# A Scientific Opportunity

The discovery of susceptibility genes for bipolar disorder and schizophrenia is thought to be one of the most intractable current problems in human genetics. The epidemiological data argue that a substantial portion of the genetic variance seen in these disorders results from a limited number of genes with small effects. This is similar to the situation for many other common diseases with complex inheritance patterns. Nevertheless, recent scientific advances in human genetics, combined with recent findings on bipolar disorder and schizophrenia and the availability of family samples through the U.S. National Institute of Mental Health (NIMH) (www-grb.nimh.nih.gov/gi.html), suggest that a scientific opportunity now exists to identify susceptibility genes for these disorders.

In the absence of compelling candidate genes, positional strategies are the most comprehensive genetic approach to these diseases. Positional cloning is currently feasible and is typically implemented as a two-part process: genome-wide linkage scanning to identify a chromosomal region or regions linked to the disease phenotype, followed by mutational analysis and association studies on genomic DNA within the linkage region. Recent scientific advances have greatly increased the appeal of this approach. The successes of the Human Genome Project have made it feasible to study all the genes in the sizeable linkage regions found in common disease, without first spending years developing a physical map of the region. Less well known is the revolution resulting from the discovery of extensive linkage disequilibrium within the human genome, particularly in the very large and outbred Caucasian population. That is, the chunks of chromosome within which genotypes are correlated in unrelated individuals are larger than expected, which means that fewer markers and smaller sample sizes will be needed to detect susceptibility genes. New statistical methods can tease apart subtle genetic components contributing to common diseases with complex inheritance patterns.

**It's time to search for susceptibility genes for major mental illnesses.**

The recent detection of susceptibility genes for non–insulin-dependent diabetes mellitus* and for inflammatory bowel disease† through follow-up of linkage studies offers encouragement to researchers of other common diseases. Before these breakthroughs, the linkage results on inflammatory bowel disease and non–insulin-dependent diabetes mellitus were apparently inconsistent among studies, although a consistent conclusion could be reached by meta-analysis. The state of the linkage data for bipolar disorder and schizophrenia at this time is strikingly reminiscent of the data for inflammatory bowel disease and non–insulin-dependent diabetes mellitus then. In retrospect, this was not sufficient reason to discourage attempts, based on the positive linkage samples, to discover susceptibility genes. The unreliability of linkage findings may be more apparent than real. In simulations of diseases that result from the effects of a few genes acting together, replication of a valid linkage may occur very inconsistently.‡ When results from multiple genome scans are combined, a statistically significant overall conclusion may be reached for linkage at a particular chromosomal region. Reanalyses and meta-analyses are beginning to paint consistent pictures of bipolar disorder and schizophrenia.

Within the scientific community, many still believe that we do not have the ability to discover susceptibility genes for bipolar disorder or schizophrenia. Back in 1997, a NIMH workgroup recommended "large-scale molecular genetics studies" of bipolar disorder, schizophrenia, and early-onset major depressive disorder but did not see the time as ripe for favoring a particular molecular strategy. These 1997 recommendations were made in view of then-extant data and technology. It is time to reconsider. Although the U.S. National Institutes of Health have supported pedigree collections and genome-wide linkage scans, we believe that positional cloning has been neglected. We now have the foundation of understanding and the tools to embark on innovative and meticulous analysis of disequilibrium with illness in suitable samples and thorough molecular scrutiny of disequilibrium regions. Investigators should enter the quest for susceptibility genes for major mental illnesses, and funding agencies should give new consideration to programmatic support for the discovery of susceptibility genes for psychiatric disease. The current situation represents a stalling of the positional cloning process at the midpoint and may be impeding scientific progress.

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*Y. Horikawa *et al.*, *Nature Genet.* **26**, 163 (2000). †J.-P. Hugot *et al.*, *Nature* **411**, 599 (2001). ‡B. K. Suarez, C. L. Hampe, P. V. Van Eerdewegh, in *Genetic Approaches to Mental Disorders*, E. S. Gershon, C. R. Cloninger, Eds. (American Psychiatric Press, Washington, DC, 1994), chap. 2.