# New Hope for Pharmacogenetic Testing

In this issue, readers will find an article by Perlis et al. (which includes data from the Broad Institute of Harvard and Massachusetts Institute of Technology, the Systematic Treatment Enhancement Program for Bipolar Disorder [STEP-BD] Consortium, and University College London) that targets lithium response using genomewide association methods (1). The STEP-BD cohort included 1,177 bipolar patients, of whom 458 were treated with lithium. The University College London sample added lithium response data for 359 patients. These are sizable samples for pharmacologic studies. The results do not meet formal criteria for genomewide significance. However, there are a number of areas of interest, including single nucleotide polymorphisms (SNPs) in and near *GRIA2*, which codes for a glutamate receptor subunit. A particular polymorphism in the *GRIA2* region, rs9784453, appears to be associated with time to recurrence of a mood episode while on lithium (Kaplan-Meier log rank: p=0.001). By my reading of Figure 3, the median time to recurrence is about 230 days for homozygote carriers with the "poor response" allele and about 520 days for homozygote carriers with the "good response" allele, with heterozygote carriers falling in between. Differences such as this are of clinical interest.

*"Bipolar pharmacogenetics is no longer arcane and is increasingly clinically oriented."*

Of course there are many caveats to this study as it presently stands, and I summarize the results not to describe a test that should be considered useful today, but to indicate that work in bipolar pharmacogenetics is no longer arcane and is increasingly clinically oriented. Forty years after the wide availability of lithium therapy for bipolar illness in the United States, we still do not really know which patients should be receiving it. As our populations of bipolar patients age, we see more who are discomfited or endangered by side effects of maintenance mood stabilizers, such as weight-gain related to lithium or valproate, chronic renal insufficiency or diabetes insipidus related to lithium, or complaints of memory impairment or poor muscular coordination that may be related to lithium. We still must hesitate when prescribing mood stabilizers for women of childbearing age who have bipolar disorder. And despite a series of groundbreaking investigations of mechanisms of action involving glycogen synthase kinase, the inositol triphosphate system, and adenyl cyclase, we still cannot specify the key cellular events related to the therapeutic action of lithium or any other mood stabilizer.

Genetic studies promise to change the continuing reliance of psychiatric therapeutics on serendipity. By all measures, we have benefited from careful observations of behavioral changes in patients taking drugs developed for other purposes. We have then used initial theories, based on monoamine regulation, to design new generations of drugs for mood disorder and schizophrenia. These "bootstrapped" studies have revolutionized the field of psychiatry in a generation. We now require rational therapeutics.

The obstacles are many, but a number have been overcome. We have agreed to criterion-based diagnosis in the clinic as well as in the research ward. We increasingly accept the necessity for standardized symptom measurement in clinical practice. In clinical research, we have agreed to work together and to share data across national and international consortia. That this is necessary for genetic studies cannot now be doubted. The genomewide association studies (GWAS) of bipolar disorder have recently been summarized in an article published in the *Journal* (2). Individual samples in the range of 1,000 patients and 1,000 comparison subjects have not been successful at identifying genomewide significant loci (3–7). However, a combination of samples (8), with over

4,000 patients and 6,000 comparison subjects, has identified one locus that clearly meets genomewide criteria (ANK3, which codes for a sodium channel modulatory protein) and one locus that may meet such criteria (CACNA1C, which codes for a calcium channel subunit). In comparison, the studies of type 2 diabetes went from one locus identified to 10 loci identified as their sample numbers approached 20,000 case subjects and 20,000 comparison subjects. The National Institute of Mental Health is fully aware of the need for massive samples in order to maximally utilize such studies, and these efforts are under way for bipolar disorder and schizophrenia.

We will arguably need to consider sample sizes in this range for other types of studies as well. The treatment effects assignable to specific mood stabilizers in STEP-BD (strategy described in ref. 9), for instance, are still modest, with sample sizes in the range of 1,000 in different subgroups of patients. Clinical therapeutic studies of diabetes and common cardiovascular disorders often use samples 10 to 20 times as large. Neuroimaging studies also suffer from the effects of modest sample size and site-to-site variation in equipment, behavioral protocol, and data analytic methods. We must use our best results to argue for an increased priority for studies of psychiatric brain disorders, which are, as we know, the most disabling disorders in the modern world (10).

The psychiatric GWAS should start to point us toward biochemical pathways for pathophysiology and therapeutics. Already we may say that they lead toward a greater emphasis on ion channels (from ANK3 and CACNA1C). Recently published pathway studies based on GWAS results emphasize myelination, ion channel structural (11) and regulatory genes (12) and pathways related to adrenergic and dopaminergic receptors (13). Other such efforts are in progress. Information specifying genes and pathways may be accessible at lower sample sizes than that for the information we are currently seeking through GWAS, i.e., the confirmation of specific gene variants in the form of modified alleles. We need this more specific information for use in genetic counseling and for understanding the molecular mechanisms involved in pertinent mutations, and we will obtain this information through large samples and through careful sequencing of selected case and comparison subjects. But we may already be able to glimpse the broad outlines of genetic structure for complex psychiatric disorders by analyzing the data with an eye toward pathways rather than individual genes or gene variants.

Thus, the Perlis et al. article is the first in what should become a critical series of studies on lithium response and response to other mood stabilizers. It is not perfect, and one may reasonably object that its definition of lithium response does not adequately track a consistent cohort of patients over a period of years. Another notable omission is the lack of lithium blood levels, which are an essential part of clinical practice. The University College London cohort includes only retrospective data on lithium response by global clinician rating. This would ideally be supplemented by prospective controlled observations. Nevertheless, this is a good start, and by presenting the first data it becomes the reference article for the field. One should note that Grof and coworkers (14) have been pioneering the separation of bipolar patients by treatment response for some years now and that Turecki et al. (15) published a genomewide linkage study (less precise methodology than that of current GWAS) identifying a locus at 15q14 as the most likely area for lithium response-related genes (findings in the Perlis et al. article on chromosome 15 are some distance from this). Recent work by Mamdani et al. (16) and Tseng et al. (17) implicates cAMP response element binding and brain-derived neurotrophic factor genes in lithium response using candidate gene methods and functional studies.

The GWAS methodology used by Perlis et al. has the distinct advantage of being a true survey of the genome, with polymorphisms tested in probably more than 90% of the genes in the human genome (the exact figure cannot be calculated because of continuing ambiguities of annotation of the human sequence data). Nevertheless, candidate gene studies are still valuable and are much more practical in modestly sized clinical samples. Functional studies are still necessary supplements to candidate polymor-

phism identification and to GWAS SNP identification. The way forward for psychiatric pharmacogenetics presumably involves a combination of methods such as this, with an emphasis on the genomewide studies for the "aerial view" and supplementation with candidate and functional studies to hone in one specific gene, gene variants, and mechanisms of action.

The expected output of such studies is twofold: a panel of gene-based tests to help separate lithium responders from nonresponders and 2) an understanding of the mechanism(s) of action of lithium. Both of these outcomes may be anticipated to change psychiatric practice dramatically in the next several decades.

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