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Research Summary

Is the diagnosis of a genetic disorder important for children with intellectual disability?

The Cerebra Centre for Neurodevelopmental Disorders

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Thank you.

Is the diagnosis of a genetic disorder important for children with intellectual disability?

This briefing has been prepared to help parents and carers of children with intellectual disability consider if, or when, a genetic diagnosis can be helpful in understanding their child's needs. It is based on an academic book chapter written by the research team at the University of Birmingham's, Cerebra Centre for Neurodevelopmental Disorders that was published in 2010 [1].

What are genetic disorders that are associated with intellectual disability?

For many children with intellectual disability, the cause is unknown. For others, the cause can be traced to exposure to damaging substances during pregnancy, such as alcohol or drugs, or traumatic or other incidents that occur during or just after birth, such as lack of oxygen. For some children the cause is due to differences in either the number of chromosomes, loss of part of a chromosome or other disruptions to the codes for genes that are carried on chromosomes. These genetic disorders can cause physical, developmental and psychological differences and this cluster of differences is called a syndrome. Often, a syndrome will be named after the person who first described children with the genetic disorder, such as Down or Angelman syndrome, but sometimes the syndrome will be referred to by describing which chromosome the disorder is on and where on the chromosome it occurs (e.g. 1p36 deletion disorder). In total, there are more than 1700 genetic disorders associated with an intellectual disability.

How common is a genetic diagnosis in intellectual disability?

The prevalence of genetic disorders within the total population of people with intellectual disability varies depending on the level of intellectual disability. For children with severe to profound intellectual disability, prevalence estimates are around 60% [2]. For children with mild to moderate intellectual disability, the prevalence is lower, but steadily increasing with the advent of technologies for genetic screening and new but rare genetic disorders are discovered.

Individually, the genetic disorders are all very rare. Incidence rates range from 1 in 800-1,000 births for Down syndrome, to, for example, 1 in 380,000 births for Lesch-Nyhan syndrome. Across the UK, the total number of people with a genetic disorder associated with an intellectual disability is estimated to be between 350,000 to 750,000 [3]. This number is increasing as technology for the identification of genetic disorders improves and becomes more widely available.

Why would identifying a genetic cause to intellectual disability be an issue for debate?

Some parents feel it is very important to know the cause of their child's intellectual disability. It can often provide relief and release from a sense of guilt. However, history reveals times when information about genetics and psychology was misused in order to segregate and oppress people with intellectual disability. This was most prominent during the Eugenics movement at the start of the last century. Sadly, discrimination based upon a specific genetic diagnosis can still be identified, albeit to a lesser

extent. One example of this was the decision to withhold heart surgery for some young children with Down syndrome during the 1980's.

This sort of misuse of information has sometimes led to a wholesale rejection of the use of diagnostic labels, including those of syndrome names. It led to a belief that there is little or no merit in knowing whether or not somebody had a genetic disorder. This is erroneous. Whilst it is the case that at times a diagnosis should be irrelevant, just as someone's gender, ethnicity or sexuality should at times be irrelevant, there is now strong evidence to suggest that the cause of an individual's intellectual disability can be extremely important in determining and maximising their well being. This is not to say that a genetic disorder will determine all aspects of a person's life. Rather, it is to say that, at times, it is helpful to know that someone has a genetic disorder alongside everything else that is known about them.

Within this article, we discuss and describe some genetic causes of syndromes in order to understand cognitive, behavioural and physical phenotypes (phenotypes are the outward expression of the genes, or genotype). We will consider how aspects of the phenotypes might interact more or less positively with the environment around the child. The issue of using the diagnosis of a genetic disorder to prepare for the future will also be considered, with specific reference to physical disorders and health. We will then conclude by highlighting both the benefits and difficulties of using this diagnostic approach, both now and in the future.

What is a phenotype?

A phenotype is defined as the observable characteristics or traits of an organism or person. Some definitions say that these are caused purely by genetics, whilst others state that they are due to interactions between genes and the environment.

Some phenotypic characteristics are easy to spot in humans, good examples are hair colour, eye colour and detached or attached earlobes. These are all called physical phenotypes, as they refer to a physical characteristic of a person. They are caused by a specific combination of genes, called the genotype. Whilst these are easy for most of us to identify, it is often harder to think about emotional or behavioural phenotypes. This may be because we tend not to think of such things being genetically driven, as this suggests that they may not be totally within our control.

By studying genetic syndromes, caused by specific genotypes, we can understand how a person's genetic make-up can affect their thought processes, preferences, motivation and behaviour in different places and times.

When thinking about phenotypes, especially behavioural phenotypes, different authors suggest different ways of thinking about them. Some suggest that behaviours within a behavioural phenotype should show a direct relationship with the syndrome. This means that a specific behaviour only occurs in one genotype, and all individuals with that genotype will show that behaviour. This is known as "total specificity". There are very few examples of this sort of relationship, including the hand-wringing movements in Rett syndrome and high-pitched "cat-like" cry in individuals with Cri du Chat (or 5p deletion) syndrome.

These direct one-to-one relationships may be more the exception than the rule, and so a more flexible, "partial specificity" approach has also been suggested. This proposes that there is a higher chance of seeing a particular behaviour within a given syndrome. Examples of this include the preference for routine seen in many individuals with Prader-Willi or Fragile-X syndrome. This behaviour is also seen in typically developing children, but is higher in prevalence and/or intensity within these syndromes and persists for a longer developmental period.

This partial specificity approach is used within Dykenss [4] definition of a behavioural phenotype, which suggests the term describes behaviours that are seen more frequently in individuals with a particular genetic syndrome than in individuals without the syndrome after degree of intellectual disability has been taken into account.

How might genes affect behaviour?

The link from an individual's genes to the increased or decreased chance of showing a behaviour is complex and not fully understood. It is known that genes can affect physical, physiological or neuronal (brain cell) development. If these genes are telling the neurons to connect or act in a certain way at a particular stage of development, that may then change a person's capacity for thinking and/or their behaviour. For example, it might increase their sensitivity to everyday sounds (hyperacusis, seen in William's syndrome), which means they may avoid certain places or things, or place their hands over their ears. It could also alter how much children enjoy particular things, such as social contact and interaction. In some cases, the level of enjoyment of social interactions is increased (such as in Angelman syndrome) and in others it may be decreased (as seen in adolescents and adults with Cornelia de Lange syndrome).

These differences, or preferences, in a child's thinking or behaviour, may interact with each other and with the environment. For example, children with Angelman syndrome show a high preference for social interaction. In a one-to-one setting where they are able to receive all of the attention of anyone with them, you will see high levels of smiling and laughing behaviour from the child with Angelman syndrome. However, if the person who is with the child has to remove their attention for any reason, the child with Angelman syndrome may show a variety of behaviours to regain the attention, which may including pulling the adult's clothes or hair. This is often described as a gene x environment interaction, as both the gene disorder and the environment combine to cause the behaviour. However, it is probably more accurate to describe this as a phenotype x environment interaction.

Sometimes, behaviours can appear to be common in many syndromes, but when examined more closely, subtle between-syndrome differences can appear. One example of this is the high prevalence of "temper outbursts" in a number of syndromes, including Prader-Willi, Fragile-X, and Smith-Magenis, as well as in typically developing children. When considered at this crude level, this behaviour does not appear to have any specificity to any particular genetic disorder or syndrome. However, if the behaviours, are described in more detail, such as "temper outbursts due to high levels of uncontrollability and increased physiological arousal", syndrome-specific differences can be seen.

The importance of detailed descriptions is further highlighted when describing challenging behaviour. One form of challenging behaviour is self-injurious behaviour, which is described as '*Any behaviour, initiated by the individual, which directly results in physical harm to that individual. Physical harm (includes) bruising, lacerations, bleeding, bone fractures and breakages, and other tissue damage*' [5]. Self-injurious behaviour is commonly reported in a number of syndromes, including Lesch-Nyhan, Fragile-X, Cornelia de Lange and Smith-Magenis. However, when these behaviours are examined in more detail, specific forms can be seen within some of the genetically caused syndromes. Examples of this include the hand-directed self-injurious behaviour seen in Cornelia de Lange syndrome [6], hand biting in Fragile X syndrome, skin picking in Prader-Willi syndrome and the insertion of objects into body orifices seen in Smith-Magenis syndrome.

How might information about genetic diagnoses help parents or professionals?

Being aware of a child's genetic disorder can help inform parents and professionals about a number of areas, ranging from physical health to useful environmental modifications. Such knowledge is not necessarily essential, but it can be used to help understand an individual's behavioural presentation in the context of the cause of their intellectual disability. This could therefore potentially reduce the time needed to assess and understand problems and maximise the potential for early intervention.

The areas where such knowledge is known and utilised are discussed below.

1. Physical health and disorders

Children and adults with intellectual disability do not necessarily fit in well to a healthcare system in which no care is received unless actively and specifically requested. For this reason, many people advocate routine screening services (e.g. [7]) and caregiver vigilance. Some syndromes are associated with a higher risk of physical health conditions. Being aware of which health conditions are associated with a specific syndrome can help to minimise delay to diagnosis and any detrimental impact.

Examples of physical health conditions associated with specific syndromes include congenital heart defects, hypothyroidism, early menopause and early dementia (discussed further below) in Down syndrome (e.g. [8,9]). There is also a higher risk of otitis media (middle ear infections), heart disorders and epilepsy in Fragile-X syndrome (e.g. [10,11]). William's syndrome is associated with a high risk of heart and kidney problems in adulthood, and premature arteriosclerosis has been reported in Turner's and Kleinfelter syndromes (see [12] for a review). Gastro-intestinal disorders are commonly seen in Cornelia de Lange syndrome [13], which is associated with considerable pain and, often, self-injurious behaviour.

Recognising that these painful and chronic health conditions are more common within the specific syndromes at specific ages can help parents and professionals to be proactive in identification and treatment.

2. Sensory impairments

Being aware of someone's sensory impairments can help inform an understanding of their behavioural presentation. Some sensory impairments or differences are more frequently noted within specific syndromes. As with the physical health difficulties noted above, being aware of their prevalence and impact can be beneficial for rapid diagnosis and treatment.

An example of sensory impairment in a syndrome is evident in Cornelia de Lange syndrome. Hearing impairments are frequently noted within this syndrome and, if left undiagnosed and untreated, can have obvious impact upon an individual's ability to engage with others and develop speech. This highlights a potential gene x environment interaction, one which will have a significant impact upon an individual's well-being and empowerment.

Sensory differences are as important as sensory deficits. Hyperacusis, mentioned above, is reported to be presented in almost all (95%) of individuals with William's syndrome [14]. The severity level of the hyperacusis is such that it can disrupt normal daily activities for many people, and even cause challenging behaviour. Being aware of such sensory differences means that environments can be tailored in order to minimise their impact.

3. Cognitive phenotypes

Some syndromes are associated with specific differences in cognitive abilities. This means that some syndromes may be associated with certain types of thinking styles or that people may find it hard to think in particular ways.

One example of this is seen within Prader-Willi syndrome, which is associated with deficits in attentional shift. This means they have difficulties with moving their attention from one thing to another. This is more noticeable when the shift needs to be made quickly or unexpectedly. If such unexpected or rapid changes occur, these can give rise to some of the previously described phenotypic behaviours, such as temper outbursts [15].

Knowledge of this cognitive phenotype has provided a framework for developing new intervention approaches that may potentially be effective. For example, using a change signal card – which makes changes less unexpected – seems to make it less likely that a change will trigger a temper outburst for a person with Prader-Willi syndrome [16]. And playing a specially designed computer game can improve attentional shifting and so, in principle, may have a beneficial impact on behavior for some individuals [17].

4. Motivational or emotional phenotypes

Each individual is motivated by their own preferences. Such preferences are not always given as much consideration as they might warrant, especially since they can potentially explain many difficult behaviours. However, as with many internal states, they are not easy to define or measure.

Children with Angelman syndrome show excessive smiling and laughing. Initially it was thought that these behaviours were shown indiscriminately, regardless of the environment. However, more recent research suggests that these behaviours are more common when adults are giving attention suggesting enhanced enjoyment of adult contact may form part of the motivational phenotype for this syndrome

Horsler and Oliver [18] observed children with Angelman syndrome in different settings, including typical social interaction, social interaction without eye contact, and no social interaction. They found that the laughing and smiling occurred most during the typical social interaction setting, suggesting the children gain a great deal of pleasure from such events. Studies which followed up on this work found that not only did the adult's behaviour influence the child's levels of smiling and laughing, but that this behaviour also changed with age [19,20]. Some researchers [21] found that children with Angelman syndrome were more likely to be aggressive (by pulling the hair or clothes of the adults around them) when they were not receiving any attention or social interaction. These results together suggest that individuals with Angelman syndrome are internally driven, or motivated, to engage in social interaction and receive social contact and when this contact is limited, aggression occurs. These results have led to investigations into the underlying genetics of social behaviours, investigating a pathway from genes to behaviour via a difference in preference or internal motivation [22].

5. Changes across the lifespan

Within some syndromes, the effect of the genetic disorder on some areas of the brain or behaviour is not visible until later in life. Knowing that these changes occur within specific syndromes allows for planning and proactive screening. It also allows others to understand why

there may be changes in an individual's physical appearance, sensory abilities, preferences, behaviours or cognitive skills.

A well-researched example of this is the development of dementia in individuals with Down syndrome. Nearly all adults with Down syndrome over the age of 40 show the neuropathological markers of Alzheimer's disease in their brains at autopsy [23]. However, the prevalence rates for the clinical presentation (i.e. what carers or professionals actually see) differ significantly from this figure. Age-specific prevalence rates range from 0-2% of 30-39 year olds up to 33.3-54.5% of 60-69 year olds [24]. For comparison, the prevalence of Alzheimer's disease in individuals without Down syndrome or an intellectual disability aged 65-69 is 1% [25].

Just as for dementia in individuals without Down syndrome, the development of Alzheimer's disease has an impact upon an individual's cognitive and behavioural phenotype. The work of Holland et al. [24] suggests that behavioural changes, such as increased apathy and disinhibition, are noted by carers earlier than changes in memory or cognitive function. Because both the cognitive and behavioural changes are so common within ageing adults with Down syndrome, there is the potential for professionals to correctly interpret change as a possible sign of dementia and provide early intervention accordingly. However, if the knowledge of the increased prevalence rate for dementia was not widely known, the assessment would have to start with a much broader basis, and potentially lengthen the time until intervention is provided.

6. Environmental considerations

This briefing has continually highlighted the importance of the environment and considering its role within the gene-behaviour-environment interaction or pathway. However, it is important to note that such interactions can be reciprocal; it is possible for a person to change the environment, and for the environment to change a person. It is incorrect to suggest that because a behaviour, preference or phenotype is genetically 'caused' that it is inevitable and nothing can be done. This therapeutic nihilism (or exclusion) would ignore the contribution of the environment and those around the child and their capacity to contribute to change.

Summary

The discussion within this briefing highlights the importance of considering a bio-psycho-social model when trying to understand why people might think, feel or behave in the way that they do. This is especially important for individuals with intellectual disability caused by genetic disorders as there is such strong evidence for the impact of genetics, behaviour and the environment on all of these elements, including upon family experiences and parental mental health [24].

Some of the implications for genetic diagnoses are clear. For example, knowing the increased prevalence of painful chronic or acute health conditions at specific ages should promote proactive assessments and rapid treatment. Being aware of sensory impairments, differences or preferences can help both families and professionals to consider the impact of the environment and ways in which it could be helping or hindering an individual's well-being.

Other implications may be more subtle. For example, knowing that an individual with a particular genetic diagnosis has a specific cognitive deficit means they might find certain tasks more difficult and therefore require more support or help. Knowing more about an individual's diagnosis can therefore help to promote inclusion and access to activities or services.

These examples clearly highlight why recognising and understanding genetic diagnoses can be helpful. However, one cannot ignore the potential for the oversimplification of gene-behaviour relationships, and the potential for therapeutic exclusion, as evidenced by the examples at the beginning of this briefing.

Finally, knowing an individual's diagnosis does not mean that other individual characteristics, such as personality, likes and dislikes, personal history, beliefs, strengths and needs should be ignored or their importance minimised. These are clearly important. Also, use of a diagnosis does not necessarily devalue or marginalise someone because a difference is highlighted. It is the use to which that information is put that determines whether it is in the person's best interest and ulitmately contributes to their wellbeing.

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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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