

Genetics and the Future of Clinical Psychiatry

The field of human genetics has advanced rapidly in the past 50 years, from the determination of the correct number of human chromosomes to the development of a reference map of the approximately 25,000 genes in the human genome. Moreover, we are now systematically identifying common variations in the DNA sequence of the human family (1) that likely affect the biological processes that contribute to individual differences in behavior. Although uncertainties abound (e.g., the definition of a gene is still under revision [2, 3]), the integration of human genetics and neuroscience is leading to major advances in our understanding of the biology of human mental health and disease.

Although individual differences in brain information processing and function cannot be explained by genes alone, variations in genetic sequence that affect gene function very likely contribute substantially to the variance in the resulting complex behavioral phenomena.

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For example, studies of twins have revealed that 40%–70% of various aspects of cognition, temperament, and personality are attributable to genetic factors (4). For some psychiatric disorders, specific genes have been identified as putative risk factors across populations. Indeed, the majority of the susceptibility for certain psychiatric disorders, such as bipolar disorder and schizophrenia, is due to inheritance (5). Thus, the study of human genetics offers the potential to identify

at-risk individuals and determine novel molecular targets for therapeutic interventions.

Understanding the pursuit of this promise requires knowledge of two approaches—genetic linkage and genetic association—that are used to identify the contributions of alternative forms of a gene or DNA sequence (i.e., alleles) to phenotypic outcomes. The combination of two alleles, one inherited from each parent, at a specific chromosomal location or locus is referred to as a genotype. Genetic linkage and genetic association capture somewhat different pictures of the relationship between genes and behavior. Linkage studies are designed to determine whether a behavioral phenotype, such as a dimensional trait (e.g., personality or temperament) or a clinical disorder, is physically linked to a genetic marker—a segment of DNA with a known physical location on a chromosome. The identification of significant linkage then permits the detailed sequencing of genes in that general region of the chromosome in search of specific variants or alleles that may alter gene function in a manner that influences the expression of the trait or increases the risk for the disorder. Often such variants are in the form of a polymorphism, which is defined as a difference in the DNA sequence that occurs in >1% of the population. Most of the variants studied to date, such as single-nucleotide polymorphisms, have minor allele frequencies exceeding 10%, which suggests that they have the potential to broadly affect the risk for psychiatric illness. Mutations, by contrast, are variants that occur in <1% of the population and are unlikely to contribute to the general risk for illness. However, because mutations often have substantial effects on the function of the protein encoded by the gene, they can contribute to rare familial forms of psychiatric illness.

The study by Kassem et al. in this issue of the *Journal* effectively illustrates how genetic linkage studies designed to identify novel genetic mechanisms contributing to psychiatric illness can be buttressed by astute clinical observations and the dissection of current diagnostic categories. By stratifying patients with bipolar disorder along the polarity of their first episode (depression, mania, or mixed), Kassem et al. found that polarity at onset

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is significantly familial—it occurs more commonly in siblings than would be expected by chance. Moreover, restricting their analyses to patients whose onset episode was manic substantially increased the genetic linkage with a locus on chromosome 16p, a region that was only weakly linked with bipolar disorder broadly in the same sample population (6). These results suggest that polarity at onset defines subtypes of bipolar disorder that reflect distinct underlying genetic mechanisms. These findings also provide a new impetus for studies to systematically query this region of chromosome 16p for variants in specific genes that could contribute to the pathophysiology of the mania-at-onset subtype of bipolar disorder by affecting the amount or function of the encoded protein.

In contrast to using genome scans with hundreds of gene markers to implicate genetic loci through linkage approaches, genetic association studies search for a relationship between specific alleles in a given gene and a target behavior. This approach typically involves 1) the selection of a certain feature of an illness (such as heightened threat sensitivity in anxiety disorders or impaired working memory in schizophrenia), 2) the identification of variants in genes (such as serotonin transporter or catechol *O*-methyltransferase, respectively) that are thought to affect the candidate biological process (serotonin or dopamine neurotransmission, respectively), and 3) the determination of whether a particular allele of the candidate gene is found at a greater frequency among individuals who exhibit the target behavior. The association of a specific allele with a target behavior suggests that the genetic variant is potentially a causative factor for that phenotype. Causality is bolstered if the candidate polymorphism has a clear functional effect on the relevant neurobiological processes at the molecular, cellular, or circuit level.

This type of functional candidate gene analysis is at the core of the report by Reynolds et al. in this issue. These investigators examined the moderating effects of a functional single-nucleotide polymorphism in the human gene for the serotonin receptor 1A subtype (5-HT_{1A}) on antipsychotic treatment response in a group of treatment-naïve patients with first-episode psychosis. At this polymorphism in the promoter region of the gene, a guanine nucleotide is exchanged for a cytosine [G(–1019)C]. Promoter regions are located upstream or before the exons (i.e., coding regions) of a gene that contain the information needed to direct the amino acid sequence of the functional protein product. Thus, variations in promoter regions do not directly affect protein function but regulate the level of gene expression via the binding of various transcription factors. In vitro studies have suggested that the G(–1019) allele reduces the ability of transcription factors to repress or shut down promoter activity, leading to increased expression of the 5-HT_{1A} autoreceptor. The 5-HT_{1A} autoreceptor mediates negative feedback regulation of serotonin neuron activity in the brainstem and, in turn, serotonin release in target regions such as the amygdala and prefrontal cortex. Thus, the G(–1019) allele, through increased autoreceptor expression and negative feedback mediation, may function to reduce serotonin release.

Reynolds et al. show that after 3 months of antipsychotic treatment, the presence of a 5-HT_{1A} G(–1019) allele was associated with no improvement in negative symptoms and less improvement in patients' general psychopathology compared with patients who were homozygous for the C allele. Patients who were homozygous for the G allele actually showed a worsening of depressive symptoms relative to those who were homozygous for the C allele. Improvement in psychotic symptoms, however, did not differ as a function of genotype. Thus, these data suggest that the impact of the G allele on 5-HT_{1A} expression, and presumably on 5-HT neurotransmission, predicts aspects of the response of first-episode psychotic patients to antipsychotic treatment. Of course, this naturalistic treatment study does not reveal how this polymorphism influences treatment response, especially given the lack of specificity of antipsychotic drugs for the 5-HT_{1A} receptor. However, the functional nature of the 5-HT_{1A} G(–1019)C polymorphism represents an important foothold for launching basic studies to identify these mechanisms.

The type of genome-wide linkage studies conducted by Kassem et al. may lead to the identification of genes that contribute to the pathogenesis of psychiatric illnesses with specific

phenotypes, whereas genetic association studies like those employed by Reynolds et al. will be instrumental in establishing direct associations between specific genetic polymorphisms and target behavioral or biological processes. Although linkage findings implicate genetic loci in a behavior or illness that can differ across families, association studies imply that the same allelic polymorphism is predictive of the trait in the same way for all individuals in a population. However, both effects need to be replicated in independent samples of populations from different genetic backgrounds, because the true relevance of any genetic difference must be established against the remarkable variability of the entire human genome.

Although the findings of these studies are not readily translated to the clinical practice of psychiatry today, they do provide examples of how the integration of advances in molecular and functional genetics with clinical phenomenology will lead to the eventual application of genotyping in the diagnosis and treatment of psychiatric illness. Such integrated studies of another common functional polymorphism in the serotonin family, the serotonin transporter promoter length variant (5-HTTLPR), have illustrated how candidate genotyping can rapidly expand our understanding of the mechanisms through which genes can influence the risk for psychiatric illness by biasing the response of brain systems to environmental challenges (7).

To date, we have identified only a handful of informative genetic polymorphisms, and these account for only a modest proportion of the variance in certain behaviors or risk for psychiatric disorders. We can improve this yield by identifying additional polymorphisms in candidate genes, which will increase the power of association studies. At the same time, the identification of novel genes within chromosomal regions identified through linkage studies is critical for the development of a comprehensive catalog of genetic variation that contributes to specific behaviors and illness risk. The parallel dissection of environmental factors will permit the construction of gene-by-environment interaction backgrounds that will likely account for a greater degree of the liability for a given illness. A growing synergy across such studies and with basic neuroscience investigations (8) is needed before we can genotype patients for candidate polymorphisms with enough confidence to allow us to determine the nature of their illness and predict the most effective course of treatment.

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