The Pharmacogenetics of Depression: Enter the GWAS

Pharmacogenetics involves the use of molecular genetic information to assist in the prediction of drug efficacy and drug-induced adverse events. In a heterogeneous disorder such as depression, pharmacogenetic data could be vital to the development of individualized treatment approaches as well as provide a better understanding of the molecular substrates of antidepressant action. Considerable advantages of this approach include the ease of collecting DNA samples for genotyping, commonly via venipuncture or saliva sample; the immutability of genotype information, such that a patient's genotype need only be measured once per lifetime; and the rapidly decreasing costs of genotyping assays (1).

Progress to date, however, in the pharmacogenetics of depression has been limited. Several factors may be responsible. First, depression is an extremely heterogeneous disorder (or group of disorders), in which multiple genetic and environmental factors may interact in as yet unknown ways to contribute to the development of the full syndrome. Among the major psychiatric disorders, this can be observed by examination of heritability estimates for axis I adult psychiatric disorders. For schizophrenia and bipolar disorder, heritability estimates approximate 80%, but for depression, the considerably lower estimates of less than 40% (2) suggest that the underpinnings of this disorder may be even more complex. A second challenge is the difficulty in assuring that the assessment of the pharmacogenetic phenotype is sufficiently accurate to allow for detection of presumably subtle genetic effects. In clinical trials of depression, adherence rates may be as low as 50% (3). This may be permissible to some degree in clinical trials utilizing effectiveness models but will result in underestimation of the true effect sizes between genotypes and phenotypes in studies intended to assess a drug's effect on biological systems. Similarly, variable treatment with concomitant medications may further obscure genotype-phenotype relationships. Finally, placebo response rates are relatively high in depression, and "true" antidepressant drug responders may be grouped with a substantial number of placebo responders, thereby confounding pharmacogenetic analyses intended to identify specific gene-drug interactions.

"Pharmacogenetic prediction...is not yet refined enough for clinical application"

The study conducted by Uher and colleagues (4) in this issue of the *Journal* represents one of the most ambitious psychiatric pharmacogenetic experiments conducted to date. In contrast to most other pharmacogenetic studies that utilize samples of convenience from preexisting clinical trials, the Genome-Based Therapeutic Drugs for Depression (GENDEP) project was specifically designed for pharmacogenetic purposes. Therefore, all subjects were drawn from a single ethnic group, there was a limited number of treatment arms (escitalopram and nortriptyline), antidepressant drug selection was based upon distinct biological hypotheses on the mechanisms of drug action (serotonergic versus noradrenergic), and the sample size was relatively large (N=811). A further strength of the project was the inclusion of a large proportion of subjects with no history of antidepressant drug treatment, therefore minimizing variation in response that could be related to variable prior drug exposure. Moreover, the investigators incorporated two methods of analyses: a candidate gene approach that assessed 72 genes previously implicated in antidepressant drug efficacy and a genome-wide association

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study (GWAS) assessing more than 500,000 single nucleotide polymorphisms (SNPs) randomly distributed across the entire genome.

Despite these strengths, the results reported by Uher and colleagues are modest. None of the candidate genes assessed provided evidence for association with response to either of the antidepressants studied or with response to a combined phenotype assessing generalized antidepressant response. In light of substantial prior literature implicating candidates in the serotoninergic system, including the serotonin transporter polymorphism for which there is meta-analytic support (5), the lack of significant association to escitalopram response at any of these loci is disappointing. GWAS results were only slightly more encouraging, as no SNP achieved genome-wide significance in the study group as a whole, although a SNP in the uronyl 2-sulphotransferase (*UST*) gene was significantly ($p=3.6\times10^{-8}$) associated with response to nortriptyline. The lack of convincing genome-wide results is consistent with the limited number of other GWAS studies of antidepressant drug response. Ising and colleagues (6) reported on a GWAS involving two German samples, with replication genotyping conducted in a subset of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, while Garriock and colleagues (7) conducted a GWAS on level 1 of the STAR*D sample, which included more than 1,400 subjects treated with citalopram, and each of these studies did not detect genome-wide significant results. The traditional mantra of complex geneticists faced with nonsignificant results is "more subjects needed"; however, STAR*D included 1,400 subjects treated with the same agent in a relatively controlled clinical trial, and it is daunting to consider much larger single-drug treatment trials in at least the near term.

These data should also be considered in the context of a recent candidate gene study (8), also published in this issue of the *Journal*, in which comprehensive genotyping of a single gene, the -opioid receptor (*OPRM1*), resulted in significant association of variants in this gene with citalopram response, again in the STAR*D sample. It should be noted, however, that GWAS of the same data set did not provide genome-wide significant results at this locus, nor did a series of functional studies reveal any in vitro effects of this locus on -opioid receptor function.

Taken together, these studies suggest that alternative pharmacogenetic study designs should be considered. In particular, it may be productive to focus on alternative phenotypes, including intermediate phenotypes that may more closely reflect drug action. Assessment of drug-induced adverse events has proven to be enormously successful in other branches of medicine. Daly and colleagues (9) recently reported that a specific human leukocyte antigen allele markedly increases the risk for liver injury due to flucloxacillin treatment ($p=8.7\times10^{-33}$; odds ratio=80.6). Mallal and colleagues (10) have reported that the same human leukocyte antigen allele provides 100% sensitivity for predicting risk of development of an immunologically confirmed hypersensitivity reaction to a nucleoside reverse transcriptase inhibitor, abacavir, used in the treatment of AIDS. In the abacavir study, 23 subjects carried the specific human leukocyte antigen risk allele, and every one of them developed the hypersensitivity reaction relative to an overall occurrence rate of less than 3% in this population. Similar types of results may be forthcoming with psychiatric drugs that are associated with rare, yet severe, side effects. For example, clozapine-induced agranulocytosis has been linked to the human leukocyte antigen-DQB1 genotype, with odds ratios of approximately 17 in two small cohorts of subjects characterized for development of clozapine-induced agranulocytosis (11). In depression, studies have been completed that implicate specific candidate loci in antidepressant side effects that include sexual dysfunction (12) and treatment-emergent suicidal ideation (13), with higher odds ratios than observed in genetic studies of clinical efficacy.

For studies of efficacy, use of other alternative phenotypes that mediate response may be informative. For example, neuroimaging techniques that assess neurogenesis in response to antidepressant treatment may soon be available as well as more traditional

functional magnetic resonance imaging and positron emission tomography measures that have been utilized to predict response. These techniques may also be more amenable for use in rigorously designed pharmacological challenge designs that may yield larger numbers of informative data points than heterogeneous clinical trials in which DNA samples are collected as samples of convenience. Other alternative phenotypes such as neurocognitive measures, electrophysiological indices, and neuroendocrine markers may also prove useful with these designs.

The recent data suggest that pharmacogenetic prediction of antidepressant response is not yet refined enough for clinical application. Nevertheless, the development of new study designs specifically aimed at pharmacogenetic traits, the continued advances in genomic technology, and a fuller appreciation of the multiple variables that may impact drug response in the clinical setting suggest that there is still considerable progress to be made in this emerging area of discovery.

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Dr. Malhotra has served as a consultant for PGxHealth and Eli Lilly and has also served on the speaker's bureau for Merck. Dr. Freedman has reviewed this editorial and found no evidence of influence from these relationships.