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# The importance of understanding the behavioural phenotypes of genetic syndromes associated with intellectual disability

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## Abstract

Behavioural phenotype research is of benefit to a large number of children with genetic syndromes and associated developmental delay. This article presents an overview of this research area and demonstrates how understanding pathways between gene disorders and behaviour can inform our understanding of the difficulties individuals with genetic syndromes and developmental delay experience, including self-injurious behaviour, social exploitation, social anxiety, social skills deficits, sensory

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differences, temper outbursts and repetitive behaviours. In addition, physical health difficulties and their interaction with behaviour are considered. The article demonstrates the complexity involved in assessing a child with a rare genetic syndrome.

**Keywords** behavioural phenotypes; developmental delay; endophenotype; genetic syndrome

## Introduction

In this article we aim to demonstrate that understanding behavioural phenotypes is of importance to individuals with genetic syndromes and associated intellectual disability. Evidence of behavioural, physical, cognitive, and emotional differences in genetic syndromes will be presented together with discussion of how these differences can interact with environmental and developmental factors. These differences may, at times, give rise to specific psychological problems for individuals with genetic syndromes and evidence is presented to highlight how knowledge of behavioural phenotypes places practitioners in a better position to develop appropriate interventions. The review begins with a broad discussion of the value of behavioural phenotypes followed by a more detailed review of research findings.

## What is a behavioural phenotype?

A behavioural phenotype refers to observable characteristics that occur more often in individuals with a specific genetic syndrome than individuals without that syndrome. Whilst a behavioural phenotype describes observable behaviour, the term 'endophenotype' describes characteristics that are not directly observable. These characteristics may include thoughts, emotions and motivational states. In addition, a distinction is often made between behavioural phenotypes and classic clinical phenotypes that typically focus more on physical characteristics and disorders. As these phenotypes interact with one another, we make reference to all of them to adopt an integrative approach to understanding behaviour.

## How is behavioural phenotype research conducted?

Behavioural phenotype research involves exploring the pathway from genetic disorder to observable behaviour. Researchers start from the premise that a change at the genetic level can impact on physiological and neuronal development. These changes can subsequently affect cognitive, emotional and motivational processing, which may impact on behaviour. Whilst it is possible to discern a number of levels at which difference can occur, viewing the associations as a closed, linear, unidirectional pathway is likely to lead to erroneous conclusions. For example, while some phenotypic behaviours always occur in individuals with a genetic syndrome, such as over-eating in Prader–Willi syndrome, many phenotypic behaviours do not occur in everyone with a syndrome. Skin picking and temper tantrums, for example, are more likely in Prader–Willi syndrome but not inevitable. This illustrates that other variables such as environmental and developmental factors may interact with fundamental biological factors to give rise to phenotypic behaviours. This pathway from genetic disorder to behaviour illustrates that there are numerous points along the pathway at which behaviour can be influenced and consequently where interventions can be targeted.

## The scope of behavioural phenotype research

Genetic syndromes are typically very rare. For example, Down syndrome, the most prevalent genetic syndrome associated with intellectual disability, occurs in approximately 1:800 to 1:1000 live births, and rarer syndromes such as Rubinstein–Taybi syndrome occur in around 1:125,000 live births. Whilst individual syndromes are rare, overall a large number of individuals are affected by genetic syndromes with associated intellectual disability. In the UK, it is estimated that between 350,000 and 750,000 individuals are affected. Therefore, improved understanding of the behavioural phenotypes in genetic syndromes is likely to be of benefit to a large proportion of the population.

## What are the objections to the study of behavioural phenotypes?

Not everyone working within the field of intellectual disability agrees that knowledge of genetic syndromes and the associated behavioural phenotypes is beneficial. Historically, the eugenics movement adopted a social engineering agenda, whereby it was argued that genetics should be manipulated for the benefit of human society. This philosophy has been resoundingly refuted on the grounds that it would lead to further discrimination and stigmatisation of individuals with intellectual disabilities. Due to related concerns, some practitioners working within the field of intellectual disability have rejected diagnostic syndrome labels arguing that they put too much emphasis on a medical model of understanding human difficulties that is not relevant to individuals with intellectual disability and ultimately compromises their standing in society. While it is clearly imperative to be aware of the potential for diagnostic labels to be used in an oppressive manner, this does not mean that knowledge of genetic aetiology is always unhelpful to individuals with intellectual disability, particularly if the genetic syndrome impacts on the individual to a significant degree and knowledge of the syndrome is used to enhance an individual's well being.

Behavioural phenotypes are often given less emphasis because it has been demonstrated that a high proportion of behavioural difficulties shown by individuals with intellectual disability, such as self-injury and aggression, can be understood as learned behaviours, maintained by rewarding consequences within the environment. This has led to many practitioners placing greater emphasis on the current environmental contingencies than genetic influences when trying to understand behaviour. It is likely that this emphasis has continued due to learning theory approaches being demonstrably effective approaches and avoiding therapeutic nihilism, which could occur if practitioners adopt the position that behaviour cannot be changed because it is part of a genetic syndrome. Whilst learning theory can explain a high proportion of behaviours such as self-injury and aggression, choosing one position over the other is to the detriment of the individual with a genetic syndrome as it may reduce the effectiveness of behavioural formulation. This is because research clearly highlights nuanced interactions between genetic disorders and the environment in genetic syndromes.

## What are the benefits of understanding behavioural phenotypes?

The key issue is whether exploring behavioural phenotypes is likely to lead to better outcomes. Knowledge of behavioural

phenotypes can help others to understand how a person interacts with their environment and how to adapt the environment to suit their needs, and it can help researchers track the path from causal underpinnings through to the difficulty the person is currently experiencing. In genetic syndromes these difficulties can include, for example, strong adherence to routines, temper outbursts, self-injurious behaviour, risks associated with social and sexual exploitation, and social anxiety. In the next section some of these phenotypic behaviours are described, followed by a discussion of physical health difficulties and how they may interact with phenotypic behaviours in some syndromes.

## Behavioural phenotypes

When considering behavioural phenotypes it is important to establish whether every person with the syndrome engages in the phenotypic behaviour or whether the presence of a syndrome leads to a heightened likelihood of a behaviour. Within syndrome variation highlights the importance of considering how environmental and developmental factors interact with genetic disorders. In addition, it highlights the importance of avoiding a deterministic stance when considering how an individual with a syndrome will develop. Assuming that an individual will definitely develop a particular behaviour may be unhelpful because holding this belief may increase the chance that the behaviour will occur due to the expectations of others. Furthermore, it can feed into a belief that nothing can be done to prevent or to reduce the likelihood of the behaviour occurring. Therefore, behavioural phenotype research should be used to guide assessment and interventions, not determine them.

A significant body of empirical research has now accumulated that describes behavioural phenotypes in genetic syndromes. For example, repetitive behaviour has been operationalised at a fine-grained level and repetitive behaviour profiles have been compared across genetic syndromes. There is wide variation in these profiles across syndrome groups and evidence of syndrome specific repetitive behaviour including attachment to a preferred adult in Smith–Magenis syndrome and attachment to objects in Cri du Chat syndrome. Adherence to routine has been found to be elevated in Prader–Willi syndrome in comparison to Angelman and Cri du Chat syndromes. In addition, it has been found that body stereotypy occurs in Rubinstein–Taybi syndrome at a similar rate to fragileX syndrome and autism spectrum disorder (ASD) and at a significantly higher rate than in Down syndrome.

Self-injurious behaviour and aggression have been shown to be elevated in some genetic syndromes relative to individuals with heterogeneous intellectual disability. Self-injurious behaviour occurs in approaching 100% of people with Lesch–Nyhan syndrome. Children and adults with Angelman and Smith–Magenis syndromes have been shown to be over three times more likely than those without these syndromes to show aggression. Some specific forms of behaviour are more prevalent in genetic syndromes, particularly when described in detail. For example, it has been found that in Cornelia de Lange syndrome self-injury is more likely to be directed towards the hands, whereas a unique behaviour, inserting objects into body orifices, is observed in Smith–Magenis syndrome.

Behavioural phenotypes are of interest when considering Autism Spectrum Disorder. High rates of ASD have been reported

in syndromes such as Cornelia de Lange (CdLS) and fragileX (FXS). However, there is debate about whether the ASD profile of behaviours that triggers a diagnosis in these syndromes is the same as in individuals with idiopathic ASD. For example, socio-communication deficits in CdLS may be related to other phenotypic behaviours in this syndrome such as social anxiety. Similarly, it has been found that in fragileX syndrome social anxiety may contribute to elevated levels of ASD phenomenology on standardised measures in this group. This is a clear example of how a non-syndrome specific approach may lead to important differences between groups being overlooked.

Individuals with Williams syndrome have been shown to display reduced fear of strangers and excessive friendliness towards others. This can lead to individuals being at risk of social or sexual exploitation, and this risk is heightened further because cognitive ability tends to be higher in Williams syndrome relative to other disorders. In addition, individuals with Williams syndrome experience anxiety but in contrast to individuals with fragileX and Cornelia de Lange this anxiety appears to be related to specific non-social stimuli. Hence, it is clear how understanding behavioural phenotypes points towards different intervention strategies to support individuals with different genetic disorders.

### Physical pain and health difficulties

In the following section health difficulties are discussed in relation to intellectual disabilities generally and then the focus is narrowed to consider heightened prevalence of health difficulties in genetic syndromes. Physical pain can often present as an underlying cause, or increase the likelihood, of behavioural difficulties in individuals with genetic syndromes. An awareness of the health needs of individuals with intellectual disability and genetic syndromes is thus essential as part of any complete assessment of an individual's needs.

A greater proportion of individuals with intellectual disability experience health problems compared to the general population. Yet individuals with intellectual disability receive comparatively lower levels of preventative healthcare, have reduced frequency of contact with general practitioners and are less likely to have health issues identified and diagnosed. In a healthcare system where care has to be actively requested, people with intellectual disability may not receive necessary services. Pain and discomfort is a subjective experience and assessment of pain typically depends on self-report which is often impossible in individuals with severe or profound intellectual disability or communication difficulties which are common in genetic syndromes. This demonstrates the necessity for routine health screening, vigilance from caregivers and professionals and obtaining reliable self-report of health issues from more able individuals.

In addition to broad health benefits of improved awareness of the increased likelihood of health problems in people with intellectual disability, there is a growing literature reporting an association between pain and self-injurious and aggressive behaviour in people with intellectual disability. Individuals with intellectual disability are already at increased risk for both pain (as a result of health problems) and self-injurious and aggressive behaviour. Given the impact of these behaviours on the well being of those showing the behaviour and those who

care for them, it is evident that identification and treatment of painful health conditions in people with intellectual disability may have broad benefits. Recognising syndrome specific health issues may improve recognition and diagnosis of health conditions in these syndromes, thus mitigating the impact of health problems.

Specific health issues associated with genetic syndromes include gastro-intestinal disorders in Cornelia de Lange syndrome, which results in painful reflux associated with self-injury and increased prevalence of diabetes mellitus (associated with obesity due to hyperphagia) in Prader–Willi syndrome. Certain syndromes are associated with a particularly wide range of serious health conditions. Tuberous Sclerosis Complex, characterised by abnormal growths in multiple organs, is associated with brain tumours (resulting in headaches, photophobia, double vision, dizziness, nausea and vomiting), epilepsy in over 80% of those affected and renal tumours and failure are also common.

Health problems within a syndrome can be diverse and change over the lifespan; people with Down syndrome have increased rates of congenital heart defects likely to be identified at birth, hypothyroidism in childhood and premature menopause and Alzheimer type dementia affecting later life. In adulthood, individuals with Williams syndrome are at increased risk of heart problems and early onset arteriosclerosis has been reported in Turner's and Klinefelter syndromes. Furthermore, within some syndromes health conditions may vary depending on the underlying genotype, for example while seizures are highly prevalent in Angelman syndrome, the presentation of these seizures may vary depending on the precise genotype.

Increased awareness of such syndrome specific health problems, their prevalence across the lifespan and the potential for diversity in health problems within a syndrome would aid recognition of both chronic and acute painful health conditions in these populations. This is key to proactive identification and treatment of such conditions.

### Sensory impairments and difference

Sensory impairments and difference are often reported in the intellectual disability literature, with sensory sensitivity prominent in children diagnosed with an Autism Spectrum Disorder. Whilst the presentation may vary across certain populations, many genetic syndromes are associated with *specific* profiles of sensory functioning.

Hearing impairments are frequently noted in Cornelia de Lange and Smith–Magenis syndromes. Difficulty with hearing in these syndromes is associated with poor expressive communication, highlighting the importance of early identification. Vision impairments reported in Lowe syndrome include cataracts and glaucoma, which can lead to blindness if left untreated. Understanding these sensory impairments and causal pathways to behaviour can be an important early intervention.

In addition to specific impairments, some syndromes are associated with unusual responses to sensory stimuli, or sensory 'difference'. Heightened responses to auditory stimuli (hyper-acuity) are often noted in Williams syndrome (95% of children and adults) and can cause difficult behaviour in noisy environments. Hyper-arousal to sensory stimuli is also described in



fragile X syndrome, and is associated with lower performance in school activities. Lowered responsiveness, particularly to painful stimuli, is reported in Cornelia de Lange, Angelman and Prader–Willi syndromes. This has particular importance for the appropriate assessment of physical conditions and pain in these syndromes.

### Cognitive phenotypes

Many genetic syndromes are associated with uneven cognitive profiles. For example, whilst individuals with Williams and Down syndromes both show deficits in working memory, these appear to be specific to phonological working memory in Down syndrome but spatial working memory in Williams syndrome. When investigating cognitive function, including general intellectual ability, measures of which are often used for matching in group comparison studies, it is therefore critical to consider that depending on the measure, individuals with different syndromes may potentially obtain the same score for different reasons. For example, in general terms, boys with fragile X syndrome show a relative strength in verbal versus performance IQ scores; but individuals with the most common genetic subtype of Prader–Willi syndrome show the opposite pattern.

Importantly, careful cognitive assessment, taking into account known features of relevant cognitive profiles, has the potential to elucidate relationships between cognition and behavioural/emotional phenotypes that can be exploited for intervention purposes. For example, specific difficulties with cognitive attention switching are relevant to the preference for sameness seen in both Prader–Willi and fragile X syndromes. Attention switching comprises part of executive function; the capacity to control and regulate cognition and behaviour, particularly in novel and complex environments. Importantly, this specific switching deficit was only identified when appropriate cognitive assessment was applied that avoided confounds linked to the broader cognitive profiles associated with these syndromes.

It is interesting and potentially useful to observe that the same specific cognitive deficit can be linked to different phenotypic behaviours in different genetic syndromes. Whilst in both individuals with Prader–Willi and fragile X syndromes the difficulty in attention switching is linked to a preference for predictability this appears to more frequently trigger temper outbursts in Prader–Willi syndrome but expressions of extreme anxiety in boys with fragile X syndrome. This illustrates how comparison across different genetic syndromes may identify both syndrome specific and syndrome shared pathways to behaviour; which have important implications for developing effective and relatively far reaching interventions.

### Emotional/motivational phenotypes

Some genetic syndromes are associated with characteristics which may not be directly observable, including motivational states. Excessive laughing and smiling in Angelman syndrome provides one example of this. The nature of this behaviour is indicative of elevated social motivation with higher levels of laughing and smiling in the presence of adult interaction, supported by frequent social approach behaviours towards adults. It has been suggested that social motivation also underpins the heightened aggression in Angelman syndrome. Heightened

social motivation or ‘attention seeking’ has also been described in Smith–Magenis syndrome, with a particular preference for adult social interaction compared to peers. Once again, this motivational phenotype is thought to underpin the relatively high levels of aggression described in the syndrome, further highlighting the importance of understanding causal pathways to behaviour.

### Developmental change

The manner in which genes and environment interact to produce phenotypic characteristics in syndrome groups is, of course, not static across the lifespan. In Down syndrome, for example, neuropathological changes associated with Alzheimer’s disease are found in most individuals over 40 years of age. The onset of associated signs of dementia, including personality changes and declining working memory, executive function and language, will lead to profound changes over time in the behavioural and cognitive phenotypes of the syndrome.

Syndrome-specific age related changes remain less well understood in other groups. However, the characteristically high levels of laughter and smiling seen in response to social stimuli in Angelman syndrome may reduce with age, and mood may be lower in older than in younger people with Cornelia de Lange syndrome. Further understanding of the development of behavioural, cognitive, emotional and physical phenotypes across the lifespan may allow improved long term management for many syndrome groups.

### Environmental interactions

Throughout this article we have illustrated complex influences of the environment on behavioural phenotypes. Many phenotypic emotion-related behaviours, for example, are modulated in syndrome-specific ways by environmental variables (e.g., whilst pronounced anxiety responses are seen in both Cornelia de Lange and Williams syndromes, these are associated with social stimuli in the former and non-social stimuli in the latter); similarly, specific cognitive characteristics (e.g., attention-switching atypicalities in Prader–Willi syndrome) are thought to interact with specific environmental events (e.g., unexpected changes) to produce behavioural responses.

In addition, a person’s environment is itself subject to his or her own genetic influence. To take a simple example, a high frequency of smiling by a person with Angelman syndrome is likely to be reciprocated by increased environmental experience of other people’s smiles. This may in turn influence phenotypic behaviours in the person (e.g., in this case, an individual with Angelman syndrome may smile with even greater frequency, since their smiling behaviour is partially triggered by social interaction). The manner in which (to take just two of many possible further examples) the social anxiety associated with Cornelia de Lange syndrome, or the preference for adult contact seen in Smith–Magenis syndrome might shape not only an individual’s own responses but also his or her social and physical environment is not currently understood, and presents an intriguing challenge.

If we also consider the broader context of the individual’s entire genome, which is likely to be correlated with genetic factors in individuals in the immediate environment, such as

parents and siblings, and the multifarious ways in which this may interact with both the primary genetic cause of a syndrome and with the environment, then a highly complex web of relationships between genetic and environmental factors can be seen to influence behavioural phenotypes. Disentangling some of these relationships, at neurological, cognitive, emotional and behavioural levels, presents exciting challenges for future research but in the meantime there are clearly some critical points of potential intervention that are immediately identifiable because the genetic cause of a disorder is known.

## Conclusions

The main problem confronting clinicians in this area is that due to the rarity of the syndromes practitioners are very unlikely to be involved with many people who have the same disorder. In combination with the number of syndromes, this means that experience will be spread thinly and within syndrome commonalities may be missed. Consequently, condensed and accessible information on syndromes is invaluable for practitioners. This information is available on websites such as those maintained by the Society for the Study of Behavioural Phenotypes and Contact a Family. Additionally, many syndrome support groups maintain up to date information on their websites and typically the content is reviewed by researchers and clinicians in the field. These resources can provide a very useful starting point to describe the physical, cognitive and behavioural presentation of syndromes and the potential points of intervention. ♦

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## Practice points

- A pathway can be mapped from genetic disorder to behaviour in many genetic syndromes with associated developmental delay.
- Many individuals with genetic syndromes have a specific profile of psychological and healthcare needs.
- Even though a particular behaviour may be more likely to occur in a genetic syndrome this does not mean it is inevitable.

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