FUTURE DIRECTIONS: GENOMICS AND BEHAVIOR

Toward Behavioral Genomics

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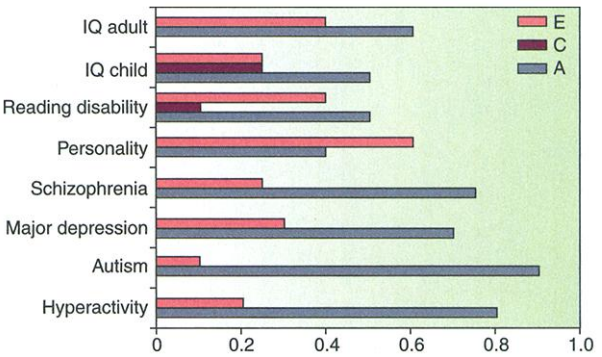
The genetics of behavior offers more opportunity for media sensationalism than any other branch of current science. Frequent news reports claim that researchers have discovered the "gene for" such traits as aggression, intelligence, criminality, homosexuality, feminine intuition, and even bad luck. Such reports tend to suggest, usually incorrectly, that there is a direct correspondence between carrying a mutation in the gene and manifesting the trait or disorder. Rarely is it mentioned that traits involving behavior are likely to have a more complex genetic basis. This is probably because most journalists—in common with most educated laypeople (and some biologists)—tend to have a straightforward, single-gene view of genetics. But single genes do not determine most human behaviors. Only certain rare disorders such as Huntington's disease have a simple mode of transmission in which a specific mutation confers the certainty of developing the disorder. Most types of behavior have no such clear-cut pattern and depend on interplay between environmental factors and multiple genes. Genes in such multiple-gene systems are called quantitative trait loci (QTLs), because they are likely to result in continuous (quantitative) distributions of phenotypes that underlie susceptibility to common disorders.

Although in many ways behavior presents geneticists with the same challenges as other complex physiological and medical traits, behavior is unique in that it is the product of our most complicated organ, the brain. Most valuable for behavioral genetics will be the sequencing of multiple human genomes and identification of the several million DNA base pairs that differ among us. These DNA variations are responsible for the ubiquitous genetic influences on individual differences in behavioral dimensions and disorders. The most solid genetic findings about individual differences in human behavior come from quantitative genetic research such as twin and adoption studies that consistently converge on the conclusion that genetic variation makes a substantial contribution to phenotypic variation for all behavioral domains. The best-studied areas are psychopathology, personality, and cognitive abilities and disabilities, all of which have been assessed by recent model-fitting (see the figure). There are two striking findings. The first is that nearly all behaviors that have been studied show moderate to high heritability—usually, to a somewhat greater degree than do many common physical diseases (*1*). Second, although environment plays a role, its contribution tends to be of the nonshared type, that is, environmental factors make people different from, rather than similar to, their relatives.



How much heritability? Estimates of genetic and environmental effects from recent twin studies (*11*). A, additive genetic variance, or heritability; C, variance explained by shared environment; E, variance resulting from nonshared environment and errors of measurement.

Such quantitative approaches, however, can no longer be seen as ends in themselves, and the information and techniques generated by the human genome sequence will be valuable in locating and identifying genes involved in behavior. Although some genes that have major effects on behavior have been identified (see the table), progress so far has been slow, partly because genes with effects large enough to be readily detectable by linkage are probably rare. For example, a recent genome scan in schizophrenia in almost 200 families effectively excluded a gene having a large effect from most of the genome (*2*). A further issue is the definition of phenotypes. Modern methods allow reliable diagnosis of disorders such as schizophrenia but there are several competing diagnostic schemes, raising the question of which one is "most valid" for genetic research (*3*).

It has long been known that a complementary approach, allelic association, can detect genes that account for as little as 1% of the variance in a trait (*4*). Until recently this approach was hampered by the lack of sufficiently detailed marker maps. Now, with the human genome sequence available, association studies should be able to locate QTLs with the aid of a greatly improved map based on hundreds of thousands of single-nucleotide polymorphisms (SNPs) and new methods of very high-

CURRENT UNDERSTANDING OF THE GENETIC BASIS OF SELECTED BEHAVIORAL DISORDERS AND TRAITS (*2*)

Behavioral trait	Pattern of inheritance	Gene mapping
Huntington's disease	Rare autosomal dominant dynamic mutation	Gene identified (huntingtin) with unstable trinucleotide repeat.
Early onset (familial) Alzheimer's disease	Rare autosomal dominant	Three distinct genes identified (presenilins 1 and 2, and amyloid precursor protein).
Fragile X mental retardation	Nonstandard X-linked dynamic mutation	Two genes identified (*FMR1* and *2*), both with unstable trinucleotide repeats.
Late onset Alzheimer's disease	Common complex	Increased risk with apolipoprotein e4 allele.
Attention deficit, hyperactivity disorder	Common complex	Three contributory loci in the dopamine system, *DRD4*, *DAT1* and *DRD5*; *DRD4* best replicated, others less certain.
Dyslexia	Common complex	Two contributory loci suggested on chromosomes 6 and 15; findings replicated.
Schizophrenia	Common complex	Numerous reported linkages including chromosomes 1, 5, 6, 10,13, 15, and 22 but no consensus; a few promising candidate genes include *5-HT*$_{2A}$ and *CHRNA7*.
Aggression	Common complex	Mutation reported in X-linked *MAO A* gene in one family; no evidence of broader relevance.
Male homosexuality	Common complex	Linkage reported at X-linked marker locus in sib pairs; not replicated.

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throughput genotyping, as discussed in this issue by Peltonen and McKusick (*5*). Another new benefit is that much of the hard work of positional cloning has been replaced by cloning by computer. Thus, gene sequences, and even polymorphisms can be identified by searching appropriate computer databases.

Identifying QTLs is one thing, but understanding their effects will take much more time. Functional genomics and proteomics (*6*), where the focus is on gene products, their structure and expression, can be generally viewed as bottom-up strategies. But there are other levels of analysis at which we can understand how genes work. A top-down approach highlights the behavior of the whole organism. For example, we can ask how the effects of specific genes unfold in behavioral development and how they interact and correlate with experience. This top-down, behavioral genomic level of analysis (*7*) will complement the current functional approaches in the human species. Furthermore, genome sequences of other organisms will be especially important because of the great similarity of genes and gene organization between, for example, mouse and man (*8*).

Ultimately, the human genome sequence will revolutionize psychology and psychiatry. The most important impact will be on understanding the neurobiological basis of individual differences and achieving a better grasp of the etiology of diseases. The latter, in turn, should lead to the discovery of new and more specific drug treatments. The use of genomics as a path to drug discovery holds considerable potential (*9*). It is also probable that DNA testing will be used to predict which patients will respond to different drugs or be susceptible to particular side effects (*10*). However, there are two built-in limitations to this DNA revolution. The first is that all behavior involves gene-environment interplay. The second is the unsolved question of the distribution of effect sizes of QTLs; some may involve effects so small or so complicated that they will never be detected.

The probabilistic rather than deterministic influence of genes on behavior means that some of the ethical specters raised by the advent of behavioral genomics probably have little substance. For example, it has sometimes been suggested that geneticization is likely to increase the stigma of mental disorders. To the contrary, far from increasing the stigma, advances in genetics have the opposite effect. As a case in point, it is now perfectly acceptable for an ex-president of the United States and his family to acknowledge that he has Alzheimer's disease, a disorder for which much progress has been made in understanding its basis at a molecular level. In the recent past this might have been called "going senile" and would have been seen as somehow morally reprehensible. We predict that this is the start of a trend and that identifying genes involved in behavioral disorders will do much to improve public perception and tolerance of behavioral disorders.

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FUTURE DIRECTIONS: POLICY ISSUES

Political Issues in the Genome Era

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Regulating use of genetic information. President Clinton signing an executive order prohibiting civilian federal agencies and departments from using genetic information in any hiring.

The sequencing of the human genome heralds a new age in medicine, with enormous benefits for the general public. For example, it will allow scientists to identify all of the genes contributing to a given disease state, leading to a more accurate diagnosis and precise classification of disease severity. In addition, healthy patients can know the diseases for which they are at risk, giving them the opportunity to make beneficial lifestyle changes or to take preventive medications to protect their health. Understanding the genetic bases of heritable diseases also will allow researchers to develop therapeutics at the molecular level, resulting in better treatments with fewer side effects.

Despite the potential benefits, many ethical, legal, and social concerns exist. The U.S. Congress recognized this early in the development of the publicly funded human genome project and so set aside approximately 5% of the budget, starting in 1990, to fund the ELSI program (Ethical, Legal, and Social Implications of Human Genetics Research) (*1*). Initially, the ELSI program focused efforts on four areas: Privacy and fair use of genetic information, clinical integration of genetic technologies, issues surrounding research ethics, and public and professional education. Later these goals were expanded to include studies of the societal impact of knowing the complete human genome sequence, the interpretation of genetic variations among individuals, integration of genetic technologies into clinical and nonclinical settings, and the implications of genetic technologies for religious, philosophical, ethical, and socioeconomic concerns.

One of the most difficult issues is determining the proper balance between privacy concerns and fair use of genetic information. The growing number and use of genetic tests has many worried about discrimination due to inappropriate access to, and use of, private genetic information. A Gallup poll by the Institute for Health Freedom released this past September revealed that 86% of U.S. adults 18 years of age or older believe that physicians should obtain permission before doing any genetic testing beyond routine testing (*2*). Similarly, 93% of adults believe that their permission should be granted before researchers use their genetic information. Francis Collins, Director of the National Human Genome Research Institute (NHGRI), has written, "It is estimated that all of us carry dozens of glitches in our DNA—so establishing principles of fair use of this information is important for all of us" (*3*). Without adequate safeguards, the genetic revolution could mean one step forward for science and two steps back-

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