Behavioural phenotypes

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Abstract
The study of behavioural phenotypes is of both research and clinical significance. It assists in the identification of genes that influence the development of cognitive and social skills, and as such may be vital in order to further the understanding of the development of neural systems within genetic disorders. The study of this field will also help to support families in understanding and managing the behavioural presentation of an individual with a genetic disorder. This article examines the mechanisms that underlie genetic disorders and discusses the difficulties associated with studying behavioural phenotypes across the lifespan. It considers the importance of understanding cognitive and behavioural phenotypes through the examination of specific genetic disorders.

Keywords behavioural phenotype; cognitive phenotype; genetic disorders; genetic mechanisms; genotype

Definition

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 – that are consistently associated with, and specific to, a syndrome that has a chromosomal or 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 individual 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*.[1]

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Clinical value

The identification of behavioural phenotypes has clinical value.[2,3] 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 and 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 anomaly; 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.

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, even if those characteristics are known to be strongly heritable. 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 both 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 (such as the visuospatial skills deficit of 45,X Turner syndrome[4]) can manifest in one way during childhood (e.g. failure to learn geometry) and another in adulthood (e.g. inability to navigate in a car). Progressive changes in cognition and behaviour may be genetically programmed, but their manifestations are dependent on the influence of environmental contexts. Occasionally, candidate genes for a specific behavioural phenotype may be found in association with gross structural anomalies, such as *EFHC2* and deficits in fear recognition in X-monosomy.[5]

Another reason for the variable expression of behavioural or cognitive 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. There have been recent concerns that these epigenetic mechanisms could have a role in the disruption of patterns of DNA methylation in the embryo, leading to potential developmental alteration in the offspring and persistent changes in the germline.[6]

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 ability.[7]

Idiopathic autism is an example of a condition that is presumed to have a relatively simple genetic aetiology, in the sense that a handful of genes is involved in the predisposition to the syndrome. There is no evidence of a unique endophenotype, and phenocopies of many autistic behavioural features are seen in other conditions, including 22q11.2 deletion syndrome[8] and Prader–Willi syndrome.[9] However, 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 germline 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 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 not with mutations in a particular gene, but 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, more rarely, the loss of a substantial part of a chromosome (such as the short arm of an X chromosome). Structural anomalies may sometimes be associated with the doubling or tripling of segments of a chromosome, thereby lengthening it. They can also result from the aberrant translocation of a part of one chromosome on to another. Structural abnormalities can arise in a variety of ways, including deletions of part of the long or short chromosomal arms, which may be terminal or interstitial (occurring within the arm).

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

Chromosomal deletions and duplications are spontaneously occurring chromosomal aberrations that 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 as to 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 no other knowledge than its approximate location), several important discoveries were made simply because rare cytogenetic abnormalities in one patient, 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).

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 equivalent chromosome inherited from the other parent) there may be few phenotypic consequences. Recently, it has been discovered that there are numerous inherited and *de novo* variations in segments of chromosomes (known as copy number variations).[10] The finding potentially indicates a new perspective on genetic predisposition to disease, which has already been shown to have relevance to autism.[11]

Williams syndrome

Williams syndrome is a rare sporadic disorder with an incidence of about 1 in 7500 live births. It is associated with a distinctive cognitive and behavioural profile, a superficial facility with language, sociability, good facial recognition, and very poor visuospatial skills. In more than 90% of clinically diagnosed patients there is a submicroscopic deletion on the long arm of chromosome 7 at 7q11.2. This microdeletion contains several genes of possible relevance to the phenotype. Up to 20 genes may be deleted; the extent of the deletion is variable but the classical Williams syndrome phenotype is always associated with deletion of *ELN*, and of the gene *LIMK1*. There is a considerable discrepancy between verbal and non-verbal abilities; verbal IQ averages about 70 but patients' visuospatial skills are generally about 2.5 standard deviations below population norms. There is relatively preserved verbal short-term memory and verbal fluency, although it is qualitatively abnormal. Claims regarding the cognitive strengths of children with Williams syndrome (e.g. their innate musical ability) are based on an ascertainment bias (a situation that applies equally to many other neurodevelopmental syndromes). Language acquisition in the syndrome is delayed,

