The Pharmacogenetics of Major Depression: Past, Present, and Future

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Much has been said and written in recent years about the promise of pharmacogenetics. The vision is one of a world where we will be able to match medications with patients, maximizing efficacy while minimizing—or eliminating—adverse effects. This vision has been widely embraced out of a real desire to better help patients. But we are now some years into the pharmacogenetics enterprise, and we are beginning to accumulate real-world data in juxtaposition to our perhaps somewhat idealistic expectations. Some of the assumptions underlying the vision are beginning to be scrutinized more closely. Can we really match medications with patients when the range of available treatments is still quite small compared with the range of clinical presentations? Can genetics really provide the keys? How much of the difference between patients in efficacy and adverse effects will actually be attributable to differences in life experience and circumstances that we can neither measure biologically nor address medically? The technological advances of human genetics over the past decade, along with the recent availability of large treatment cohorts for study, are beginning to answer these questions. Pharmacogenetics is being transformed from a small field of promising leads into one of the foundations of evidence-based medicine. Few specialties stand to benefit as much as psychiatry, where all of our treatment options are empirical and the matching of patients with treatments is largely a question of clinical judgment.

The pursuit of genetic markers that can help predict response to treatment or important adverse events has been the focus of many investigations but so far has led to few clinical applications (1). This may be changing, as specific genetic association findings gain validity. Recently, the U.S. Food and Drug Administration added pretreatment genetic testing to the prescribing information for the anticoagulant drug warfarin, which has a narrow therapeutic index. About 40% of the variance in warfarin dose is attributable to variation in cytochrome P450 and vitamin K metabolism genes (2).

Major depression, which is predicted to be the second leading cause of death and disability by the year 2020 (3), is an ideal target for pharmacogenetic approaches (4). Although many treatments exist, initial response rates are stuck at about 50%, and only a minority of patients fully remit (5). Choosing the best treatment for each patient is difficult, and clinical predictors of differential response are scarce (6). Although adverse events are uncommon in the age of selective serotonin reuptake inhibitors (SSRIs), concern about some adverse events, such as treatment-emergent suicidality, may reduce access to, and acceptability of, treatment (7). In the face of all this, good genetic markers of treatment outcome in major depression might have immediate clinical relevance—yet in many ways, the search for such markers has barely begun.

Here, we address some of the past history, ongoing research, and near future of pharmacogenetic studies of major depression. Rather than attempt a comprehensive review of the literature, which has already been done well in some recent papers (4,8), we aim to highlight some of the key issues facing the field and sketch a vision for the future. Throughout, we use the term pharmacogenetic rather than the grander pharmacogenomic but consider both terms synonymous.

The Past: Small Samples and Few Genes

A MEDLINE search using the terms pharmacogenomics or pharmacogenetics and depression in humans yields about 100 articles, almost half of which are labeled as reviews. This would suggest that since 1968, the year of the first cited article, much has been written but not as much new information has been acquired. This characterization is not confined to the pharmacogenetics of major depression; it applies almost as well to the pharmacogenetics of other fields. In retrospect, without many of the necessary genetic tools and large samples to study, rapid progress could hardly have been expected.

Faced with these limitations, past approaches have been geared toward a limited number of markers in a small fraction of the ~20,000 human genes. These include genes in the cytochrome P450 system, a major pathway of drug metabolism, and genes involved in the production, release, binding, and reuptake of monoamines, especially the serotonin transporter (SERT). Only the P450 genes have found a clinical application and this has been so far quite limited (1), probably owing to the decline in the use of tricyclic antidepressants, the information that comes directly from a careful medication history, and the clinically small effects of the P450 system on the most widely prescribed SSRIs.

The serotonin transporter and a functional polymorphism in its promoter region (known as the linked polymorphic region [LPR]) have received the most attention by researchers. The serotonin transporter is undoubtedly the proximal target for the SSRIs and the LPR seems to affect gene expression in important ways (9), but consistent association with SSRI response has been difficult to demonstrate. A recent meta-analysis of 15 published studies concluded that there was evidence in favor of a significant association of the L-allele with better response to SSRIs (10). This result may reflect publication bias—since there is a lack of even small studies that report an effect size below the pooled odds ratio—but may be consistent with a true effect of the SERT LPR on treatment outcome. Recent studies, reviewed below, suggest that genetic variation in the SERT LPR has an impact on SSRI-related side effects. This might explain some of the outcome findings.

The Present: Picking Up Speed

There have been two big developments in recent years that have greatly accelerated progress in the field: the availability of large, well-characterized samples and the advent of genomic technologies of unprecedented power and efficiency. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D)
The Future: Knocking at the Clinic Door

Since the recent publication of the first Encyclopedia of DNA Elements (ENCODE) data (19), it has become clear that protein-coding genes are only a very small part of the genome and that most human DNA has significant biological activity: there may be no “junk” DNA. Until we fully understand the mechanisms that regulate gene function, we should maximize the results we obtain from available samples. Near-future technology can add significant amounts of information to what we already have. In addition to ever denser genome-wide sets of SNP markers, such as the million SNP chips that are already coming into use, ultra-high throughput sequencing technology may make the complete genome sequence a standard part of each patient’s medical record. This will pose an enormous challenge to clinicians, who will need to interpret this large quantity of data for patients and their families.

It is also likely that single nucleotide polymorphisms are not the sole genetic regulators of antidepressant response. We will need to interrogate other types of variation such as copy number polymorphisms and epigenetic signatures. Accumulating evidence demonstrates that copy number polymorphism is a common source of human genetic variation that may have major effects on gene function (20). Epigenetic variation—heritable changes in gene expression that are influenced by parent-of-origin and environmental factors—is another previously unrecognized but important source of human genetic variation. Early findings suggest that antidepressant medications affect epigenetic signatures, and agents that modify epigenetic signatures can exert antidepressant effects (21).

In addition to novel genetic investigations, the future of pharmacogenetics in mood disorders will depend heavily on the availability of large, well-characterized samples. Along with frequent, prospective assessment during treatment, these samples should ideally provide a detailed clinical and diagnostic picture that reflects both current and prior episodes, along with medication history, ethnic background, and psychosocial history. The latter may be an important source of individual differences in treatment outcome owing to temperament, resilience, and the cumulative impact of adverse life events (22). Although direct information on in vivo gene expression in the brain may be beyond the reach of near-future technology, neuroimaging techniques such as positron-emission tomography (PET) or magnetic resonance spectroscopy (MRS) may provide valuable data on the impact of antidepressant medications on brain chemistry in vivo.

In summary, the next decade should bring significant progress for pharmacogenetics in psychiatry. This progress will require a significant effort in sample collection, genetic assays, and clinical validation. For the promise of clinically useful tools to be realized, the field must produce clinically meaningful findings and not just statistically significant associations. If we succeed, the payoff will be big: more personalized care, more effective medications, fewer adverse events, and a reduction in the burden of mood disorders for both patients and society.

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