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

Gonzalo Laje and Francis J. McMahon

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)

From the Genetic Basis of Mood and Anxiety Disorders Unit, Mood and Anxiety Program, National Institute of Mental Health, Bethesda, Maryland.

Address reprint requests to Francis J. McMahon, M.D., 35 Convent Drive, Room 1A202, Bethesda, MD 20892-3719; E-mail: mcmahonf@mail.nih.gov.

Received September 18, 2007; accepted September 19, 2007.

0006-3223/07/$32.00
doi:10.1016/j.biopsych.2007.09.016

study (11) has for the first time provided a sample of well-characterized patients large enough to detect even modest genetic effects. Although not designed specifically to answer pharmacogenetic questions, STAR*D provides DNA from a clinically representative cohort of about 2000 adults with major depression, all treated with citalopram for at least 6 weeks and evaluated prospectively for treatment response, remission, and adverse events. Patients who failed to respond adequately to the initial treatment were switched to a variety of other treatments. The large size of the uniformly treated sample is crucial, since it represents an order-of-magnitude increase over all previously studied samples with major depression. Large samples are a key element of robust genetic association findings (12).

Candidate gene association studies in the STAR*D sample have already begun to uncover alleles associated with citalopram response and adverse events such as treatment-emergent suicidal ideation (13–17). The published effect sizes for the response-associated alleles are modest, with odds ratios on the order of 1.5 to 1.7. The effect sizes for the adverse event associations appear to be larger, but the true effect sizes cannot, of course, be accurately estimated in a single sample. In any case, effect sizes will need to be much larger if genetic markers are to help guide treatment decisions. Such effect sizes might be achievable with multimarker, multigene tests, but this remains to be seen.

The results in the large STAR*D sample have also begun to clarify some of the questions concerning the role of the SERT LPR: while there is no convincing evidence for association with treatment response in the STAR*D sample (18), the data suggest that a novel functional allele related to the traditional S-allele is associated with perceived side-effect burden (13). This result might have been mistaken for an association with treatment response if side effects had not been considered, since patients with a high side-effect burden may not be able to take a sufficient dose of medication to achieve a good response.

The second big development has been the new technologies that allow the screening of genome-wide sets of genetic markers. These technologies have opened the door for genome-wide association (GWA) studies that use large numbers of single nucleotide polymorphism (SNP) markers (now 500,000 to 1,000,000) to screen the entire genome for alleles that influence a trait of interest. For pharmacogenetics, this is a crucial advance, since it transcends candidate gene studies, which are limited by the genes chosen, and supplants linkage methods, which require families and are impractical for most pharmacogenetic questions.

At least two GWA studies of antidepressant treatment outcome are currently underway. Each has interrogated over 300,000 markers. The results of these studies will provide the most comprehensive view to date of genetic influences on antidepressant response. However, GWA studies are usually underpowered to detect alleles of small effect. If antidepressant treatment outcome is influenced by many genes, each of small effect, which seems likely, then GWA studies may miss many of them. Alternatively, such genes may be implicated by markers with modest effects (and statistical significance), the importance of which may only be recognized after several replications and the demonstration of functional alleles. Additional large samples of uniformly treated and longitudinally assessed patients will thus be essential for validating the results of the GWA studies already underway.

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.

Supported by the Intramural Research Program of National Institute of Mental Health (NIMH), National Institutes of Health (NIH), U.S. Department of Health and Human Services (DHHS), and by the National Alliance for Research on Schizophrenia and Depression (NARSAD). The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

The authors report no competing interests.

1. Swen JJ, Huizinga TW, Gelderblom H, de Vries EG, Assendelft WJ, Kirchheiner J, *et al.* (2007): Translating pharmacogenomics: Challenges on the road to the clinic. *PLoS Med* 4:e209.
2. Wadelius M, Chen LY, Downes K, Ghori J, Hunt S, Eriksson N, *et al.* (2005): Common VKORC1 and GGCX polymorphisms associated with warfarin dose. *Pharmacogenomics J* 5:262–270.
3. Murray CJ, Lopez AD (1996): Evidence-based health policy—lessons from the Global Burden of Disease Study. *Science* 274:740–743.
4. Perlis RH (2007): Pharmacogenetic studies of antidepressant response: How far from the clinic? *Psychiatr Clin North Am* 30:125–138.
5. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, *et al.* (2006): Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: Implications for clinical practice. *Am J Psychiatry* 163:28–40.
6. Nierenberg AA (2003): Predictors of response to antidepressants: General principles and clinical implications. *Psychiatr Clin North Am* 26:345–352.
7. Gibbons RD, Brown CH, Hur K, Marcus SM, Bhaumik DK, Erkens JA, *et al.* (2007): Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. *Am J Psychiatry* 164:1356–1363.
8. Binder EB, Holsboer F (2006): Pharmacogenomics and antidepressant drugs. *Ann Med* 38:82–94.
9. Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, *et al.* (1996): Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* 274:1527–1531.
10. Serretti A, Kato M, De RD, Kinoshita T (2007): Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with selective serotonin reuptake inhibitor efficacy in depressed patients. *Mol Psychiatry* 12:247–257.
11. Rush AJ, Fava M, Wisniewski SR, Lavori PW, Trivedi MH, Sackeim HA, *et al.* (2004): Sequenced treatment alternatives to relieve depression (STAR*D): Rationale and design. *Control Clin Trials* 25:119–142.
12. Ioannidis JP, Trikalinos TA, Ntzani EE, Contopoulos-Ioannidis DG (2003): Genetic associations in large versus small studies: An empirical assessment. *Lancet* 361:567–571.
13. Hu XZ, Rush AJ, Charney D, Wilson AF, Sorant AJ, Papanicolaou GJ, *et al.* (2007): Association between a functional serotonin transporter promoter polymorphism and citalopram treatment in adult outpatients with major depression. *Arch Gen Psychiatry* 64:783–792.
14. Laje G, Buervenich S, Manji H, Rush AJ, Wilson AF, McMahon FJ (2007): Genetic markers of suicidal ideation emerging during antidepressant treatment. *Am J Psychiatry* 164:1530–1538.
15. McMahon FJ, Buervenich S, Charney D, Lipsky R, Rush AJ, Wilson AF, *et al.* (2006): Variation in the gene encoding the serotonin 2A receptor is associated with outcome of antidepressant treatment. *Am J Hum Genet* 78:804–814.
16. Paddock S, Laje G, Charney D, Rush AJ, Wilson AF, Sorant AJ, *et al.* (2007): Association of GRIK4 with outcome of antidepressant treatment in the STAR*D cohort. *Am J Psychiatry* 164:1181–1188.
17. Perlis RH, Purcell S, Fava M, Fagerness J, Rush AJ, Trivedi MH, *et al.* (2007): Association between treatment-emergent suicidal ideation with citalopram and polymorphisms near cyclic adenosine monophosphate response element binding protein in the STAR*D study. *Arch Gen Psychiatry* 64:689–697.
18. Kraft JB, Peters EJ, Slager SL, Jenkins GD, Reinalda MS, McGrath PJ, *et al.* (2007): Analysis of association between the serotonin transporter and antidepressant response in a large clinical sample. *Biol Psychiatry* 61:734–742.
19. Birney E, Stamatoyannopoulos JA, Dutta A, Guigo R, Gingeras TR, Margulies EH, *et al.* (2007): Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. *Nature* 447:799–816.
20. Feuk L, Carson AR, Scherer SW (2006): Structural variation in the human genome. *Nat Rev Genet* 7:85–97.
21. Duman RS, Newton SS (2007): Epigenetic marking and neuronal plasticity. *Biol Psychiatry* 62:1–3.
22. Nemeroff CB, Vale WW (2005): The neurobiology of depression: Inroads to treatment and new drug discovery. *J Clin Psychiatry* 66(suppl 7):5–13.