The Future of Psychiatric Genetics

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The articles in this section of Current Psychiatry Reports show the great strides that have been made in understanding the genetics of mental disorders. After more than a century of family, twin, and adoption studies, we can now state with certainty that genes influence the etiology of most mental disorders. Genetic epidemiologic research also shows that the inheritance of most psychiatric disorders is complex. Although rare single gene variants of psychiatric disorders may exist, most cases of psychiatric illness can be attributed to the joint actions of many genes along with environmental risk factors [1].

Despite the strong evidence implicating genes as causes of psychiatric illness, complex inheritance has stymied efforts to find susceptibility genes for specific disorders. Although current molecular genetic technologies have made gene finding routine for many medical conditions, the papers in this section show that findings for psychiatric illness have been only suggestive and sometimes contradictory. These difficulties have led to a new phase of molecular genetic research in psychiatry. This new work promises to find genes and thereby open up new vistas for research and treatment.

New Molecular Genetic Technologies for Psychiatric Genetics

The human genome comprises 3 billion base pairs, but only 150 million are the building blocks of the approximately 100,000 human genes. The United States government’s Human Genome Project seeks to separate the genes from the nonfunctional DNA by the year 2003. The findings of the Human Genome Project will help psychiatric genetics in several ways.

Scientists find genes through linkage analysis by using a map of genetic markers. Many of these markers were byproducts of the Human Genome Project, and more are in development. Because the power of a linkage study increases with the variability of markers (how many different versions there are) and the proximity of markers to the unknown gene, the more markers we have, the easier it is to find genes.

Human Genome Project scientists are also sequencing the base pairs that constitute our genome. In doing so they will discover much information about the structure of genes and their function in the human body. By also mapping and sequencing the genomes of other organisms, scientists will be able to make comparisons between species that may yield insights into how genes function in humans.

From the perspective of psychiatric genetics, the Human Genome Project is an immense factory producing and refining the tools we will need to discover the genes that cause mental illness. These tools come in the form of improved genetic markers, faster methods of genotyping, denser genetic maps, and statistical methods for the analysis of complex genetic diseases. Will these new high-tech tools be sufficient for finding mental illness genes? Or, do we also need to also improve the low-tech tools of psychiatric diagnosis and clinical nosology?

The Variable Expression of Psychiatric Disorders

Variable expression is a common feature of psychiatric illness. The genes that predispose to schizophrenia may lead to schizoaffective disorder, schizotypal personality, atypical psychotic disorders, and a spectrum of neurocognitive and neurophysiologic dysfunction. The genes for bipolar disorder can be expressed as major depression and bipolar II disorders. The genes that cause panic disorder also express themselves as childhood anxiety disorders and laboratory measures of inhibited behavior. Obsessive-compulsive disorder and chronic tics are alternate manifestations of Tourette’s disorder. Genes that make people susceptible to attention deficit hyperactivity disorder may lead to mood, conduct, or anxiety disorders.

Better demarcating the variable expression of psychiatric phenotypes may be useful for linkage analyses. It seems unlikely that there will be a one to one correspondence between genetically influenced processes in the brain and the clinical phenomena that we observe. Because psychiatric signs and symptoms may be the relatively remote effects of genes, psychiatric genetic studies might be more fruitful if they focus on more direct measures of brain function.

For example, it has been known for some time that schizophrenic patients find it difficult to filter or “gate”
sensory input from the environment. Thus, several experimental paradigms have been used to assess sensory gating. Each presents a conditioning stimulus that is followed by a test stimulus. Unlike normal subjects, the schizophrenic patient cannot filter out, or gate, the second stimulus. These sensory gating abnormalities are heritable and, in schizophrenia families, show evidence of linkage to a region of chromosome 15, even though linkage could not be shown using diagnoses alone [2]. A similar pattern of findings has been shown for eye-tracking deficits in schizophrenia [3].

Alternative phenotypes like sensory gating and eye tracking deficits must be used cautiously. When many phenotypic indicators are available for a single disease, testing each of them separately increases the risk that a positive linkage finding will be due to chance alone. This problem occurs because whenever we do many statistical tests, a fraction will always come out significant due to chance alone. There are statistical solutions to this problem, but each of these is accompanied by some loss in statistical power.

A second problem hampers the use of alternative phenotypes: it is possible for such phenotypes to be useless, even though their prevalence among relatives of diseased subjects is statistically greater than the prevalence in the population [4]. Alternative phenotypes are helpful because they decrease the false negative rate (i.e., they increase penetrance). However, this decrease in the false negative rate is usually accompanied by an increase in the false positive rate (i.e., the phenotypic indicators are usually more prevalent among controls than the disease under study).

Risch [5] showed that the power of a linkage study is directly related to the ratio of two prevalences: the prevalence among relatives of ill probands and the prevalence in the general population. The greater the ratio, the more power. Thus, one way to increase the statistical power of linkage analysis is to define a phenotype that is highly prevalent among relatives of ill probands but rare in the general population. It follows that an alternative phenotype will be most useful if it increases Risch's [5] prevalence ratio.

The Future of Predictive Genetic Testing
Unlike other diseases for which DNA testing has become routine, our knowledge of the molecular genetics of psychiatric disease is too rudimentary for use in genetic counseling. Currently, the genetic counseling for psychiatric disorders relies on empiric risk figures from family studies [1]. Whether genetic tests will ever be useful for psychiatric disorders depends not only on gene discovery, but also our knowledge about the features of the gene in the population.

Before the discovery of a gene mutation leads to genetic tests, we need detailed information about the mutation, such as its frequency in the population, its penetrance among gene carriers, and its frequency among those with the disease. Without such data we cannot readily use and interpret test results.

Sometimes, the discovery of a disease gene is not useful. For example, studies of two genes known to cause breast cancer have found over 140 different mutations. However, only about 5% to 10% of breast cancers have a strong genetic component, and these two genes account for about 65% of these cases. Moreover, genes do not necessarily cause disease with absolute certainty. The BRCA-1 breast cancer gene leads to cancer only 80% of the time. These facts have led to DNA testing guidelines for breast cancer that preclude screening in the general population.

Adding to this uncertainty are technical limitations. Commercially available genetic tests for breast cancer only screen for the most common mutations. Issues of cost and feasibility make it impossible to design a cost-effective clinical test that screens for all known mutations. That would simply be too expensive. Therefore, only positive results from breast cancer testing are completely informative. Negative results indicate the absence of common mutations but they cannot rule out the presence of rare mutations.

For psychiatric disorders, the lesson from the breast cancer story is clear. The discovery of a pathogenic gene does not immediately (and may never) lead to a clinically useful genetic test.

The Future of Mental Health Treatment: Primary Prevention
Although genes may never predict with certainty who will and will not onset with psychiatric illness, one goal of future work is to determine if genes (once they are discovered) in combination with other known risk factors, can be used to identify children at very high risk for mental illness. If that becomes possible, researchers will be able to select participants for primary prevention protocols.

Figure 1 outlines the rationale for prevention by showing three levels of disease manifestation: a neurodevelopmental proeminent, the onset of frank psychopathology, and degeneration into chronic illness. The figure illustrates two distinctions made in the prevention literature: primary versus secondary prevention, and universal preventive interventions versus selective preventive interventions.

Primary prevention refers to any intervention that stops the onset of disease. As the figure shows, primary prevention could focus on two levels. It could block early environmental insults, and prevent neurodevelopmental abnormalities and subsequent disease. Primary prevention protocols could also block later environmental insults to prevent the onset of psychopathology but not the earlier-onset neurodevelopmental abnormalities. Secondary prevention does not prevent illness, it mitigates its course. For example, treatment early in the course of schizophrenic illness is believed to lessen chronicity and improve the course of illness compared with treatment later in the course of illness [6].