TR diagnostic manuals is such that, inevitably, diagnoses using these descriptive criteria alone are based on a subjective judgement only and this may lead to problems of validity and with reliability, even between expert clinicians.

The diagnosis of ASD and identification of ASD symptomatology is particularly problematic in individuals affected by genetic disorders in which social, communication and behavioural difficulties are also present, and particularly in those syndromes associated with a severe to profound degree of intellectual disability. As noted in Section I, it is extremely difficult to identify ASD specific behaviours and impairments in individuals with such complex difficulties. Many of the diagnostic criteria outlined in the DSM-IV-TR and ICD-10 manuals are heavily reliant upon the individual reaching a certain level of development. Thus, individuals with a more severe degree of intellectual impairment may appear to fulfil certain criteria for ASD purely because they have not yet reached the developmental level required to demonstrate these behaviours. Moreover, recent studies that have investigated the validity of assessments such as the ADOS and ADI-R in children with intellectual disability have indicated poor to moderate agreement between the ADI-R and clinical judgement and between the ADI-R and ADOS. There are also indications that sensitivity and specificity of both the ADI-R and the ADOS are reduced in very young children and in individuals with low developmental age (Chawarska et al., 2007; Gray et al., 2008; Ventola et al., 2006). However, other studies have reported validity and reliability to be good in individuals with severe intellectual disability (deBilt et al., 2004). It must also be recognised that standardised
assessments such as the ADI-R (Rutter et al., 2003) or ADOS (Lord et al., 2000), were not designed to distinguish between neurodevelopmental conditions in which social-communication impairments are common but complex and somewhat different in nature to those that are typical of idiopathic autism; nor were they designed to be sensitive to often subtle differences between groups.

The importance of employing a detailed and fine grained analysis of the relationship between ASD and other conditions is well illustrated in the examples of Fragile X and Rett syndromes (see section I). Initial descriptions at a superficial behavioural level suggested a significant, even causal, relationship with ASD. However, further systematic and standardised investigation of the specific phenomenology of ASD characteristics within these groups revealed very different developmental, behavioural and cognitive profiles to those found in individuals with idiopathic ASD. For example, eye gaze avoidance in FXS and ASD was initially considered to be a shared characteristic in both populations. However, it is now suggested that in FXS eye gaze avoidance occurs in response to hypersensitivity to sensory stimuli, hyperarousal and social anxiety, while in ASD the same behaviour is reported to result from a more general impairment in understanding social interaction (Cornish et al., 2007; Cornish et al., 2008). These examples highlight the need for caution in drawing conclusions about the relationship between ASD and a given syndrome group. The complex and often unusual behavioural and cognitive patterns that are characteristic of many genetic syndromes may result in individuals obtaining scores above the autism cut-off on a standard assessment, even when the underlying mechanisms of these characteristics are different to those of individuals with idiopathic ASD. It is therefore important that investigations of the association between ASD and a genetic disorder be conducted meticulously, at both the classification/diagnostic and behavioural level.

Implications for intervention in individuals with differential diagnosis
There is sometimes a tendency within clinical and educational settings to attribute all the behaviours and difficulties shown by an individual, directly to the specific genetic syndrome from which he/she suffers, rather than considering the possibility of other additional or differential diagnoses. ‘Diagnostic overshadowing’ (Dykens, 2007; Reiss et al., 1982) of this kind can be a particular problem in the case of rare genetic syndromes, with the result that other causes and, more importantly, possible interventions may not be considered by parents or professionals.

For example, Jeremy was an 18 year-old with Cornelia de Lange syndrome (CdLS). In his teens he became progressively more withdrawn and uncommunicative and was diagnosed as being selectively mute. However, his eye contact had always been poor and since childhood he had a keen preference for routine and engaged in various repetitive and stereotyped behaviours. The possibility of ASD was not considered until he was 17 years old, despite his parents’ previous requests for assessment. The move to college, where the emphasis was on flexibility and student choice, rather than the structure and routine he needed, led to significant deterioration in his mood and behaviour. The college were unwilling to modify their programme, insisting that Jeremy needed to ‘learn to be more flexible and cope with the changes’. Jeremy became increasingly tearful and withdrawn, stopped taking part in his usual daily activities and refused to go to college. Although he has since received a formal diagnosis of ASD, Jeremy still remains at home, with no educational provision. His outcome contrasts markedly with that of David, another 18 year-old with CdLS for whom, following a period of regression in his late teens, the recognition that he showed many characteristics of ASD, led to his being transferred to specialist autism provision, resulting in significant improvements in his mood and behaviour.

Leber's congenital amaurosis is another condition that has been linked to ASD (Rogers & Newhart-Lawson, 1989). Ivan was an 11 year-old boy with this disorder, attending a school for visually impaired children. His parents were concerned about his limited eye contact and his inability to maintain eye contact with adults. Despite the parents' repeated requests for assessment, the school did not consider the possibility of ASD.

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2 Please note that each of the case studies reported here use individual cases that have been observed/assessed by the authors in clinical or research settings, all cases are reported using pseudonyms.
impaired children. Although he had some very specific areas of skill, especially in music, he showed no interest in other children, had very stereotyped and repetitive language and very fixed routines. The headmaster did not agree with the possibility that he might have ASD and therefore did not support his parents’ request for transfer to a specialist ASD unit. Ivan became increasingly isolated, self-injurious behaviours increased, and his parents found it more and more difficult to cope. He eventually required placement in a residential school.

In another case, Jake an eight year-old boy with Down syndrome, showed a typical ASD profile of repetitive, non-communicative speech, poor eye contact, limited interaction with other people and a host of repetitive and restricted interests. Although his parents had become increasingly concerned about his lack of progress, school staff interpreted his behaviours as being ‘difficult’ or ‘naughty’ and again rejected the possibility of comorbid ASD. Over time, Jake’s behaviour became steadily more disruptive and aggressive. Diagnostic assessment for ASD indicated that he met all the criteria for this disorder and transfer to a specialist autism unit was recommended (see Howlin, Wing & Gould 1995 for further examples).

Such vignettes illustrate how failure to recognise the possibility of ASD or the implications of ASD symptomatology can have negative and long lasting effects. However, whilst clinically it is important to recognise that individuals with a given genetic syndrome may have similar educational and support needs to those with idiopathic autism (Rutter et al., 1994), there is a need to be cautious about over-inclusive use of the term “autistic”. Mathew, for example, was a young man with Williams Syndrome who, unusually for this condition, also had profound learning disabilities. His limited communication skills, lack of sociability and highly stereotyped behaviours resulted in his being given the additional diagnosis of ASD, despite the fact that these difficulties were explicable in terms of his very low IQ. His parents, having read about various “cures” for ASD, believed that
enrolment in an intensive behavioural autism unit would solve all his difficulties, and were bitterly disappointed when the unit would not accept him because of his severe intellectual impairment.

Whilst recognition of shared ASD characteristics may be extremely important for appropriate behaviour management and school placement, we are not aware of any research to date that has considered the suitability and effectiveness of ASD specific interventions for use in children and adults with genetic syndromes who have a differential diagnosis of ASD or ASD related characteristics. Children with genetic syndromes may not receive a differential diagnosis of ASD until much later than individuals in the wider ASD population. Given the late diagnosis and considering the complex behavioural, communication and intellectual impairments that are often associated with genetic syndromes, adaptation to current autism specific interventions may be required in order to be effective in such cases. Additionally, better dissemination of information to professionals and care workers, regarding the association between ASD symptomatology and genetically determined syndromes may be important for increasing recognition of these shared characteristics. Future research to consider the effectiveness of various autism specific interventions may be helpful in guiding appropriate management and educational placement of individuals with genetic syndromes and ASD.

**Implications for understanding the wider ASD population**

Unsubstantiated claims that X % of children with condition Y have ASD, or conversely that X % of children with ASD have condition Y, are not helpful for advancing research or clinical practice. Many of the earlier claims about the association between Fragile X syndrome and ASD, for example, were made in the absence of reliable genetic testing or standardised diagnostic assessments. When standardised diagnostic and behavioural assessments of ASD began to be used, a far weaker association was identified and studies have since identified specific differences that may distinguish the two disorders (See Section I for details).
Rutter *et al.* (1994) made the point that in a number of conditions that are claimed to have a high association with autism (e.g. Phenylketonuria, Rubella), the ASD profile tends to be atypical. The fact that so many different syndromes are associated with communication and social deficits and stereotyped behaviours raises the issue of how unique this ‘triad of impairments’ is to ASD. Moreover, even those individuals who clearly fall within the ‘broader’ autism spectrum and show a number of ASD related characteristics, do not always demonstrate the full triad of impairments (Charman & Swettenham, 2001). The fact that the phenomenology of ASD appears to differ, not only across genetic syndromes but also between individuals with an ASD diagnosis, has particular implications for the debate concerning the boundaries of the autism spectrum.

The apparent heterogeneity of autism spectrum phenomenology across different syndrome groups is also relevant at the level of aetiology. Traditionally, it has been considered that the three core characteristics of ASD share a single underlying aetiological pathway (Morton & Frith, 1994). However, there is now some evidence that the components of the triad are in fact, fractionated at the level of aetiology. Thus, the different domains have different developmental trajectories (Charman *et al.*, 2005; Charman & Swettenham, 2001). Repetitive behaviours, in particular, may become evident later than social and communication impairments; they are also less likely to improve over time (Charman *et al.*, 2005; Fécteau *et al.*, 2003; Piven *et al.*, 1996). Genetic studies of the general population (Ronald *et al.*, 2006) also suggest that the three domains are only moderately associated with one another and that there may be different aetiological explanations underlying each domain. This observed divergence at the aetiological level might account for the different types of profiles observed across genetic syndromes, particularly in conditions where one or two components of the triad of impairments are more evident than others.

**Summary of diagnostic considerations and implications for intervention and conceptual and theoretical frameworks.**
There is sometimes a tendency, when working with individuals with genetic syndromes, to attribute all behavioural and emotional difficulties to the presence of the syndrome itself, rather than to consider that there may be shared characteristics with other disorders and that in many cases a comorbid diagnosis might be appropriate. As indicated in the vignettes described above, recognition of shared features between specific genetic syndromes and ASD may be crucial in ensuring that individuals receive appropriate and effective behaviour management and educational placement. However, it is also important to apply the differential diagnosis of ASD appropriately and cautiously. The review of ASD and associated characteristics in the specific syndrome groups outlined above highlights the importance of conducting fine-grained assessment of ASD in these syndromes. Subtle differences in the quality and nature of specific ASD-like impairments may only be revealed when conducting detailed analyses of behavioural characteristics, and may be masked at the broader level of clinical or algorithm based diagnoses. Recognition of atypicalities in the profile and phenomenology of ASD in genetic syndromes may be crucial for developing appropriate, individually tailored, interventions. Continued research in this area is also important in further understanding the aetiology or underlying mechanisms and network structures involved in idiopathic ASD and in further unravelling the structure of the triad of impairments.
References


ASD in genetic syndromes


ASD in genetic syndromes


ASD in genetic syndromes


ASD in genetic syndromes


ASD in genetic syndromes


ASD in genetic syndromes


Table 1: Number of articles identified via literature search.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Dates of studies</th>
<th>Number of articles with different samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fragile X</td>
<td>1982-2006</td>
<td>95</td>
</tr>
<tr>
<td>Tuberous Sclerosis</td>
<td>1979-2006</td>
<td>32</td>
</tr>
<tr>
<td>Rett</td>
<td>1985-2006</td>
<td>31</td>
</tr>
<tr>
<td>Down</td>
<td>1979-2006</td>
<td>16</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>1969-2003</td>
<td>9</td>
</tr>
<tr>
<td>CHARGE</td>
<td>1998-2006</td>
<td>7</td>
</tr>
<tr>
<td>Angelman</td>
<td>1996-2004</td>
<td>6</td>
</tr>
<tr>
<td>Neurofibromatosis</td>
<td>1998-2007</td>
<td>4</td>
</tr>
<tr>
<td>Joubert</td>
<td>1991-2005</td>
<td>4</td>
</tr>
<tr>
<td>Williams</td>
<td>1985-2006</td>
<td>2</td>
</tr>
<tr>
<td>Goldenhar</td>
<td>1992-2002</td>
<td>2</td>
</tr>
<tr>
<td>Hypomelanosis of Ito</td>
<td>1991-2002</td>
<td>2</td>
</tr>
<tr>
<td>Noonan</td>
<td>1983-1994</td>
<td>2</td>
</tr>
<tr>
<td>Sotos</td>
<td>1990-2001</td>
<td>2</td>
</tr>
<tr>
<td>VCF</td>
<td>1998-2006</td>
<td>2</td>
</tr>
<tr>
<td>Leber’s amaurosis</td>
<td>1989-2007</td>
<td>2</td>
</tr>
<tr>
<td>Cohen syndrome</td>
<td>2001-2005</td>
<td>1</td>
</tr>
<tr>
<td>CdLS</td>
<td>2006</td>
<td>1</td>
</tr>
<tr>
<td>Ehlers-Danlos</td>
<td>1992</td>
<td>1</td>
</tr>
<tr>
<td>Lujan-Fryns</td>
<td>2005</td>
<td>1</td>
</tr>
<tr>
<td>Moebius</td>
<td>1989</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 2: Prevalence studies of ASD in Fragile X Syndrome.

<table>
<thead>
<tr>
<th>Author</th>
<th>N Participants with FXS</th>
<th>Autism Diagnostic Assessment/Criteria</th>
<th>N (%) meeting autism/ASD criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levitas et al., 1983</td>
<td>10 males</td>
<td>DSM-III$^1$</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Brown et al., 1986</td>
<td>150 males</td>
<td>DSM-III$^1$</td>
<td>26 (17%)</td>
</tr>
<tr>
<td>Hagerman et al., 1986</td>
<td>50 males</td>
<td>DSM-III$^1$; ABC$^2$</td>
<td>16 (32%); 15 (30%) additional participants met criteria in early childhood but not on current behaviour. 15 (31%) met ABC criteria; ‘Autistic traits’ identified in almost all cases.</td>
</tr>
<tr>
<td>Reiss &amp; Freund, 1990</td>
<td>17 males</td>
<td>DSM-III-R$^1$</td>
<td>3 (18%); 3 additional cases met criteria in early childhood; 7 (41%) met PDD-NOS criteria</td>
</tr>
<tr>
<td>Cohen et al., 1991</td>
<td>13 multiplex families (total N = 35)</td>
<td>DSM-III$^1$</td>
<td>11 (31%); 3 of 7 probands (43%); 4 of 28 (15%) remaining males in family met current criteria.</td>
</tr>
<tr>
<td>Kerby &amp; Dawson, 1994</td>
<td>9 males</td>
<td>DSM-III-R$^1$</td>
<td>FXS significantly &gt;autistic characteristics than controls with ID.</td>
</tr>
<tr>
<td>Turk &amp; Graham, 1997</td>
<td>49 males</td>
<td>HBS$^3$; DSM-III-R$^1$</td>
<td>14 (29%) FXS</td>
</tr>
<tr>
<td>42 males with ‘idiopathic’</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turk &amp; Graham, 1997</td>
<td>45 Down Syndrome males (DS)</td>
<td>DSM-III-R$^1$</td>
<td>5 DS (11%)</td>
</tr>
<tr>
<td>42 males with ‘idiopathic’</td>
<td></td>
<td></td>
<td>18 ID (43%)</td>
</tr>
<tr>
<td>Study</td>
<td>Sample Size</td>
<td>Assessment Tool(s)</td>
<td>FXS</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------</td>
<td>--------------------</td>
<td>-----</td>
</tr>
<tr>
<td>Mazzocco et al., 1997</td>
<td>30 females</td>
<td>NDI&lt;sup&gt;4&lt;/sup&gt;, DSM-III-R&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1(3%) FXS</td>
</tr>
<tr>
<td></td>
<td>31 age/ IQ matched controls</td>
<td></td>
<td>5 (17%) FXS vs 2 (6%) controls met PDD criteria</td>
</tr>
<tr>
<td>Bailey et al., 2001</td>
<td>55 males</td>
<td>CARS&lt;sup&gt;5&lt;/sup&gt;</td>
<td>14 (25%) autistic behaviour'; 12 (22%) 'mildly-moderately autistic'; 1 (2%) 'severely autistic'</td>
</tr>
<tr>
<td>Demark et al., 2003</td>
<td>15 males</td>
<td>CARS&lt;sup&gt;5&lt;/sup&gt;</td>
<td>6 (40%) FXS vs. 8 (38%) PDD ‘mildly-moderately autistic’; 1 (7%) FXS vs. 11 (52%) PDD ‘severely autistic’</td>
</tr>
<tr>
<td>Sabaratnam et al., 2003</td>
<td>18 males</td>
<td>DSM-III-R&lt;sup&gt;1&lt;/sup&gt;</td>
<td>None</td>
</tr>
<tr>
<td>Kau et al., 2004</td>
<td>55 males</td>
<td>ADI-R&lt;sup&gt;6&lt;/sup&gt;, DSM-IV&lt;sup&gt;1&lt;/sup&gt;</td>
<td>14 (26%) FXS vs. 7 (32%) DLD met autism criteria</td>
</tr>
<tr>
<td></td>
<td>22 males with developmental language delay (DLD).</td>
<td></td>
<td>18 (33%) FXS vs. 3 (14%) DLD met PDD criteria</td>
</tr>
<tr>
<td>Hatton et al., 2006</td>
<td>142 males &amp; 32 females</td>
<td>CARS&lt;sup&gt;5&lt;/sup&gt;</td>
<td>38 (21%; 36M, 2 F)</td>
</tr>
</tbody>
</table>

<sup>1</sup> Diagnostic and Statistical Manual (American Psychiatric Association; 1987, 1994).  
<sup>2</sup> Autism Behavior Checklist (Krug et al., 1980)  
<sup>3</sup> The Schedule of Handicaps, Behaviour and Skills (HBS; Wing, 1980)  
<sup>4</sup> Neuropsychiatric Developmental Interview (Reiss & Freund, 1990)  
<sup>5</sup> Childhood Autism Rating Scale (Schopler et al., 1988)
Table 3: Prevalence of ASD in Rett Syndrome

<table>
<thead>
<tr>
<th>Author</th>
<th>N Girls with RS</th>
<th>Autism Diagnostic Assessment/Criteria</th>
<th>N(%) meeting autism/ASD criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Witt-Engerstrom &amp; Gillberg, 1987</td>
<td>47</td>
<td>DSM-III¹</td>
<td>18 (38%) autism diagnosis &amp; 19 (40%) autistic-like behaviours reported prior to diagnosis of RS.</td>
</tr>
<tr>
<td>Naidu et al. 1990</td>
<td>22</td>
<td>ABC²</td>
<td>None</td>
</tr>
<tr>
<td>Zappella et al., 1998</td>
<td>30 (with preserved speech variant)</td>
<td>DSM-IV¹</td>
<td>29 (97%)</td>
</tr>
<tr>
<td>Sandberg et al., 2000</td>
<td>8</td>
<td>DSM-IV¹</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Mount et al., 2003b</td>
<td>15</td>
<td>ABC²</td>
<td>6 (40%) RS vs. 1 (7%) ID scored above autism cut-off</td>
</tr>
</tbody>
</table>

¹Diagnostic and Statistical Manual (American Psychiatric Association; 1987, 1994).
²Autism Behavior Checklist (Krug et al., 1980)
### Table 4: Prevalence of ASD in Tuberous Sclerosis Complex

<table>
<thead>
<tr>
<th>Author</th>
<th>N Participants with TSC</th>
<th>Autism Diagnostic Assessment/Criteria</th>
<th>N/% meeting autism/ASD criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smalley et al. (1992)</td>
<td>13</td>
<td>ADI&lt;sup&gt;1&lt;/sup&gt;</td>
<td>7 (54%)</td>
</tr>
<tr>
<td></td>
<td>14 controls with autism</td>
<td>ICD-10&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Gillberg et al., 1994</td>
<td>28</td>
<td>CARS&lt;sup&gt;5&lt;/sup&gt;; DSM-III-R&lt;sup&gt;1&lt;/sup&gt;</td>
<td>17 (61%)</td>
</tr>
<tr>
<td>Hunt &amp; Shepherd (1995)</td>
<td>21</td>
<td>DSM-II-R&lt;sup&gt;1&lt;/sup&gt;</td>
<td>5 (24%) met autism criteria; 9 (43%) met PDD criteria.</td>
</tr>
<tr>
<td>Williamson &amp; Bolton, 1995</td>
<td>2 siblings with TSC</td>
<td>ADI</td>
<td>1: atypical autism</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1: no signs of autism.</td>
</tr>
<tr>
<td>Webb et al., 1996</td>
<td>131</td>
<td>ICD-10&lt;sup&gt;4&lt;/sup&gt;</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Bolton &amp; Griffiths 1997*</td>
<td>18</td>
<td>ICD-10&lt;sup&gt;4&lt;/sup&gt;</td>
<td>9 (50%; two with IQ ≥ 70)</td>
</tr>
<tr>
<td>Baker et al., 1998</td>
<td>20</td>
<td>ABC&lt;sup&gt;2&lt;/sup&gt;</td>
<td>12 (60%) above cut-off on ABC.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADI&lt;sup&gt;3&lt;/sup&gt;</td>
<td>8 of 9 participants (89%) assessed on ADI met autism criteria, 4 also met DSM-IV autism criteria. (All had IQ within/above mild ID range)</td>
</tr>
<tr>
<td>Gutierrez et al., 1998</td>
<td>28</td>
<td>ADI&lt;sup&gt;3&lt;/sup&gt;</td>
<td>8 (29%) met autism criteria; 12 (43%) met PDD criteria.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADOS&lt;sup&gt;6&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Park &amp; Bolton, 2001*</td>
<td>43</td>
<td>ADOS&lt;sup&gt;6&lt;/sup&gt;</td>
<td>14 of 34 for whom a confident diagnosis possible (41%) met PDD criteria; PDD subgroup had significantly lower IQ scores than non-PDD group.</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Sample Size</td>
<td>Methodology</td>
<td>Description</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Bolton et al., 2002*</td>
<td>53</td>
<td>ADOS&lt;sup&gt;6&lt;/sup&gt;</td>
<td>19 (36%; 14 autism, 4 atypical autism and 1 PDDNOS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADI-R&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ICD-10&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Humphrey et al., 2006</td>
<td>1</td>
<td>ADOS</td>
<td>Met autism criteria at 24 months after period of regression and onset of seizure disorder.</td>
</tr>
</tbody>
</table>

* Study participants overlapped across these studies.

<sup>1</sup> Diagnostic and Statistical Manual (APA; 1987, 1994).
<sup>2</sup> Autism Behavior Checklist (Krug et al., 1980).
<sup>3</sup> Autism Diagnostic Interview (Lord et al., 1994; Rutter et al., 2003).
<sup>5</sup> Childhood Autism Rating Scale (Schopler et al., 1988).
<sup>6</sup> Autism Diagnostic Observation Schedule (Lord et al., 2000).
Table 5: Studies of ASD in Down Syndrome

<table>
<thead>
<tr>
<th>Author</th>
<th>N Participants with DS</th>
<th>Autism Diagnostic Assessment/Criteria</th>
<th>N/% meeting autism/ASD criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gillberg et al., 1986</td>
<td>20</td>
<td>DSM-III(^1)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Lund 1988</td>
<td>44</td>
<td>HBS(^8)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>Ghaziuddin et al., 1992</td>
<td>40</td>
<td>DSM-III-R(^1); ABC(^2)</td>
<td>Estimated 4-5%</td>
</tr>
<tr>
<td>Turk &amp; Graham, 1997</td>
<td>45 males</td>
<td>HBS(^8); DSM-III-R(^1)</td>
<td>5 DS (11%)</td>
</tr>
<tr>
<td></td>
<td>42 males with ‘idiopathic ID’.</td>
<td></td>
<td>14 FXS (29%)</td>
</tr>
<tr>
<td></td>
<td>49 FXS males</td>
<td></td>
<td>18 ID (43%)</td>
</tr>
<tr>
<td>Kent et al., 1999</td>
<td>58 (only 33 completed all measures)</td>
<td>ASSQ(^7)</td>
<td>3 (7%) met criteria for atypical autism.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CARS(^5)</td>
<td>1 (2%) met autism criteria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ICD-10(^4)</td>
<td></td>
</tr>
<tr>
<td>Starr et al., 2005</td>
<td>13 (all IQ &lt;50)</td>
<td>PL-ADOS(^6)</td>
<td>5 (39%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADI-R(^3)</td>
<td></td>
</tr>
<tr>
<td>Capone et al., 2005</td>
<td>471 clinic referrals</td>
<td>DSM-IV(^1)</td>
<td>87 (19%); met criteria for an ‘autistic-like condition’</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>61 (13%) met ASD criteria; 41 (9%) for autism</td>
</tr>
<tr>
<td>Lowenthal et al., 2007</td>
<td>180</td>
<td>ASQ(^9)</td>
<td>28 (15.6%) PDD, of these 10 (5.58%) had autism and 18 (10.05%) had PDD-NOS</td>
</tr>
</tbody>
</table>
Studies reported in this and the following tables are those that have employed standardised assessment and diagnostic criteria of autism. Case studies and other descriptions of autistic like behaviour and those that have not employed such measures and criteria are reported in the text.

2 Autism Behavior Checklist (Krug et al., 1980).
3 Autism Diagnostic Interview (Lord, et al., 1994; Rutter, et al., 2003).
5 Childhood Autism Rating Scale (Schopler et al., 1988).
6 Prelinguistic Autism Diagnostic Observation Schedule (DiLavore et al., 1995).
7 Asperger’s Syndrome Screening Questionnaire (Ehlers & Gillberg, 1993).
8 The Schedule of Handicaps, Behaviour and Skills (HBS; Wing, 1980).
9 The Autism Screening Questionnaire (Berument et al., 1999).

**Table 6: Studies of ASD in CHARGE Syndrome**

<table>
<thead>
<tr>
<th>Author</th>
<th>N Participants with CHARGE</th>
<th>Autism Diagnostic Assessment/Criteria</th>
<th>N(%) meeting autism/ASD criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al., 2005</td>
<td>13</td>
<td>SCQ¹</td>
<td>2 (15%) autism</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 (23%) ASD</td>
</tr>
<tr>
<td>Hartshorne et al., 2006</td>
<td>160</td>
<td>ABC²</td>
<td>44 (28%)</td>
</tr>
<tr>
<td>Johansson et al., 2006</td>
<td>18</td>
<td>ABC², ADI-R³, DSM-IV⁵</td>
<td>9 (50%)</td>
</tr>
</tbody>
</table>

¹Diagnostic and Statistical Manual (APA, 1987; 1994).
²Autism Behavior Checklist (Krug et al., 1980).
³Autism Diagnostic Interview (Lord et al., 1994; Rutter et al., 2003).
⁴Social Communication Questionnaire (Rutter et al., 2003).
Table 7: Studies of ASD in Angelman Syndrome

<table>
<thead>
<tr>
<th>Author</th>
<th>N Participants with AS</th>
<th>Autism Diagnostic Assessment/Criteria</th>
<th>N(%) meeting autism/ASD criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trillingsgaard and Ostergaard, 2004</td>
<td>16</td>
<td>ADOS(^1)</td>
<td>10 (63%) autism</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>13 (81%) ASD (inclusive of those meeting autism cut-off)</td>
</tr>
<tr>
<td>Peters et al., 2004</td>
<td>19</td>
<td>ADOS(^1)</td>
<td>8 (50%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DSM-IV(^2)</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Autism Diagnostic Observation Schedule (Lord et al., 2000)
\(^2\) Diagnostic and Statistical Manual (APA, 1998; 1994).
Table 8: Summary of prevalence figures and associated degree of intellectual disability within syndrome groups.

<table>
<thead>
<tr>
<th>Genetic Syndrome</th>
<th>Associated Degree of Intellectual Disability</th>
<th>Estimated Prevalence of ASD</th>
</tr>
</thead>
<tbody>
<tr>
<td>FXS</td>
<td>Moderate to severe</td>
<td>21-50%</td>
</tr>
<tr>
<td>RS</td>
<td>Severe to profound</td>
<td>25-40% (classic), 97% (mild)</td>
</tr>
<tr>
<td>TSC</td>
<td>Normal to profound</td>
<td>15-89%; 17% (normal IQ)</td>
</tr>
<tr>
<td>DS</td>
<td>Moderate to severe</td>
<td>5-39%</td>
</tr>
<tr>
<td>PKU</td>
<td>Normal to severe</td>
<td>5%</td>
</tr>
<tr>
<td>CHARGE</td>
<td>Normal to severe</td>
<td>15-50%</td>
</tr>
<tr>
<td>AS</td>
<td>Severe to profound</td>
<td>50-80%</td>
</tr>
</tbody>
</table>
Acknowledgements

The authors would like to thank Professor James Harris for his insightful comments and ideas regarding the association between ASD and genetic syndromes which stimulated the author’s conceptualisation and review of this area of study.