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Complex Genetic Systems and Diseases

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Most traits of interest in medical (including psychiatric) contexts are complex traits of varied etiology including genetic factors. The study of genetic aspects of such traits presents a level of complexity not seen elsewhere in genetics. New molecular techniques provide promise for a solution to this problem.

Complex Genetic Systems

Every phenotypic trait of every organism is the result of a complex history of developmental interactions between the organism's genome and its formative environment. Even so, some traits show remarkable constancy across the whole range of 'normal' environments (i.e. those in which the organism can develop to reproductive maturity), provided that a small specifiable set of alleles is present in the genome. In diploid organisms, the inheritance of such traits follows the patterns specified by Mendel's laws of segregation and independent assortment (as modified by linkage relationships). These traits are straightforwardly under genetic control and are often called 'Mendelian'. In humans, for example, polydactyly (the presence of more than five digits on a hand) is controlled at a single locus by one (dominant) allele, the MN blood group is transmitted as a single locus with two alleles, and the ABO blood group system is transmitted as a single locus

with three alleles. These are the type of trait that have been traditionally studied most successfully by genetics.

But the role of genes in the development of most traits is not so straightforward. Mendel knew that some traits depend on alleles at more than one locus. As early as 1914, Nilsson-Ehle (1914) noted that some traits are 'plastic'; in other words, the same genotype leads to a different predictable phenotype in different environments. Vogt (1926) introduced the terms 'expressivity' and 'penetrance' in an attempt to capture some of this complexity: the expressivity of an allele is the degree to which the corresponding trait is manifested; the penetrance is the conditional probability that the trait is manifested at all, given the presence of the allele (Sarkar, 1999). The need to introduce such concepts reflects an inability to provide a simple Mendelian interpretation of the inheritance or expression of such traits; besides the locus in question, either other loci or environmental factors (or both) are essential to their genesis. If the penetrance of an allele

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is significantly less than one, all that the allele does is to confer a 'susceptibility' to the trait. This is, at most, what is true for many alleles that are said to be linked to human diseases such as hypertension and cardiovascular diseases.

Another method for describing this complexity is through the construction of norms of reaction; that is, graphical representations in phenotype–environment space of the phenotypic trajectories of a trait for different genotypes in different environments (Woltereck, 1909; Hogben, 1933). If the norms of reaction for different genotypes are not parallel to each other, then the factors responsible for the origin of the trait cannot be partitioned into additive genotypic and environmental components (Sarkar, 1998). Norms of reaction have been constructed for many plants and a few animals (mainly insects). Parallel norms of reaction have almost never been observed. This fact underscores the complexity of the interactions between the genome and environmental factors during development.

At the other extreme from simple Mendelian traits are traits under the control of a multitude of relatively unspecific alleles, each with a small effect, in addition to environmental factors. These are called 'quantitative traits' and are studied using the techniques of quantitative genetics pioneered by Fisher (1918). Examples include the height and weight of many animals. Quantitative traits have continuous distributions: if all the alleles act additively, it can be proved mathematically that the trait will be distributed normally in a population. At an intermediate level are traits that are influenced by many loci, each presumed to have an identifiable effect. These traits are called variously 'complex', 'multifactorial' or 'polygenic', although the last term is also used sometimes to refer to quantitative traits. (Sometimes traits controlled by more than one locus, but less than four, are called 'oligogenic'.)

Techniques of Analysis

The use of techniques of quantitative genetics to study a trait usually reflects a lack of detailed genetic knowledge of the system. Once specific loci are implicated in the etiology of a trait, detailed genetic studies become possible in which genetic models with epistasis (interactions between loci) can be constructed and predicted patterns of inheritance can be potentially compared with experimental data. However the identification of such loci has proved to be much more difficult than was anticipated originally (Lander and Schork, 1994).

Two strategies are used to identify such loci. In the segregation or 'candidate gene' approach, an educated

guess is made to identify a gene that may be etiologically involved in a trait, and the inheritance of this gene is then probed in a pedigree in which that is present. For susceptibility to cardiovascular disease, for example, at least 20 candidate genes were easily identified by characterizing the proteins involved in lipid metabolism alone (Weatherall, 1991). All of these loci interact in the production of physiological traits, the malfunction of which leads to cardiovascular disease. The linkage analysis approach involves systematically collecting data from families with individuals showing a trait and searching for statistical correlations, for example, using probes based on restriction fragment length polymorphisms.

For both segregation and linkage analyses, the techniques that have been used traditionally to infer genetic etiologies do not have sufficient power of resolution for analyzing complex traits. Reports of genetic etiologies that are based only on such analyses are now generally recognized to be unreliable in the scientific literature, although they often receive an inappropriate amount of attention from the popular media. For example, a partial genetic etiology has been often suggested for susceptibility to bipolar disease on the basis of linkage studies. These studies have implicated at least 14 different loci. However there has been a consistent failure in the replication of such studies; frequently, additional data have dissolved previously positive statistical correlations (Risch and Botstein, 1996; Moldin, 1999). Results from segregation analysis are also similarly inconclusive (Moldin, 1999). The same pattern has been seen for many mental and behavioral traits for which genetic etiologies have been postulated.

This situation is not unexpected. If, as is usually the case, the expression of alleles at each locus is sensitive to a few different environmental cues, then the involvement of multiple loci is likely to lead to a confounding role for several environmental cues (further decreasing penetrance and increasing variable expressivity). For many complex traits, especially mental and behavioral traits, this problem is aggravated by the problem of etiological heterogeneity: whereas the presence of the trait might be attributed to the expression of specific alleles in many (perhaps most) cases, there might also be false positives (sometimes called 'phenocopies') that have a different etiology. At the very least, such phenotypes should be partitioned into classes with specific genetic etiologies and others with no such determination. Unfortunately, at present there is no systematic methodology to accomplish this at the phenotypic level without having explicit genetic models (with specified alleles) already available.

Since the advent of molecular techniques, three new methods have been developed for the potential

identification of alleles involved in the etiology of complex traits: first, the allele-sharing method, in which a positive etiology is postulated when trait-carrying individuals in a pedigree inherit identical alleles at some locus with greater than Mendelian expectations; second, allelic association studies, which attempt to find statistical correlations between specific alleles and traits; and third, quantitative trait locus (QTL) mapping, in which pure lines of model organisms are created and then backcrossed systematically to tease out the effects of individual alleles with small effects. All three methods potentially offer more resolving power than do traditional segregation and linkage analysis.

Social Ramifications

For all complex traits, but especially in medical and social contexts in which decisions often have ethical and sociopolitical ramifications, explicit care must be taken to avoid facile inferences to a genetic explanation of the etiology of traits. In medical contexts, the construction of an incorrect gene-based etiological model could lead to problems in at least two ways: first, strategies of medical intervention might be directed inappropriately to genes and gene products rather than to environmental determinants; and second, the wrong gene or gene product might be targeted for attention. In social contexts, genetic testing and screening may select inappropriate targets for attention. In both contexts there is an additional problem: in most cases, alleles only confer susceptibilities to traits and not the traits themselves. This leads to undesirable situations such as those in which the 'asymptomatic ill' (individuals with an allele but no existing condition) are subject to exclusionary practices (e.g. the denial of healthcare benefits; Nelkin and Tancredi, 1989).

To guard against these problems, at least two criteria should be satisfied for postulating genetic etiologies for complex traits: first, studies must be replicated several times; and second, the strength of statistical inferences (as determined by meta-analyses of the results of more than one study) must increase with each replication. As noted above, reports of genetic linkages for bipolar disease did not meet either of these criteria. Reports of an etiological role of a locus linked to chromosome Xq28 in male sexual orientation have faced similar problems (Rice *et al.*, 1999). Perhaps the exact role of genes in the phenogenesis of any trait will be resolved only after

the construction of a detailed molecular model of the development of that trait from the level of deoxyribonucleic acid (DNA) to higher physical levels of organization until the trait itself is manifested. For any trait, this remains a task for the future. Understanding the development of complex traits may be a precondition for understanding their genetics.

See also

Complex Multifactorial Genetic Diseases
Polygenic Disorders

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