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EDITORIAL

On the Future of Genetic Research in Bipolar and Schizophrenic Syndromes

According to suggested statistical guidelines (Lander and Kruglyak, 1995), there are several confirmed BP susceptibility loci across the human genome (18p11.2, 21q21, 18q22, 4pter, Xq26, and possibly others). Similarly there are several confirmed loci for SZ (6p22–4, 8p22-4, 13q32, 22q11 and possibly others). The actual susceptibility sequences for these loci have not been identified, despite substantial effort. It is anticipated that several of these susceptibility loci will yield specific disease genes, so it is useful to consider what types of studies might improve our understanding of these genetic influences on risk for BP and SZ disorders

It is probable that susceptibility sequences will be identified from novel genes in those candidate regions, as most known candidate genes have been scanned without detecting obvious mutations which are transmitted with illness. The novel susceptibility genes may be cloned by investigators searching for such genes, or they may be detected through one of the databases (e.g., www.ncbi.nlm.nih.gov). These studies (in the best of all possible worlds) may be anticipated as follows:

1. A novel gene is detected in an implicated region.
2. Sequence variants in this gene are transmitted with illness in kindreds linked to this region.
3. Susceptibility variants in this gene are transmitted more often than by chance from heterozygous parents to unrelated affected children and are more common among cases compared to ethnically-matched controls.
4. Transient transfection in cultured cells or yeast two-hybrid studies of the implicated sequence variants reveals functional difference between the wild type and those variants associated with illness.

Although BP disorder and SZ are found across all cultures of the world, at relatively comparable frequencies, not all susceptibility genes may be detected in all populations. The historical population genetics of Homo sapiens are poorly understood. For example, common ancestors of Chinese and European populations may have diverged (with little mixing thereafter) prior to the appearance of a given susceptibility gene in one of the two populations. Thus, in one population, this susceptibility gene will be detected, while in the other, it may be relatively rare. The hallmark of this situation will be the discordant frequencies of the susceptibility allele in unaffected individuals from the two populations. However, consider this additional complexity: suppose that (among the genetic causes of SZ) there are two susceptibility genes for SZ, gene A (which has been cloned and is under study) and gene B (which remains unidentified). Because there is an epistatic interaction, both A and B susceptibility alleles must be present in the same individual for the syndrome to become manifest. Suppose further that the gene A susceptibility allele is present in 20% of both Chinese and European populations, but the gene B SZ susceptibility allele is rare among the Chinese and common among Europeans. In this scenario, a gene A susceptibility allele will be associated with SZ among Europeans, but not among the Chinese, despite the fact that the gene A SZ susceptibility allele is present at similar frequencies in both populations among affected individuals.

The functional implications of these susceptibility sequences will not be obvious in most cases. While there may be a few instances in which premature stop codons or missense mutations at conserved amino acids are found, it must be anticipated that most of the susceptibility sequences may not have obvious functional implications. Thus, it will be essential to study these sequence differences in cultured cells and other systems (e.g., yeast two hybrid techniques).

The next generation of such studies will probably involve knockout and transgenic mouse models of these newly-discovered susceptibility genes. Here, a careful

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assessment of murine behavior will be essential. The phenotype may not be evident unless there is a "permissive" genetic background. It is likely that these susceptibility genes do not operate in isolation, but require epistatic influences for manifestation of the syndrome. This raises the possibility that the relevant murine phenotype may not be evident in all genetic backgrounds. It may be necessary to create these genetically unique mice on multiple strain backgrounds, e.g., C3H, DBA, C57, AKR, etc. Even when the appropriate genetic background is present, the relevant murine phenotype may be observed only when environmental (possibly age-specific) precipitants are introduced, such as early maternal separation, neonatal hypoxia, etc. These and other possible complexities should be considered by those brave souls attempting to model these disorders in mice. For example, to what extent is the murine behavioral phenotype rescued by an appropriate pharmacologic intervention? To what extent can the murine behavioral phenotype be exacerbated by interventions that make the human syndromes worse?

It can be anticipated that populations of patients with similar susceptibility alleles at one or more loci across the genome can be assembled. The possibility that such genetically homogenous populations of BP or SZ patients may define syndromal subgroups with uniform pharmacologic responses is a hypothesis that can be tested in both retrospective and prospective designs. In fact, the impact of pharmacologic strategies is yet to be fully realized in the field of neuropsychopharmacology. The more valuable of these studies is the prospective type. Such studies will be enormously expensive, in part because large populations of patients must be screened, and the appropriate subsets followed over years to define a therapeutic benefit for disorders which have a variable course of illness.

Similarly, these genetically homogenous populations of patients offer new opportunities in the field of neuroimaging. It is conceivable that such subgroups of patients will offer new insights into specific neuronal effects of identified susceptibility alleles in the intact patient. These specific neuronal effects may be evident only when the brain is challenged by a specific pharmacologic agent. For example, the important functional effect of a SZ susceptibility allele may be evident in a neuroimaging protocol only after the genetically appropriate patients are given IV naloxone.

In summary, the anticipated cloning of several susceptibility genes for BP and SZ disorders will create multiple opportunities to expand our understanding of these syndromes, including, perhaps, animal models that could accelerate so much research. The complexities involved cannot be over-emphasized, however. Identification of several susceptibility genes is only a starting point for novel research opportunities. We hope to read the results of those exploring these new research opportunities in the pages of this journal.

Wade H. Berrettini, M.D., Ph.D.
The Karl E. Rickels Professor of Psychiatry
Department of Psychiatry and
the Center for Neurobiology and Behavior
University of Pennsylvania
Philadelphia, PA

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