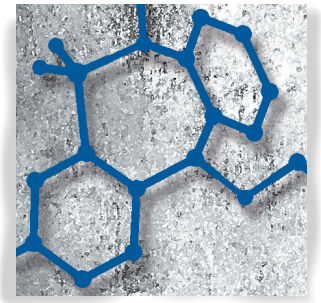
Psychiatric pharmacogenomic testing in clinical practice

David A. Mrazek, MD, FRCPsych



The clinical adoption of psychiatric pharmacogenomic testing has taken place rapidly over the past 7 years. Initially, drug-metabolizing enzyme genes, such as the cytochrome P450 2D6 gene (CYP2D6)*, were identified. Genotyping the highly variable cytochrome P450 2D6 gene now provides clinicians with the opportunity to identify both poor metabolizers and ultrarapid metabolizers of 2D6 substrate medications. Subsequently, genes influencing the pharmacodynamic response of medications have been made available for clinical practice. Among the earliest "target genes" was the serotonin transporter gene* (SLC6A4) *which has variants that have been shown to influence the clinical response of patients of European ancestry when they are treated with selective serotonin reuptake inhibitors. Genotyping of some of the serotonin receptor genes is also available to guide clinical practice. The quantification of the clinical utility of pharmacogenomic testing is evolving, and ethical considerations for testing have been established. Given the increasingly clear cost-effectiveness of genotyping, it has recently been predicted that pharmacogenomic testing will routinely be ordered to guide the selection and dosing of psychotropic medications.*

Dialogues Clin Neurosci. 2010;12:69-76.

Clinical pharmacogenomics consists of the application of research that links measurable genetic variants with the prediction of drug response.[1] Every medical specialty can utilize the results of pharmacogenomic probe studies to inform the adoption of individualized pharmacotherapy. However, psychiatric pharmacotherapy is particularly likely to benefit from the introduction of pharmacogenomic testing, because there are many psychotropic agents available for selection that target specific symptoms.

The terms pharmacogenetics and pharmacogenomics are currently used interchangeably. However, with the growing understanding that multiple intragenic variations should be considered in making predictions related to medication response, the use of the term pharmacogenomics has become more frequently chosen to designate the process of using documented genetic variation to guide medication selection and dosing.

Historically, psychiatrists have used empirical strategies to select medications. In the best practices, the choice of medications has evolved based on a rational trial-and-error process that has used clinical indicators to select medications and then relied on documenting treatment responses to titrate the optimal dose for a particular patient. Psychiatrists learn to "start low and go slow" in order to minimize side effects. They also know that it is

Keywords: *pharmacogenomic testing; cytochrome P450 gene; serotonin transporter gene* (SLC6A4)*; serotonin receptor 2A gene* (HTR2A)*; serotonin receptor 2C gene* (HTR2C)*; poor metabolizer phenotype; ultrarapid metabolizer phenotype*

Author affiliations: Chair, Department of Psychiatry and Psychology, Mayo Clinic; Professor of Psychiatry and Pediatrics, Mayo Clinic College of Medicine, Rochester, Minnesota, USA

Address for correspondence: David A. Mrazek, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA
(e-mail: mrazek.david@mayo.edu)

necessary to provide their patients with an "adequate" trial of each medication. Unfortunately, these strategies can result in a 3- to 4-week interval during which the patient continues to experience symptoms. In recent years, the potential iatrogenic harm associated with psychotropic medications has become increasingly obvious, with "black-box warnings" being attached to antidepressants, antipsychotic medications, stimulants, and mood stabilizers.

Despite a growing awareness of this potential harm, there are powerful pressures to try to accelerate the achievement of therapeutic benefit. At the most basic level, patients are impatient. They do not want to wait a month to achieve symptom relief. Additionally, with an increasing focus on the relief of specific symptoms, strategies using multiple psychotropic medications have become a standard of practice. Research supports the common practice of augmenting an initial medication with a second psychotropic drug.[2] However, there is no scientifically available evidence to support the practice of using four or five psychotropic medications simultaneously. Nevertheless, patients routinely receive multiple psychotropic medications in an attempt to identify the "right combination." While some patients do achieve a good therapeutic response using this trial-and-error approach to individualized medicine, it is also true that others become overmedicated or suffer from iatrogenic side effects.

Pharmacogenomic testing provides an innovative strategy to improve the likelihood of selecting an effective psychotropic medication. The earliest medical texts recognize that individual patients experience quite dramatically different responses to the same drug. There is also a longstanding observation that unusual drug responses can occur in members of the same family. The identification of specific gene variants associated with idiosyncratic responses is about 50 years old,[3] and the recognition that some psychiatric patients metabolize antidepressants at dramatically different rates has been documented for several decades.[4] However, with the use of newer antidepressant medications that rarely have life-threatening complications, the relatively expensive practice of monitoring the serum levels of newer antidepressant medications has become uncommon in the United States. This change has occurred despite the fact that serum levels of these newer agents also have dramatic variations based on the metabolic capacity of each patient.

A decade ago, the cost of genotyping began to become more affordable, and individual laboratories initiated pharmacogenomic testing that would provide genotyping of individual cytochrome P450 genes. However, there was no standard or well-validated methodology for the genotyping of these informative genes. There was also considerable variability in the interpretation of the results. In 2004, the US Food and Drug Administration (FDA) approved the use of a new product, the AmpliChip.[5] The introduction of the AmpliChip provided reference laboratories with a standard method for identifying variations in two of the cytochrome P450 genes: cytochrome P450 2D6 *(CYP2D6)* and cytochrome P450 2C19 *(CYP2C19)*. The approval of the AmpliChip was an important landmark in the history of psychiatric pharmacogenomic testing, and within 3 years, *CYP2D6* and *CYP2C19* were being genotyped by every reference laboratory in the country. However, this advance also highlighted some of the challenges associated with the introduction of clinical testing. One of the most obvious challenges that must be addressed is how to begin to assess new variants of these two genes in updated versions of the assay. Ideally, the methodology for establishing drug-metabolizing phenotypes should be updated regularly based on new molecular genetic findings showing how new genotypic variants influence gene function. Also, the clarification of the predictive capacity of previously identified gene variants influencing gene function is similarly evolving, and newly identified associations between gene structure and function should ideally be incorporated into algorithms that define the metabolic capacity of psychiatric patients.

The evolution of pharmacogenomic research should inform modifications in pharmacogenomic testing. However, an implication of the rapid increase in our knowledge base is that these new studies demonstrate limitations in the accuracy of older genotyping methodologies that were designed prior to the discovery of more recent variants. What is often not well appreciated is that even older pharmacogenomic methods provided important information for many patients, as these early innovations were a major advance over psychopharmacological practice without pharmacogenomic insights. However, as newer methodologies have further improved the accuracy of the prediction of medication response, the clinical utility of pharmacogenomic testing continues to increase.

Pharmacogenomic testing in psychiatric practice initially focused on identifying pharmacokinetic variability that

would influence the responses of patients who had atypical genotypes. Pharmacokinetic variation influences the concentration of a drug at its sites of action. Pharmacogenomic testing of drug-metabolizing enzyme genes provides a prediction of how an individual patient will metabolize a specific psychotropic medication. More recently, the focus of pharmacogenomic testing has expanded to include determining variability in the pharmacodynamic response of a patient to a specific medication. This variability reflects the capacity of the individual patient to respond to adequate exposure to the drug. Prediction of response is estimated based on the documentation of variations in "target genes" that code for receptors and transporters that influence the response of the patient to a particular medication.

This review will first identify the most widely genotyped drug-metabolizing enzyme genes that influence the pharmacokinetic metabolic capacity of a patient. Then, it will focus on genes that influence the pharmacodynamic responses of individual patients, before concluding with a brief discussion of the clinical utility of pharmacogenomic testing and some of the ethical considerations related to its routine use.

Pharmacogenomic testing to establish the metabolic capacity of psychiatric patients

Many genes code for enzymes that influence drug response. However, only the clinical implications of genotyping four of the most commonly tested cytochrome P450 genes will be reviewed. The focus of this discussion will be the clinical benefit for the patient of identifying individualized molecular variations, and the implications for those patients who have a quite significant decrement in their capacity to metabolize specific psychotropic medications. Identifying these individual patients provides clinicians with a clear method of minimizing side effects. This determination of decreased metabolic capacity is the most obvious benefit of pharmacogenomic testing, but implications of the pharmacogenomic testing for patients with increased metabolic capacity will also be discussed, as these patients are less likely to respond to specific psychotropic medications.

The cytochrome P450 2D6 gene *(CYP2D6)*

CYP2D6 was the first drug-metabolizing enzyme gene that was genotyped to identify psychiatric patients with increased or decreased metabolic capacity. It is located on chromosome 22 and consists of 4382 nucleotides. *CYP2D6* codes for an enzyme that is composed of 497 amino acids.

The CYP2D6 enzyme plays a primary role in the metabolism of more than 70 substrate medications, including twelve psychotropic medications. *CYP2D6* is one of the most highly variable drug-metabolizing enzyme genes. However, many of the other 29 P450 drug-metabolizing enzyme genes are also highly variable. The specific genetic variations that define variable phenotypes can be located on a Web site maintained by the Karolinska Institute (http://www.cypalleles.ki.se/). Each newly identified variant is included on the Web site after confirmation that it is unique.

There are currently 75 distinct *CYP2D6* alleles posted on this site, as well as an additional 55 *CYP2D6* variants that closely resemble one of the primary variants. Traditionally, these variants have been classified as being normal, deficient, or inactive drug-metabolizing alleles. Additionally, some alleles have more recently been demonstrated to code for an increased amount of enzyme which enhances the metabolic activity of the patient. Furthermore, patients can have a variable number of copies of *CYP2D6*. The most common number of copies of *CYP2D6* that patients carry is two. However, some patients have only one copy and, rarely, none at all. It is also possible to have more than two copies, and one patient has been reported to have 13 copies.[4] The development of several different classification systems to categorize 2D6 substrate metabolic capacity of patients into four phenotypic categories has been problematic. The use of alternative methodologies by different research teams has made it more difficult to study the implications of this variability.

The most important *CYP2D6* phenotype to identify is the poor 2D6 substrate metabolizer phenotype. Patients who are poor metabolizers are at increased risk for adverse events when they are prescribed 2D6 substrate medications, because of their low metabolic capacity. Patients are now classified as poor metabolizers if they have two inactive alleles, or one inactive allele and one deficient allele.

The second most clinically important *CYP2D6* phenotype is the ultrarapid metabolizer phenotype. Patients are ultrarapid metabolizers if they have either three or more active copies of *CYP2D6* or two or more enhanced copies of *CYP2D6*. They are unlikely to respond to 2D6

substrate medications at standard doses because their ability to rapidly metabolize these medications makes it difficult to sustain therapeutic serum levels.

The third clinically important *CYP2D6* phenotype is the intermediate metabolizer phenotype. These patients have one normal copy of *CYP2D6*, and one copy that is either deficient or inactive. While these patients can normally benefit from 2D6 substrate medications at low-to-moderate doses, they are at increased risk for the development of side effects at higher doses because of their decreased metabolic capacity, and they are more at risk for enzyme inhibition as a consequence of drug-drug interactions. When intermediate metabolizers are exposed to powerful 2D6 inhibitors such as paroxetine or fluoxetine, their metabolic capacity can be further decreased to the level of a poor metabolizer.[6]

There are many psychotropic medications metabolized by the 2D6 enzyme. Specifically, this enzyme:

- primarily metabolizes five antidepressants: fluoxetine, paroxetine, venlafaxine, desipramine, and nortriptyline
- substantially metabolizes amitriptyline, imipramine, doxepin, duloxetine, trazodone, and mirtazapine
- primarily metabolizes risperidone and four of the typical antipsychotic medications: chlorpromazine, thioridazine, perphenazine, and haloperidol
- has substantial involvement in the metabolism of aripiprazole and olanzapine
- primarily metabolizes atomoxetine and dextroamphetamine.

Beyond the prescription of psychotropic medications, psychiatric patients are given many other 2D6 substrate medications. Specifically, dextromethorphan is a cough suppressant that is metabolized by the 2D6 enzyme. Patients who are poor metabolizers of 2D6 substrate medications are at increased risk for cognitive side effects if taking standard doses of preparations that contain dextromethorphan. Another example is codeine, which is a prodrug. A prodrug must be converted to an active metabolite in order to have a therapeutic effect. Patients who are poor 2D6 metabolizers do not receive analgesic benefit from codeine because they do not metabolize codeine to morphine. Tamoxifen is also a prodrug that is the most frequently prescribed treatment for breast cancer. Poor metabolizers have little or no benefit from tamoxifen because they are not able to metabolize tamoxifen to endoxifen.[7,8] Additionally, paroxetine, fluoxetine, or bupropion should not be given to patients who are receiving tamoxifen because they inhibit the 2D6 enzyme. Giving these inhibitors to intermediate metabolizers can convert them to functional poor metabolizers. Consequently, they become unable to produce endoxifen.[9]

The cytochrome P450 2C19 gene *(CYP2C19)*

CYP2C19 was the second drug-metabolizing enzyme gene that was widely genotyped to identify patients with increased or decreased metabolic capacity. It is a large gene located on chromosome 10. It consists of 90 209 nucleotides, but codes for an enzyme that contains only 490 amino acids.

The identification of patients with low 2C19 metabolic capacity is clinically important because it allows clinicians to decrease the risk of iatrogenic side effects.

The 2C19 enzyme:

- primarily metabolizes citalopram, escitalopram, clomipramine, and amitriptyline
- has substantial involvement in the metabolism of sertraline, imipramine, nortriptyline, and doxepin
- plays an important role in the metabolism of clozapine and a minimal role in the metabolism of thioridazine
- is the primary enzyme involved in the metabolism of diazepam.

Recently, a new variant of *CYP2C19* has been identified which has enhanced function.[10] Patients who are homozygous for this new allele are less likely to respond to 2C19 substrate medications at standard doses. The identification of ultrarapid 2C19 metabolizers can be helpful in evaluating patients who do not respond to standard doses of any of these psychotropic medications.

The cytochrome P450 2C9 gene *(CYP2C9)*

CYP2C9 is located on chromosome 10 in relative close proximity to *CYP2C19*. However, it is only about half the size of *CYP2C9* as it consists of 50 708 nucleotides. Like *CYP2C19*, *CYP2C9* codes for an enzyme that contains 490 amino acids.

CYP2C9 is a drug-metabolizing enzyme gene that is less routinely genotyped to identify the increased or decreased metabolic capacity of psychiatric patients for 2C9 substrate medications. It does not play a primary role in the metabolism of any currently prescribed psychotropic medications. However, the 2C9 enzyme provides the only secondary pathway for the metabolism of fluoxetine, so patients who are poor metabolizers of

both 2D6 substrates and 2C9 substrates are at very high risk for adverse effects if treated with standard dose of fluoxetine.

The cytochrome P450 1A2 gene *(CYP1A2)*

CYP1A2 is a less well-studied drug-metabolizing enzyme gene, but it codes for an enzyme that plays an important role in the metabolism of fluvoxamine. It is also involved in the metabolism of duloxetine and olanzapine. *CYP1A2* is located on chromosome 15 and consists of 7758 nucleotides. *CYP1A2* codes for an enzyme that is composed of 516 amino acids.
A somewhat atypical aspect of the CYP1A2 gene is that there are alleles of this gene that are inducible by smoking tobacco or consuming cruciferous vegetables, such as cabbage or Brussels sprouts. Consequently, patients who smoke tobacco and have two alleles of *CYP1A2* that are inducible by their smoking can be difficult to maintain on 1A2 substrate medications. A relatively common problem occurs when these patients are treated with olanzapine or clozapine on an inpatient psychiatric unit that does not allow them to smoke. When they begin to smoke after they are discharged, their serum level drops and their psychotic symptoms often reoccur. In some populations of European ancestry, as many as 25% of the population can have an inducible ultrarapid *CYP1A2* phenotype.

Pharmacogenomic testing to identify variability in pharmacodynamic responses

A goal of individualized molecular psychopharmacology is to identify medications for an individual patient that will not only be safe, but will be effective. Progress in making predictions of medication response has occurred, and while the goal of being able to predict this response with certainty has not been achieved, we can make increasingly accurate probabilistic predictions of the likelihood of response. Psychiatrists are familiar with this limitation. While hundreds of randomized clinical trials of psychotropic medications have been conducted to identify effective psychotropic drugs, the results of these trials only provide assurance that for a sample of patients there is reasonable likelihood that the medication will be of more benefit than a placebo. While selective serotonin reuptake blockers are among the most widely prescribed medications in the world, many patients do not respond. Specifically, the largest clinical effectiveness study of citalopram reported that less than 30% of the entire sample of patients experienced a complete remission of their symptoms.[11] While the ultimate goal of pharmacodynamically designed pharmacogenomic testing is to identify a drug for a specific patient that will definitely be effective, at the current stage of our understanding, it is only possible to identify a medication that is more likely to be effective.

The serotonin transporter gene *(SLC6A4)*

SLC6A4 is located on chromosome 17 and consists of 37 800 nucleotides. It codes for an enzyme that is composed of 630 amino acids.
SLC6A4 is the most widely genotyped pharmacogenomic "target" gene. A meta-analysis of studies of the relationship between the more active long form of the indel promoter variant of this gene and responses to selective serotonin reuptake inhibitors[12] confirmed the early finding that the long form is associated with a more rapid and better response.[13] However, this has not consistently been demonstrated in patients of Asian ancestry.[14,15] The importance of ancestral heritage has been further demonstrated by multiple analyses of the large STAR*D effective treatment study.
Analyses that did not consider ancestral background did not demonstrate a significant association,[16] while those that focused on patients who identified themselves as "white" but not "Hispanic" did confirm the relationship that patients who were homozygous for the more active long form of the indel promoter polymorphism were more likely to respond to citalopram. Other variants, such as rs25531[17] and the second intronic VNTR[18] are likely to influence the activity level of the gene and, consequently, its response to medications that block its ability to reuptake serotonin in the synapses of the central nervous system.

The serotonin receptor 2A gene *(HTR2A)*

HTR2A is located on chromosome 13 and consists of 62 663 nucleotides. Despite its large size, it codes for an enzyme that is composed of only 471 amino acids.
There have been a series of studies examining the association between variants of *HTR2A* and antidepressant response. A large study examining the response of depressed patients of European ancestry to citalopram

found that a positive response to citalopram was associated with having a copy of the adenine allele of rs7997012.[19]
Another study examining a different *HTR2A* variant, rs6313, reported that patients who were homozygous for the cytosine allele were less likely to tolerate taking paroxetine than those who had one or more copies of the thymine allele.[20]
A series of studies have reported a better response to clozapine in patients who had the thymine allele of rs6313. The thymine allele of rs6313 has also been associated with a lower risk for the development of extrapyramidal side effects when taking antipsychotic medications.[21-23]

The serotonin receptor 2C gene *(HTR2C)*

HTR2C is a very large gene that is located on the X chromosome and consists of 326 074 nucleotides. However, it codes for a protein product that is composed of only 458 amino acids.
Variations in the *HTR2C* gene have been associated with a better clinical response to clozapine. Specifically, patients with schizophrenia who have a copy of the cytosine allele of rs6318 have achieved better control of their psychotic symptoms than patients with the guanine allele.[24,25] However, this same variant has been associated with a higher risk for the development of extrapyramidal side effects in patients who are taking typical antipsychotic medications.[26]
An increased risk for the development of weight gain has been linked to a different *HTR2C* variant. Specifically, the cytosine allele of rs518147 is associated with increased weight gain, while the thymine allele is conceptualized as providing protection against weight gain.[27-29]

The clinical utility of pharmacogenomic testing in psychiatric practice

Assessing the clinical utility of pharmacogenomic testing is an ongoing process, given that the accuracy of genotyping is continually improving, and new research is identifying additional genetic variants that influence medication responses. Reports of adverse responses to 2D6 substrate medications in patients with decreased 2D6 metabolic capacity support the use of testing at this most basic level. Specifically, poor 2D6 metabolizers have had quite dramatic side effects to 2D6 substrate medications[3] and some toxic reactions have been lethal.[30,31] However, there have been no large randomized clinical trials to demonstrate the clinical utility of pharmacogenomic testing. Such trials would reinforce the use of testing. However, it is unlikely that these trials will ever be conducted because, by definition, they are not designed to concentrate on those patients who are the most likely to benefit from pharmacogenomic testing. Trials that screen vulnerable populations and identify patients at risk for suboptimal responses to medications are a more efficient method to address the clinical usefulness of testing patients with decreased metabolic capacity. These screened patients could then be enrolled in protocols designed to provide optimal response for their specific genotypes and predicted pharmacogenomic phenotypes.

Ethical considerations for pharmacogenomic testing in psychiatric practice

The provision of pharmacogenomic testing involves relatively few risks, but ethical safeguards are still important to consider. These are essentially the same considerations that are important to think through when ordering any laboratory test that has the potential to direct a treatment decision.
First, clinical pharmacogenomic testing requires obtaining appropriate consent. This has become a guiding principle for all diagnostic and therapeutic procedures. Clinicians should provide the basic rationale for proceeding with pharmacogenomic testing so that their patients have the opportunity to provide explicit informed consent.
Secondly, as a component of obtaining clinical consent, it must be clear that clinical testing is a voluntary procedure. This is true for virtually all clinical laboratory testing with the relatively rare exceptions of mandatory testing that can identify a condition with a potential negative influence on the public health of the community. A common example of compulsory testing is the monitoring of infections in order to prevent contagion.
A third principle is that clinicians must insure the confidentiality of sensitive medical information that becomes a part of the medical record of the patient. This is true whether the information is derived from a pathological specimen that reveals a malignant carcinoma or from magnetic resonance imaging that demonstrates atrophy

of the hippocampus. The security of the medical record is the responsibility of the clinician.

Finally, any diagnostic medical procedure must have an acceptable level of reliability. The degree of accuracy of any clinical laboratory testing is dependent on a number of key variables. Two of these variables are the seriousness of the prognosis for the patient if the test is positive and the efficacy of available treatments. In designing the treatment plan for a potentially lethal condition that is likely to respond well to a relatively benign intervention if it is administered early in the course of the illness, a laboratory test with high sensitivity is desirable. The most important objective in this situation is to identify as quickly as possible those patients who will benefit from treatment.

Future developments that will influence pharmacogenomic testing in psychiatric practice

In the 2009 presidential lecture of the American Psychiatric Association, it was predicted that pharmacogenomic testing would become a part of everyday psychiatric practice.[32] Ironically, in many academic health centers, pharmacogenomic testing has been utilized since 2004—the time of the introduction of the AmpliChip. Over the intervening years, early adopters have integrated pharmacogenomic testing into their inpatient protocols and ultimately into their outpatient practices. However, this testing has not yet been included in many clinical guidelines.

Pharmacogenomic testing is an innovation, and it takes time for innovations to become integrated into standard practice. While it is difficult to predict with accuracy just how quickly pharmacogenomic testing will become an essential component of clinical psychopharmacological practice, there is no question that this will happen. Ironically, given advances in our ability to sequence genes both rapidly and inexpensively, there will come a time in the near future when most patients will know their 2D6 phenotype in the same way as today they know their blood type. However, well before we reach a state of universal awareness of our informative genotypes, our patients will no longer accept avoidable side effects, and will demand basic pharmacogenomic testing prior to taking antidepressant or antipsychotic medications. ❑

REFERENCES

1. Mrazek DA. *Psychiatric Pharmacogenomics*. New York, NY: Oxford University Press; 2010.
2. Thase ME, Friedman ES, Biggs MM, et al. Cognitive therapy versus medication in augmentation and switch strategies as second-step treatments: a STAR*D report. *Am J Psychiatry*. 2007;164:739-752.
3. Weinshilboum R. Inheritance and drug response. *N Engl J Med*. 2003;348:529-537.
4. Dalen P, Dahl ML, Ruiz ML, Nordin J, Bertilsson L. 10-Hydroxylation of nortriptyline in white persons with 0, 1, 2, 3, and 13 functional CYP2D6 genes. *Clin Pharmacol Ther*. 1998;63:444-452.
5. Mrazek D. Out of the pipeline: pharmacogenomic DNA chip. *Curr Psychiatr*. 2005;4:67-73.
6. Preskorn S. Reproducibility of the in vivo effect of the selective serotonin reuptake inhibitors on the in vivo function of cytochrome P450 2D6: an update (part II). *J Psychiatr Pract*. 2003;9:150-158.
7. Goetz MP, Knox SK, Suman VJ, et al. The impact of cytochrome P450 2D6 metabolism in women receiving adjuvant tamoxifen. *Breast Cancer Res Treat*. 2007;101:113-21.
8. Schroth W, Goetz MP, Hamann U, et al. Associaiton between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. *JAMA*. 2009;302:1429-1436.
9. Henry NL, Stearns V, Flockhart DA, Hayes DF, Riba M. Drug interactions and pharmacogenomics in the treatment of breast cancer and depression. *Am J Psychiatry*. 2008;165:1251-1255.
10. Sim SC, Risinger C, Dahl ML, et al. A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. *Clin Pharmacol Ther*. 2006;79:103-113.
11. Trivedi M, Rush A, Wisniewski S, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry*. 2006;163:28.
12. Serretti A, Kato M, De Ronchi D, Kinoshita T. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with selective serotonin reuptake inhibitor efficacy in depressed patients. *Mol Psychiatry.* 2007;12:247-257.
13. Serretti A, Zanardi R, Rossini D, Cusin C, Lilli R, Smeraldi E. Influence of tryptophan hydroxylase and serotonin transporter genes on fluvoxamine antidepressant activity. *Mol Psychiatry*. 2001;6:586-592.
14. Yoshida K, Itoa K, Satoa K, et al. Influence of the serotonin transporter gene-linked polymorphic region on the antidepressant response to fluvoxamine in Japanese depressed patients. *Prog Neuropsychopharmacol Biol Psychiatry*. 2002;26:383-386.
15. Kim DK, Lim SW, Lee S, et al. Serotonin transporter gene polymorphism and antidepressant response. *Neuroreport*. 2000;11:215-219.
16. Peters E, Slager S, McGrath P, Knowles J, Hamilton S. Investigation of serotonin-related genes in antidepressant response. *Mol Psychiatry*. 2004;9:879-889.
17. Hu XZ, Rush AJ, Charney D, et al. Association between a functional serotonin transporter promoter polymorphism and citalopram treatment in adult outpatients with major depression. *Arch Gen Psychiatry*. 2007;64:783-792.
18. Mrazek DA, Rush AJ, Biernacka JM, et al. SLC6A4 variation and citalopram response. *Am J Med Genet Part B.* 2009;150:341-351.
19. McMahon FJ, Buervenich S, Charney D, et al. Variation in the gene encoding the serotonin 2A receptor is associated with outcome of antidepressant treatment. *Am J Hum Genet*. 2006;78:804-814.
20. Murphy GM, Kremer C, Rodrigues HE, Schatzberg AF. Pharmacogenetics of antidepressant medication intolerance. *Am J Psychiatry*. 2003;160:1830-1835.

Pruebas farmacogenómicas en la práctica clínica psiquiátrica

La incorporación en psiquiatría clínica de las pruebas farmacogenómicas ha ocurrido rápidamente en los últimos siete años. Inicialmente se identificaron genes de enzimas metabolizadoras de fármacos, como el gen del citocromo P450 2D6. La tipificación del gen del citocromo P450 2D6 que es altamente variable da la oportunidad actualmente a los clínicos de identificar a los metabolizadores pobres y los ultrarrápidos para las sustancias que son sustrato del 2D6. Con posterioridad se ha podido disponer en la práctica clínica de genes que influyen en la respuesta farmacodinámica de los medicamentos. Entre los primeros "genes blanco" estuvo el gen del transportador de serotonina (SLC6A4), el cual tiene variantes que han demostrado que influyen en la respuesta clínica de los pacientes con ancestros europeos cuando son tratados con inhibidores selectivos de la recaptura de serotonina. La tipificación de algunos de los genes del receptor de serotonina también está disponible para guiar la práctica clínica. La cuantificación de la utilidad clínica de las pruebas farmacogenómicas está en desarrollo y se han establecido las consideraciones éticas para su realización. Considerando la cada vez más clara costo-eficacia de la tipificación génica, recientemente se ha pronosticado que las pruebas farmacogenómicas se solicitarán de rutina para orientar la selección y dosificación de los fármacos psicotrópicos.

Évaluation pharmacogénomique psychiatrique en pratique clinique

L'évaluation pharmacogénomique psychiatrique s'est rapidement imposée en pratique clinique au cours de ces 7 dernières années. Les gènes d'enzymes métabolisant les médicaments, comme le cytochrome P450 2D6 (CYP2D6), ont d'abord été identifiés. Le génotypage de ce gène très variable permet maintenant aux cliniciens d'identifier des métaboliseurs lents et des métaboliseurs ultrarapides des substrats du 2D6. Des gènes influant sur la réponse pharmacodynamique des médicaments sont ensuite devenus disponibles en pratique clinique. Parmi les premiers « gènes cibles », le gène du transporteur de la sérotonine (SLC6A4) possède des variants qui influent sur la réponse clinique des patients d'ascendance européenne lorsqu'ils sont traités avec des inhibiteurs sélectifs de la recapture de la sérotonine. Le génotypage de certains gènes du récepteur de la sérotonine est également disponible pour guider la réponse clinique. La quantification de l'utilité clinique de l'évaluation pharmacogénomique évolue et fait l'objet de considérations éthiques. Il a été récemment prédit qu'en raison de l'évidente rentabilité croissante du génotypage, l'évaluation pharmacogénomique devrait faire partie des examens de routine pour sélectionner et ajuster la posologie des médicaments psychotropes.

21. Segman RH, Heresco-Levy U, Finkel B, et al. Association between the serotonin 2A receptor gene and tardive dyskinesia in chronic schizophrenia. *Mol Psychiatry.* 2001;6:225-229.
22. Tan EC, Chong SA, Mahendran R, Dong F, Tan CH. Susceptibility to neuroleptic-induced tardive dyskinesia and the T102C polymorphism in the serotonin type 2A receptor. *Biol Psychiatry*. 2001;50:144-147.
23. Lattuada E, Cavallaro R, Serretti A, Lorenzi C, Smeraldi E. Tardive dyskinesia and DRD2, DRD3, DRD4, 5-HT2A variants in schizophrenia: an association study with repeated assessment. *Int J Neuropsychopharmcol* 2004;7:489-493.
24. Sodhi MS, Arranz MJ, Curtis D, et al. Association between clozapine response and allelic variation in the 5-HT2C receptor gene. *Neuroreport*. 1995;7:169-172.
25. Arranz MJ, Munro J, Birkett J, et al. Pharmacogenetic prediction of clozapine response. *Lancet*. 2000;355:1615-1616.
26. Gunes A, Scordo MG, Jaanson P, Dahl ML. Serotonin and dopamine receptor gene polymorphisms and the risk of extrapyramidal side effects in perphenazine-treated schizophrenic patients. *Psychopharmacology* 2007;190:479-484.
27. Reynolds GP, Zhang ZJ, Zhang XB. Association of antipsychotic drug-induced weight gain with a 5-HT2C receptor gene polymorphism. *Lancet.* 2002;359:2086-2087.
28. Templeman LA, Reynolds GP, Arranz B, San L. Polymorphisms of the 5-HT2C receptor and leptin genes are associated with antipsychotic drug-induced weight gain in Caucasian subjects with a first-episode psychosis. *Pharmacogenet Genomics.* 2005;15:195-200.
29. De Luca V, Muller DJ, Hwang R, et al. HTR2C haplotypes and antipsychotics-induced weight gain: X-linked multimarker analysis. *Hum Psychopharmacol*. 2007;22:463-467.
30. Sallee FR, DeVane CL, Ferrell RE. Fluoxetine-related death in a child with cytochrome P-450 2D6 genetic deficiency. *J Child Adolesc Psychopharmacol*. 2000;10:27-34.
31. Koski A, Ojanpera I, Vuori E, Sajantila A. A fatal doxepin poisoning associated with a defective CYP2D6 genotype. *Am J Forensic Med Pathol*. 2007;28:259-261.
32. Stotland NL. Presidential address. *Am J Psychiatry*. 2009;166:1100-1104.