



# Cerebra

Positively Different

## Autism in genetic syndromes: Implications for assessment and intervention.

### Introduction

This briefing has been prepared to help parents and carers of children with genetic syndromes understand how and why autism spectrum disorder or related characteristics might be seen in children with genetic syndromes and what this might mean for assessment and intervention. This briefing provides a summary of information presented in a peer reviewed scientific article published in 2009<sup>1</sup> and an academic book chapter published in 2011.<sup>2</sup>

### 1. What is Autism Spectrum Disorder?

Autism spectrum disorder (ASD) is a developmental disability that occurs in up to 1% of children and adults in the general population<sup>3</sup> and up to 40% of individuals within the learning disability population.<sup>4</sup> ASD is diagnosed on the basis of observable impairments and behaviours in three core areas (also known as the triad of impairments). These are: 1. impairments in communication and language, 2. impairments in social interaction and social relatedness and, 3. the presence of repetitive behaviours and restricted interests. In children with ASD, difficulties in these three areas are typically evident before the age of three years. ASD is a spectrum condition, which means that while all people with ASD share certain difficulties, there is a great deal of variability in the way in which these difficulties are seen and in their severity.

### 2. What is the cause of Autism Spectrum Disorder?

The specific causes of ASD remain unknown but most studies indicate a biological or genetic cause.<sup>5</sup> A high level of heritability (passing within families) of ASD characteristics in families and siblings of affected individuals has been reported.<sup>6</sup> However, this is not always the case and there are many individuals with ASD in which there are no familial links to the condition.<sup>7</sup>

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While several chromosomes and genetic locations have been linked to ASD, there is very little evidence to suggest that any one of these is solely responsible for the occurrence of ASD. This has led researchers to suggest that ASD is caused by complex interactions between several genes (rather than a single genetic mutation) which lead to differences on a number of different biological levels.<sup>5,8,9</sup>

### 3. Occurrence of ASD or ASD like characteristics in genetic syndromes associated with learning disability.

The term 'genetic syndrome' is used to refer to a condition in which there is a known genetic cause that results in a cluster of physical and behavioural symptoms. Approximately 50% of individuals within the learning disability population have a genetic syndrome and this figure is around 20% for individuals who have a mild learning disability.<sup>10</sup> A well known and recognised example of a genetic syndrome associated with learning disability is Down syndrome. Down syndrome is typically caused by the presence of an additional copy of chromosome 21 (trisomy 21). In a small proportion of individuals an unbalanced translocation involving chromosome 21 (meaning that material from one chromosome 21 gets stuck or translocated to another chromosome) has been identified. Individuals with Down syndrome have distinctive facial and physical features (physical phenotype), cognitive impairments and behavioural characteristics (behavioural phenotype).<sup>11</sup>

Increasingly, ASD or ASD-like characteristics have been described in individuals with a range of different genetic syndromes including: Tuberous Sclerosis Complex, Fragile X, Cornelia de Lange, Down, Angelman, Coffin-Lowry, Cohen Laurence-Moon-Biedel, Marinesco-Sjogren, Moebius, Rett and Williams syndromes.<sup>1,2</sup> The strength of association or co-occurrence between a given genetic syndrome and ASD is variable, with prevalence estimates ranging from 5% in individuals with Down syndrome to 60% in individuals with Tuberous Sclerosis Complex.

Just as the percentage of children with a genetic syndrome who have ASD varies, so the ASD characteristics also differ across syndrome groups. Some studies describe individuals with a given syndrome as showing "ASD-like characteristics" or "ASD traits", which suggest there may be some similarities with individuals with ASD but that the impairments, skills and behaviours observed are not entirely the same as those identified in individuals with ASD who do not have a genetic syndrome. Interestingly, the nature and severity of ASD characteristics when observed in genetic syndrome groups is often reported to be different, in small and subtle ways, to those identified in individuals with ASD who do not have a syndrome. However, this is not always the case and other studies describe a much stronger association between some syndromes and ASD, indicating that individuals with a given syndrome have all of the diagnostic features of ASD and may suggest that individuals have a dual diagnosis of the genetic syndrome and ASD. In either case, recognising that an individual may share some or all of the impairments,

skills and behaviours associated with ASD may help carers and professionals to understand the children's needs.

#### 4. Why do some individuals with some genetic syndromes show an association with ASD?

Some researchers suggest that the genes underlying those syndromes in which ASD characteristics are very common, lead to common differences at the biological and neurological level, which in turn give rise to the presentation of ASD characteristics.<sup>5</sup> Such researchers believe that understanding these pathways in genetic syndromes is helpful in determining the causes of ASD more widely.<sup>9</sup> However, this is not a view held by all researchers. Others suggest that it is not the underlying genetic causes which give rise to the presentation of ASD in certain genetic syndromes but an effect of the degree of learning disability associated with the syndrome, which increases the risk that ASD characteristics will occur.<sup>12</sup>

#### 5. Genetic syndromes commonly associated with ASD characteristics

Three genetic syndromes that have commonly been reported to be associated with ASD include Fragile X syndrome (FXS), Cornelia de Lange syndrome (CdLS) and Tuberous Sclerosis Complex.

##### 5.1 Fragile X Syndrome

Fragile X syndrome (FXS) is the most common cause of inherited learning disability, occurring in 1 in 3,600 males and 1 in 8,000 females.<sup>13</sup> FXS is caused by the presence of an apparently unstable or 'fragile' site located on the X chromosome. The instability is caused by an excess of genetic code in this region. Males with FXS typically show mild to severe learning disability while females with FXS usually have a mild learning disability.

Recent studies of individuals with FXS show a fairly consistent pattern of association with ASD. The percentage of individuals with FXS showing ASD characteristics or meeting ASD criteria ranges from 21% to 50%. In females, this figure is much lower; between 1 and 3%.<sup>1</sup> Severe ASD is relatively rare in FXS and a milder presentation of ASD-like features is more characteristic.<sup>14, 15</sup> On closer inspection, some of the ASD-like difficulties observed in individuals with FXS appear to be different to those identified in individuals with ASD who do not have a genetic syndrome. Impairments in social interaction in FXS are characterised by social anxiety, extreme shyness and eye gaze avoidance.<sup>16</sup> These characteristics are observed in individuals with ASD who do not have a genetic syndrome but are not considered core features of ASD. Furthermore, individuals with FXS are reported to have a strong willingness to engage socially with others.<sup>17, 18, 19, 20</sup> This is somewhat different to the social

indifference often described in individuals with ASD. In further contrast to individuals with ASD, the social impairments in FXS are thought to increase with age.<sup>21,19</sup>

## 5.2 Cornelia de Lange syndrome

Cornelia de Lange syndrome (CdLS) is primarily caused by a deletion on chromosome 5. Other deletions on chromosome 10 and X have also been identified.<sup>22,23,24,25,26,27</sup> One or more of these genetic abnormalities is thought to be identifiable in 55% of people with CdLS, suggesting that other chromosomal abnormalities are likely to contribute to the cause of CdLS. Degree of learning disability in CdLS ranges from mild to profound.<sup>28</sup>

Studies suggest that ASD-like characteristics occur in 50% to 67% of individuals with CdLS. Scores on assessments of the severity of these characteristics are significantly higher in CdLS compared to other individuals with similar levels of learning disability who do not have CdLS.<sup>29,30,31</sup> The reported occurrence rates of ASD-like characteristics in CdLS are similar to those identified in Fragile X syndrome. Similarly to Fragile X syndrome, some of the ASD-like difficulties observed in CdLS appear to be different to those identified in individuals with ASD who do not have a genetic syndrome. Social anxiety and extreme shyness are common and unusually, selective mutism (speaking in one environment but not another or speaking only to certain individuals), is particularly prominent. Social avoidance is also common.<sup>2</sup> Other studies have demonstrated that the nature of repetitive behaviours appears to be different in individuals with CdLS compared to those with ASD. In particular, individuals with CdLS show fewer sensory related behaviours such as licking, sniffing and finger flicking.<sup>32</sup>

## 5.3 Tuberous Sclerosis Complex

Tuberous Sclerosis Complex (TSC) is caused by a mutation on either chromosome 9 or 16.<sup>33</sup> These genetic mutations result in the development of benign tumours in the brain, skin and internal organs.<sup>34</sup> The effects of these tumours are extremely variable with some individuals having only superficial skin problems while others show severe physical effects and profound learning disability.<sup>35</sup>

Significant impairments in social interaction, stereotyped behaviours, absent or abnormal speech and social withdrawal were reported in the very early descriptions of TSC in the 1930s. Recently, studies have reported that between 24% and 60% of individuals with TSC show ASD-like characteristics.<sup>1,2</sup> One study has suggested that repetitive behaviours are not as frequent in individuals with TSC when compared to individuals with ASD, while the severity of social interaction and communication impairments in these groups is very similar.<sup>36</sup> These difficulties have been reported to occur both in those with mild and those with severe effects of TSC.

## 6. Other genetic syndromes associated with ASD characteristics

Above we have described the three genetic syndromes most commonly associated with ASD characteristics. In this section, we describe a number of other genetic syndromes in which ASD-like characteristics have been reported, including Angelman syndrome (AS), Down syndrome (DS) and Rett syndrome (RS).

### 6.1 Angelman Syndrome

Angelman syndrome (AS) occurs in approximately 1 in 12,000 to 15,000 individuals<sup>37,38</sup> and is caused by abnormalities on chromosome 15. Individuals with AS typically show severe to profound learning disability,<sup>39</sup> significant difficulties with mobility, communication and seizures.<sup>11</sup>

Studies report that 50% to 81% of individuals with AS meet criteria for ASD. However, the characteristic features of AS are not consistent with these findings. Individuals with AS show strong motivation to engage socially with others, showing very high levels of laughing and smiling during situations in which social contact is available.<sup>40,41</sup> While communication skills are impaired and language significantly delayed, social approaches are very frequent. When compared to individuals with ASD, individuals with AS are less impaired in some of the core features of ASD such as social smile, shared enjoyment, facial expression, unusual interests or repetitive behaviour and response to name.<sup>42</sup> While it is likely that some individuals with AS do genuinely show high levels of ASD-like characteristics, it is possible that the profound level of learning disability associated with the syndrome and the unusual social interaction skills in this group may result in overinflated scores on diagnostic measures of ASD. Such factors would need to be carefully considered when assessing an individual with AS on such assessments.

### 6.2 Down Syndrome

Down syndrome (DS) is the most common chromosomal cause of learning disability and occurs in 11.8 in 10,000 live births.<sup>43</sup> As described in Section 3, DS is typically caused by an extra copy of chromosome 21. Individuals with DS have a mild to severe level of learning disability.<sup>44</sup>

Typically, individuals with DS are skilled in social contact and are motivated to engage socially with others. Communication skills are delayed but many individuals develop good language skills. These characteristics have previously led researchers and clinicians to believe that ASD-like characteristics are relatively rare in DS. However, recent studies suggest that around 5% to 39% of individuals with DS meet criteria for ASD.<sup>1,2</sup> These figures are lower than those reported in the other syndrome groups described in this review but remain higher than that of the general population (around 1%; see Section 1). Recent studies

have suggested that individuals with DS who meet criteria for ASD have lower levels of ability and higher rates of repetitive behaviour, hyperactivity and impaired speech compared to those with DS who do not show these characteristics.<sup>44, 45</sup>

### 6.3 Rett Syndrome

Rett syndrome (RS) is a neurological disorder that is caused by a mutation on the X chromosome. RS predominantly affects females and occurs in 1 in 15,000 to 22,800 live female births.<sup>46</sup> Typically, development appears to be normal in the first six to eighteen months but this is followed by a period of regression resulting in a loss of language and motor skills, leading to severe or profound learning and physical disabilities.<sup>47</sup> A small number of individuals with RS have been reported to retain and develop their language skills.<sup>48, 49</sup>

Autistic-like behaviours were noted in the very first description of RS in 1966. Studies have since estimated that 25% to 40% of individuals with RS show ASD-like characteristics.<sup>1, 2</sup> ASD is the most common misdiagnosis in children with RS, with 18% of individuals being diagnosed with ASD prior to receiving a diagnosis of RS.<sup>50</sup> As with FXS, while ASD-like characteristics are very common in the syndrome, there are some distinct differences in these features. For example, despite severe impairments in social interaction skills, eye contact is reported to be good.<sup>47</sup> Additionally, the repetitive behaviour that is most characteristic of individuals with RS is a stereotyped hand wringing movements. This is very different to the stereotyped behaviour typically observed in individuals with ASD. Other studies have confirmed that individuals with RS are less likely to show the core features of ASD.<sup>51</sup>

## 7. Assessing ASD in genetic syndromes

In the sections above, we have described the nature of association between a number of genetic syndromes and ASD characteristics. In most cases, these descriptions are not entirely clear cut and while reported levels of association are often high, subtle differences in the characteristics have been reported. These differences can often make assessment of ASD characteristics in genetic syndromes by professionals and clinicians complex. Many of the assessment tools that are available to evaluate ASD characteristics are designed to assess and diagnose 'typical' ASD in individuals without genetic syndromes and may not always be able to detect and describe these subtle differences. The assessment tools that are considered the best to use are the Autism Diagnostic Observation Schedule (ADOS<sup>52</sup>) in combination with the Autism Diagnostic Interview (ADI<sup>53</sup>). Sometimes a 'screening' questionnaire like the Social Communication Questionnaire (SCQ<sup>54</sup>) is used.

Another factor which makes assessment of ASD in genetic syndromes difficult is the severity of learning disability associated with the syndromes. This is particularly problematic when the level of learning disability is in the severe to profound range. ASD is identified by the absence, delay or impairment of particular skills in communication and social interaction. However, there may

be other reasons why an individual shows impairments, delay or absence of skill in these areas. One reason might be the presence of ASD but another might be the presence of a learning disability. In individuals with a severe to profound level of learning disability, it is very difficult to identify which of these two reasons explains the absence or impairment of these skills, since the individual may not have yet reached the developmental level required to achieve that particular skill and, of course, both reasons may be valid and present. Additionally, individuals with this level of disability are also very likely to show repetitive behaviours, specifically stereotyped behaviours, play and movements and these behavioural similarities cause further confusion.

While these factors make it difficult to evaluate ASD characteristics in individuals with genetic syndromes, assessment may still be valuable and should be considered if appropriate. However, professionals and clinicians may be cautious in diagnosing ASD in an individual with a genetic syndrome, particularly when there may be some differences in the nature of these difficulties. Even in cases where a diagnosis of ASD is not appropriate, recognition that the individual shows some ASD-like characteristics may be helpful in understanding the needs of the individual.

## 8. Practical implications

The idea that there may be an association between particular genetic syndromes and ASD characteristics can be very confusing and may result in families feeling overwhelmed at the thought that not only does their child have a genetic syndrome but they also have another disability. However, it is important to be aware that the presence of ASD-like characteristics in an individual with a genetic syndrome does not necessarily mean that the person has two different disorders. Rather, it is perhaps more appropriate and helpful to consider that these ASD related difficulties are characteristic of the syndrome itself (i.e. part of the behavioural phenotype) and the individual. Recognition of these shared difficulties is important for ensuring that the person receives appropriate intervention and educational management and to enable parents, carers and professionals working with the individual to seek appropriate advice and resources.

Individual clinical case studies of children and adults with genetic syndromes suggest that recognising these characteristics is important for ensuring that the appropriate behavioural management and educational programmes can be put in place. However, there have been no research studies which have evaluated how useful ASD interventions, that have been designed for individuals with ASD who do not have a genetic syndrome, might be for individuals with genetic syndromes who show ASD-like characteristics. What is also unclear is whether such assessments would be appropriate for use in individuals who show some but not all of the features of ASD. In such cases, it is possible that a combination of ASD specific interventions and targeted intervention for particular difficulties, such as selective mutism in CdLS or gaze avoidance in FXS, might be appropriate. However, further research is required in order to gain a better understanding of how effective these interventions might be.

## 9. Summary and key points

- Autism spectrum disorder (ASD) is a developmental disability that affects an individual's communication and social interaction skills. The nature of ASD is very variable and characteristics may vary across individuals.
- ASD and ASD-like characteristics are commonly observed in individuals with genetic syndromes associated with learning disability. Specific examples of genetic syndromes in which a strong association with ASD has been described include Fragile X syndrome, Cornelia de Lange syndrome and Tuberous Sclerosis Complex.
- In most cases, when ASD characteristics have been described to be common in a syndrome, there are some subtle differences in the nature of these characteristics compared to individuals with ASD who do not have the syndrome.
- Recognising any shared characteristics of ASD and the areas where there may be differences to ASD is important for understanding the individual's educational and day to day needs and for enabling parents, carers and professionals to access appropriate resources and advice.
- Assessing ASD characteristics in individuals with genetic syndromes can be complex but is by no means impossible and a clinical evaluation should be conducted in situations where this might be appropriate.
- The effectiveness of ASD specific interventions for use in individuals with genetic syndromes who show ASD or ASD-like characteristics is not known. It is likely that a combination of ASD specific interventions and targeted interventions which focus on specific areas of difficulty will be appropriate. However, further research is required to evaluate such approaches.



## 10. About Cerebra Centre for Neurodevelopmental Disorders (CNDD)

The Cerebra Centre for Neurodevelopmental Disorders (CNDD) is headed by Professor Chris Oliver and situated within the School of Psychology at the University of Birmingham. The centre has been funded by Cerebra since 2008 and is the largest of its kind in the UK.

At the centre, clinical and academic psychologists, undergraduate and postgraduate students and volunteers conduct high quality research into emotional, cognitive and behavioural difference and disorder in children and adults with neurodevelopmental disorders. More information about their research can be found on the projects page of their website. In addition to carrying out research, they also translate the latest findings into effective and practical assessments and interventions. This enables the provision of information, advice and support to parents, carers and professionals.

The research work conducted at the Cerebra Centre includes the study of numerous different neurodevelopmental disorders. The majority of these are rare genetic syndromes, which have not been the subject of a great deal of research due to their rarity. CNDD believe that research in these groups is crucial in order to raise awareness of these underrepresented groups and thus enhance the quality of life of affected individuals. The research group are currently looking for participants for a range of research projects, details can be found on their website or facebook page.

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## Notes

## Notes



## Notes

The Cerebra In-house Research Team carries out desk-based research into a number of areas, based upon parent and professional requests, new scientific evidence and issues raised by our staff. We aim to provide information that is relevant to parents and carers of children with disabilities as well as the professionals who come into contact with them. By empowering parents and professionals with knowledge, we can help them to improve the lives of the children they care for and support.

If you require further information or would like to suggest avenues for further research, please get in touch.

These reports are made possible only by the kindness and generosity of Cerebra's supporters. Cerebra is a charity that works for a future where children living with neurological conditions enjoy lives filled with learning, opportunities and joy. We fund vital research that aims to improve children's lives and those of their families. We directly support more than 10,000 affected children and families around the UK.

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