Many years of research have demonstrated that mental illnesses—such as schizophrenia, bipolar disorder, early-onset depression, anxiety disorders, autism, and attention deficit hyperactivity disorder—have a genetic component. It is now clear that these disorders are not due to a single defective gene, but to the joint effects of many genes acting together with nongenetic factors. Despite the daunting complexity, progress is being made. Researchers are hunting genes because they are likely to be a vital key to deciphering what goes wrong in the brain in mental illness.

Detecting multiple genes, each contributing only a small effect, requires large sample sizes and powerful technologies that can associate genetic variations with disease, and thereby pinpoint candidate genes from among the estimated 50,000 genes that are expressed in the human brain. And even after human disease vulnerability genes are found, sophisticated tools will be needed to find out what activates them, what brain components they code for, and how they affect behavior. The prospect of acquiring such molecular knowledge holds great hope for the engineering of new therapies.

Linkage studies are often based on the identification of large, densely affected families so that the inheritance patterns of known sections of DNA (called “markers”) can be compared to the family’s transmission of the disorder. If a known marker can be correlated with the presence or absence of the disorder, this finding narrows the location of the suspect gene. Linkage-disequilibrium studies in isolated populations capitalize on the likelihood that the susceptibility genes for a particular disorder probably came from one or a few founding members. Whether the isolation is geographic or cultural, there are fewer individuals in the community’s genealogies and therefore fewer variations of the disease genes within the population. This limited variation makes the search easier. In addition, the groups of markers

Chromosomes, visualized here, are long molecules of DNA, the genetic material.
that surround each of these susceptibility genes are likely to have the same limited variation, which further simplifies identification.

Association studies depend on the investigator hypothesizing that a specific gene or genes may influence the disorder. In this type of study, the investigator examines whether those people with the disorder have a different version of the gene than those without the disorder among related or unrelated individuals. 

Evidence suggests that unaffected family members may share with their ill relatives genes that predispose for milder, but qualitatively similar behavioral characteristics. For example, some relatives of people with schizophrenia or autism may exhibit subtle cognitive problems. 

Family members may also share biological anomalies that could be clues to the underlying genetic component of the illness. For example, they may share telltale chemical signatures in cells of implicated brain circuits. NIMH-supported investigators are studying such families to characterize these behavioral and biological traits, in hopes of tracing the variations in the genetic blueprint that contribute to illness.

Some gene variants are likely to turn on too much or too little—or in the wrong place. This could interfere with the way brain cells work. It may also affect how cells migrate to other parts of the brain and connect with one another during early development. NIMH has mounted an effort to vastly expand the set of available tools for discovering the molecular mistakes that produce mental illness.

A vital resource for doing this, now under development, will be a shared scientific infrastructure called the Brain Molecular Anatomy Project (BMAP). The goals of this multidisciplinary effort are to catalog the genes that are active in various parts of the brain at different developmental stages, and to make this information readily available to investigators on a Web-based map.

The mouse’s brain is a major initial focus of BMAP. A Web-based digital mouse brain atlas will offer 3-D and 2-D views of this biological blueprint, covering different strains and ages of animals. In addition to advancing basic knowledge, the BMAP database promises to enhance clinical science, providing new leads for studying gene expression in post-mortem tissue, for the identification of candidate genes, and enhanced capacity to screen for individuals who might be at risk for developing brain disorders.

A related set of developing tools also centers on the mouse: identifying the neural basis of complex behaviors. 

The mouse has become a critical model in studying human disease because scientists have access to many inbred strains, each expressing distinctive physiological and behavioral characteristics. Researchers can now insert, knock out, or mutate mouse genes, quickly breed a generation that expresses the change, and then see how it affects behavior. When illness-linked genes are discovered, they will be inserted and expressed in mice to find out what they do at the molecular, cellular, and behavioral levels. Researchers will be able to track a wiring abnormality, a cell migration abnormality, or other anomaly that may lead to symptoms in humans.

For More Information

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References


