Behavioural phenotypes

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Behavioural phenotypes are the psychological equivalent of the somatic or physiological manifestations of a syndrome that has a genetic aetiology. They can be defined as comprising behaviours – including cognitive processes and social interaction style – which are consistently associated with, and specific to, a syndrome that has a chromosomal or a genetic aetiology. Genetic disorders do not have uniform effects, either on behaviour or on somatic aspects of the phenotype, and there is great variability in the expression of even the most 'characteristic' features of a syndrome. The remaining genotype of the affected individual will modify the behavioural expression of the anomaly, as will developmental trends and the environment in which the child is raised.

It is a mistake to describe as a behavioural phenotype the features of a disorder in which a genetic anomaly is suspected but has not been demonstrated; this is liable only to cause confusion. The term should be restricted to conditions in which a genetic deletion/mutation or chromosomal anomaly has been identified. Conditions that have not met this criterion to date could meet it at any time, if genetic investigations are successful in identifying a genetic cause for the syndrome. Rett syndrome, for example, had no known genetic aetiology until the discovery of a mutation in the gene MECP2.

Clinical value

The identification of behavioural phenotypes has clinical value. Many children with a genetic disorder possess easily identifiable somatic manifestations, such as short stature or facial dysmorphology. Behavioural or cognitive characteristics are less easily identifiable, less specific and more insidious. Parents are often perplexed by a child's disturbed behaviour that is inexplicably starkly different from that of their siblings. The hyperphagia of Prader–Willi syndrome or the self-injury associated with Lesch–Nyhan syndrome are characteristic of those disorders and are seen in the majority of children with the associated genetic anomalies; reassuring parents of that will be helpful to them. Parents often experience guilt about a child who is biologically different from normal and they need to be reassured that behavioural manifestations of the condition are not their fault, nor are they due to wilfulness on the part of the child. In spite of their congenital aetiology, such manifestations are often manageable.

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Research value

Behavioural phenotypes may guide researchers towards genes that influence the development of cognitive skills and socially appropriate behaviours. By definition, the impact of such genes on development is substantial. Accordingly, they are unlikely to account for individual differences in normally distributed traits, such as intelligence, personality or talents. The study of individual differences – one of the main tasks facing behavioural genetics – is conceptually a different issue. Understanding the aetiology of behavioural phenotypes could, however, provide an indirect route to understanding the development of neural systems that are dysfunctional in a range of neurodevelopmental disorders, in childhood and adulthood.

The context of development

The study of behavioural phenotypes in children is complicated by developmental considerations. Characteristic features may not manifest at all ages and they may not develop in an invariable progression. Interference with cognitive processes (e.g. the visuospatial deficit of 45,X Turner syndrome) can manifest in one way during childhood (failure to learn geometry) and another in adulthood (inability to navigate). Progressive changes in the cognition and behaviour may be genetically programmed, but their manifestations depend on the influence of environmental contexts.

Another reason for the variable expression of phenotypes during the lifespan relates to the fact that genes are switched on and off over time, both according to an internal clock and in response to environmental influences. The phenotypic effects of a mutated or dysfunctional gene will therefore depend on its pattern of expression during any given period of development.

The natural history of genetically specified disorders with relatively circumscribed cognitive deficits (such as the early stages of Huntington's disease) shows how dysfunction can develop in later life – it is by no means always present during infancy, or even childhood. On the other hand, remarkable talents in certain cognitive skills may develop over time in disorders with a strong genetic component, such as the enhancement of certain visuospatial skills in some boys with autism, giving rise to considerable artistic and other abilities.[1] Idiopathic autism is an example of a condition that was presumed to have a relatively simple genetic aetiology, although the optimism expressed a few years ago that a handful of genes are involved in the predisposition to the syndrome seems misplaced in view of our failure to find any candidate genes for general susceptibility. Phenocopies of many autistic features are seen in other conditions, including fragile-X syndrome and Turner syndrome, but those conditions are not associated with the savant qualities occasionally encountered in the idiopathic form.

Genetic mechanisms

Mutations: many behavioural phenotypes are caused by single gene mutations. A germ-line mutation that occurs in the DNA of cells that will produce gametes (sperm or eggs) will be inherited by the cells of subsequent generations. The term 'mutation' has come to imply an alteration in gene product that is detectable by some change in the phenotype of the organism. The genotype at any given locus

may affect the probability of disease, but does not fully determine the outcome. Environmental factors have a crucial part to play too, influencing factors such as the timing of onset of this phenotype and its severity. Conditions caused by mutations that alter fundamental properties of gene function include fragile-X syndrome (the FMR1 gene) and Rett syndrome (the MECP2 gene).

Chromosomal anomalies: some behavioural phenotypes are associated with abnormalities in chromosomal structure or in the total complement of material. Gross chromosomal anomalies affect the expression of several or even many genes. Chromosomal abnormalities can be numerical or structural.

Numerical abnormalities are associated either with the loss of one of a pair of chromosomes altogether, or with the aberrant formation of more than one copy of a chromosome (as in trisomy 21 Down syndrome or 47,XXY).

Structural anomalies are more subtle and usually involve microdeletions of a few thousand nucleotide bases or, rarely, the loss of a substantial part of a chromosome (e.g the short arm of an X chromosome). Structural anomalies may sometimes be associated with the doubling or tripling of segments of a chromosome, lengthening it. They can also result from the aberrant translocation of part of a chromosome onto another. Structural abnormalities can arise in a variety of ways, including deletions of part of the chromosomal arms, which may be terminal or interstitial.

Gene dosage is usually a delicate affair. If it is significantly interfered with (by monosomy or triploidy, for example), a phenotype results. All such phenotypes have a behavioural or cognitive correlate, although this may be subtle.

Trinucleotide expansion repeats and anticipation: some congenital conditions result in phenotypes that become more severe in successive generations. A mechanism associated with this phenomenon is known as anticipation, exemplified by fragile-X syndrome and Huntington's disease. Trinucleotide repeat expansions are the biological basis of anticipation. Trinucleotide repeats are triplets of nucleotides, usually cytosine (C), guanine (G) and arginine (A). These triplets are designated CGG, CAG, etc. The repeats may occur within genes, or they may be found in regions of DNA that lie between genes. If they lie within genes, they may be in transcribed sequences ('exons'), or within DNA sequences that are excised by the RNA-making machinery ('introns'). Expansions occur in the course of DNA replication and the repeats grow in length as they are passed from one generation to the next. As they grow, they have an increasingly severe impact on gene function. Manifestations may be subtle, especially if they are cognitive, emotional or behavioural in character. There may be a range of triplet expansions that are not associated with significant gene dysfunction, but in the most extreme expansions, complete cessation of gene activity results. It is a matter of great theoretical and clinical importance to discover whether expansions within the range considered to be benign nevertheless have some influence on gene expression, and consequently subtle adverse consequences on behaviour or learning.

Huntington's disease is an autosomal dominant condition with almost 100% penetrance. The single susceptibility locus has been identified: it produces a protein called huntingtin and is located on the short arm of chromosome 4. Individuals with more than 35 CAG repeats in this gene will develop the disease eventually, although the age of phenotypic manifestation depends on the number of such repeats present. There is no obvious or discriminating behavioural phenotype in childhood or adolescence. In a remarkable set of investigations, Gray *et al.* studied a sample of young adults who were at genetic risk, but who did not yet show any signs of the disease clinically.[2] They were compared to people who presented for genetic testing but turned out not to carry the gene for Huntington's disease. A highly selective deficit in the recognition of the facial expression of disgust was confirmed in those who were proved by genetic testing to be Huntington's gene carriers but who were free from clinical symptoms. They did not perform significantly more poorly than non-carriers on any of the background tests, or on any other face-processing tasks, including the recognition of other basic emotions. Other functional imaging studies have shown that, in normal individuals, the perception of the facial expression of disgust activates the anterior insula and the caudate-putamen. These regions are involved in the processing of unpleasant stimuli in the form of taste and smells. Development of the striatum, and the anterior insula, is compromised by Huntington's disease. This is a striking example of a subtle phenotypic feature (failure to recognize an emotion), highly discriminating of the disorder in question, which manifests because of a specific and demonstrable neurodevelopmental anomaly in a specific brain area – the same area that is specialized for the processing of that emotion in normal individuals. It is an archetypal behavioural phenotype. More recently, additional studies have identified functional brain anomalies, in particular reduced activation in the left anterior cingulate cortex, in asymptomatic carriers of the genetic mutation.[3] Potentially associated cognitive deficits, primarily involving attention and executive functions, have also been reported in such individuals,[4] further expanding our understanding of the neural and cognitive phenotype of this disease.

Chromosomal deletions and duplications: spontaneously occurring chromosomal aberrations can provide useful pointers to the existence and location of genes that are important for the development of normal cognition and behaviour. Abnormalities of chromosomes that can be observed under the microscope are known as cytogenetic abnormalities. By observing where such anomalies occur in an individual with a behavioural or other phenotype, the investigator has a clue where one or more genes might lie that are related causally to the condition.

In the early years of positional cloning (the identification of the position of a gene based on its approximate location), several important discoveries were made simply because rare cytogenetic abnormalities in one, or at most a few, patients led to the 'disease' gene. These included dystrophin (Online Mendelian Inheritance in Man (OMIM) reference number 310200), retinoblastoma (OMIM no. 180200) and neurofibromatosis 1 (OMIM no. 162200).

Obviously, the difficult part of this investigation is to identify a candidate gene in the region of the cytogenetic anomaly; discovering the correct candidate can be very time-consuming.

Microdeletions occur at various vulnerable points of the genome. They may originate *de novo* during meiosis or they may be inherited. There is an associated loss of a few megabases of DNA. A microdeletion can disrupt a large number of genes, but if the individual with the microdeletion is heterozygous (in other words, possesses an entirely normal copy of the deleted region on the

