THE JOURNAL OF FAMILY PRACTICE

Vol. 3, No. 9 / September 2004

New tool: Genotyping makes prescribing safer, more effective

2D6 enzyme variations identify patients at risk for an unexpected response

David A. Mrazek, MD
Chair, Department of psychiatry and psychology Professor of psychiatry and pediatrics Mayo Clinic, Rochester, MN

Genotyping for cytochrome P-450 2D6 gene variations is emerging as a valuable clinical tool to help psychiatrists identify patients who:

- will not benefit from a medication
- could be at risk for an adverse response.[1-4]

Genetic variation has long been known to influence how individuals metabolize drugs, but only recently could we apply this information.[5] Many academic medical centers and the two largest U.S. reference laboratories offer 2D6 testing at costs of $200 to $500.

Before long, psychiatrists may adopt routine genotyping before prescribing 2D6 substrate medications. This article and four vignettes illustrate the clinical benefits of psychiatric pharmacogenomics and suggest when prospective genotyping could help you select and dose medications.

Table 1
Drugs metabolized by the 2D6 enzyme*

Antidepressants	Antipsychotics	Stimulants	Other medications
Desipramine	Fluphenazine	Atomoxetine	Codeine

Fluoxetine	Perphenazine		Dextromethorphan
Nortriptyline	Risperidone		Oxycodone
Paroxetine	Thioridazine		
Venlafaxine			
*Evidence suggests that these medications are predominantly metabolized by the 2D6 enzyme.			
Be careful when prescribing these agents to patients who are poor 2D6 metabolizers.			

Why test for the 2D6 gene?

The 2D6 gene codes for the 2D6 enzyme, the primary enzyme required to metabolize many psychotropics ***Table 1***.

Genetic variations. A common variation in a gene is frequently called an allele. More than 100 2D6 gene variations have been described. Consequently, the 2D6 gene's enzyme activity also varies widely. Most mutations decrease the enzyme's activity, but some polymorphisms change the gene's promoter region, which can lead to upregulation and increased enzyme production.

Each 2D6 gene variation has been labeled with a standardized abbreviation (***Table 2***):

- *1 refers to the "normal" gene
- *2 stands for several variants with different activity levels.
- *3, *4, *6, *7, *8, *9, *10, *11, *12, *14, and *17 code for proteins with little or no activity.
- *5 indicates that the gene is deleted, and no enzyme can be produced.

Multiple copies. Another characteristic of the 2D6 gene is its unusually high propensity to accumulate in multiple copies on the 22nd chromosome. As many as 13 copies of the 2D6 gene have been shown on a single chromosome. Given that each gene can code for the 2D6 enzyme, patients with multiple copies can metabolize 2D6 substrate medications very rapidly.

Nonpsychiatric drugs. The 2D6 enzyme is also involved in metabolizing many nonpsychiatric drugs. To produce analgesia, for example, the 2D6 enzyme must metabolize the prodrug codeine to morphine. Thus, individuals with no 2D6 enzyme activity experience no analgesia with codeine. Approximately 7% of Caucasians metabolize codeine poorly. Conversely, individuals with multiple 2D6 gene copies metabolize codeine to morphine very rapidly, with potential for acute mental status changes, including psychosis.

4 metabolizer types. Based on variation in individual 2D6 genotype, a patient is usually categorized as being an ultrarapid, extensive, intermediate, or poor metabolizer (***Table 3***). The following case vignettes of patients in each category illustrate the clinical benefits of 2D6 genotyping.

Ultrarapid metabolizer: Extra 2D6 copies

Abdul, 49, is an Ethiopian businessman engaged in international commerce. While in the United States, he underwent a routine wisdom-tooth extraction and was treated with acetaminophen and codeine. Despite having no psychiatric history, he began to experience extreme discomfort and flashing visual hallucinations within 24 hours of taking two codeine doses. The oral surgeon instructed him to discontinue codeine, and his symptoms resolved within 24 hours.

Because of this experience, Abdul underwent genotyping for the 2D6 gene. He was found to have five

active copies on one 22nd chromosome and no copies on the other (***Figure 1***). This genotype is unusual in western European populations but common in North Africa. Abdul then received alternate analgesics; psychiatric symptoms did not recur.

A patient such as Abdul, with multiple copies of a functional 2D6 gene, is an ultrarapid metabolizer. The 22nd chromosome—where the 2D6 gene is located—is short and contains areas of high homology. As a result, uneven crossover events occur more frequently during meiosis than is typical of larger chromosomes. Uneven crossover results in one gamete with two copies of the 2D6 gene and the other gamete with none.

2D6 enzyme activity is not essential for survival, which raises fascinating questions about this gene's evolutionary importance. In certain geographic regions, many individuals have multiple copies of the gene. In Ethiopia—the country with the highest documented number of ultrarapid metabolizers—more than 25% of the population has one chromosome with multiple copies of the 2D6 gene.[6] Because these copies produce an increased amount of 2D6 active enzyme, normal doses of 2D6 substrate medications do not benefit these individuals.

Table 2
How common 2D6 gene variations (alleles) affect 2D6 enzyme activity

Allele label	2D6 enzyme activity	Allele frequency (%)†
*1	Normal	37
*2	Decreased	3.3
*2P	Modestly increased	6
*3	None	1
*4	None	18
*5	None (gene deletion)	4
*6	None	1
*7	None	<1
*9	Decreased	3
*10	Decreased	2
*11	None	0
*12	None	<1
*14	Decreased	<1
*17	Decreased	<1

†In Caucasian populations

Management of Type 2 Diabetes with DPP-4 Inhibitors: A Clinical Update

Click here for this e-newsletter series

Table 3
Four ways patients respond to 2D6 substrate drugs

Category	Patient characteristics	% of Caucasian population
Ultrarapid	Metabolize 2D6 medications rapidly resulting in poor response	1 to 2
Extensive	Metabolize 2D6 medications at a normal rate	73 to 82
Intermediate	Metabolize 2D6 medications at a slower-than-normal rate	10 to 15
Poor	Metabolize 2D6 medications very slowly with increased risk of side effects	7 to 10

When treating ultrarapid metabolizers one strategy is to increase the dosage to obtain a therapeutic effect Because some substrates have complex metabolic pathways, however, high concentrations of secondary or tertiary metabolites can accumulate. Thus, when a substance's metabolic pathway is not well-documented, a more cautious approach is to choose a medication metabolized by another pathway.

Figure 1
Genotypes and metabolizer categories of 4 illustrative patients

Go Back

Extensive metabolizer: The 'norm'

George, a 31-year-old Ethiopian architect, is Abdul's second cousin. He developed acute depression with intense suicidal ideation and sought psychiatric consultation. He had no history of atypical drug reactions, but—because of his ethnic background—his psychiatrist was concerned that George might be a rapid metabolizer.

2D6 genotyping showed that George's genotype was *1/*1, which meant he had two functional 2D6 copies (***Figure 1***). This genotype suggests that he could tolerate many antidepressants. The psychiatrist concluded—with some confidence—that George would not experience adverse effects or low serum levels when prescribed fluoxetine at usual dosages.

Extensive metabolizers have two normal 2D6 gene copies and can produce adequate active 2D6 enzyme Patients with this genotype—common in Caucasians—are generally said to have "normal" 2D6 metabolism. This means they metabolize 2D6 substrate medications at a rate within the recommended dosage ranges determined from North American or European pharmacokinetic studies.

Intermediate metabolizer: Mixed message

Katrina, 27, represents the government of her native Sweden in trade agreements. When she developed depressive symptoms (insomnia, sense of hopelessness), Katrina saw her psychiatrist. She reported that her family has a history of adverse reactions to multiple medications, but she had tolerated most

ARCHIVES
>> Applied Evidence
>> Audiocasts
>> Clinical Inquiries
>> Family Medicine Grand Rounds
>> Guideline Update
>> Hospitalist Rounds
>> InfoPOEMs®
>> Instant Polls
>> Online Exclusives
>> Original Research
>> Patient Handouts
>> Photo Rounds
>> Photo Rounds Friday
>> Practice Alerts
>> PURLs
>> Current Clinical Practice

medications. In fact, she had twice been successfully treated with relatively high doses of codeine.

Her psychiatrist suspected she was an intermediate 2D6 metabolizer and ordered testing. Her genotype was *1/*4, with one normal copy and one that produced no functional 2D6 enzyme (***Figure 1***).

Based on her clinical history and this genotypic information, the psychiatrist prescribed sertraline—metabolized by both 2D6 and 3A4 enzymes— at 50 mg/d. Because Katrina metabolized sertraline at a slower-than-usual rate, she developed a therapeutic blood level and responded well to this low dosage.

Intermediate metabolizers have a chromosome with one functional 2D6 gene copy. The other chromosome has either a copy with a defective functional polymorphism or a deletion of the gene. These patients usually tolerate 2D6 substrate drugs in low dosages.

Poor metabolizer: 'medication-sensitive'

Olga, Katrina's mother, has always lived in northern Sweden. She has no psychiatric history except for one psychotic episode that required hospitalization.

Her psychotic illness began on the summer solstice, during an all-night celebration. In addition to using unspecified recreational drugs, she took three 20-mg capsules of fluoxetine that her friend told her would make her feel high. She instead developed acute mania and dramatic paranoid delusions.

Figure 2
Possible genotypes of Brad, son of Abdul and Katrina

Go Back

Olga was hospitalized and treated with moderate doses of haloperidol that precipitated an acute dystonic reaction. She was subsequently given ben-ztropine, and her extrapyramidal symptoms resolved. After discharge, she was treated with haloperidol and benztropine for 2 years, after which she spontaneously discontinued these drugs against medical advice. Her psychotic illness has not recurred.

Knowing her own genotype, Katrina understood that her mother had a 50% probability of having one copy of the 2D6 *4 allele. Given her mother's history of medication intolerance, Katrina believed that her mother's psychiatric illness might have been related to a drug reaction. She persuaded her mother to send a blood sample to a laboratory in Stockholm.

Olga's genotype was *4/*4, indicating that she would be unlikely to tolerate even moderate doses of 2D6 substrate medications (***Figure 1***). Given her complete recovery and continued good health without medication, the most probable retrospective diagnosis was drug-induced psychosis. Her 2-year neuroleptic treatment probably was unnecessary.

Figure 3
Genogram for Brad, son of Abdul and Katrina

Go Back

Poor metabolizers without a functional 2D6 gene copy have low tolerance for many medications and often become labeled as "medication sensitive." When genotyping reveals that an individual is a poor metabolizer, prescribing medications that do not require 2D6 metabolism is usually prudent.

In rare cases, poor metabolizers have died from normal doses of 2D6 substrate medications.[7] Far more commonly, however, they spontaneously discontinue taking these drugs because of adverse side effects.

Benefits of prospective testing

When used in clinical practice, pharmacogenomic testing's two goals are to identify:

- ultrarapid metabolizers, who will not benefit from a medication
- poor metabolizers, who likely will have adverse responses to a medication.

The following case demonstrates the benefit of prospective 2D6 genotyping:

Brad, age 14, is the son of Abdul and Katrina, whose genotypes have been described. Brad developed a serious depression that was similar in severity and onset to an illness his mother experienced as a teen.

Brad's parents want him to get the maximum benefit from psychopharmacologic treatment while avoiding distressing side effects. He had been healthy and had received no prescriptions other than antibiotics in the past.

How would you proceed? Without knowing Brad's parents' genotypes, you might reason that Brad would resemble one of them in drug response. However, when you review each parent's genotype, you realize four scenarios are possible (***Figure 2***):

- Brad has a high likelihood of being an ultrarapid metabolizer because he has a 50% chance of inheriting a chromosome with five copies of the 2D6 gene from his father. He inherited the *1 or *4 form from his mother, but the effect of either will be clinically irrelevant.
- If Brad inherited the chromosome with the deletion from his father and the *1 form from his mother, he would be an intermediate metabolizer, as is his mother.
- If he inherited the chromosome with the deletion from his father and the *4 form from his mother, he would be a poor metabolizer like his grandmother, Olga. He would be at substantial risk for adverse reactions (such as intense headaches or vomiting) to 2D6 substrate medications.

On testing, Brad was found to be a poor metabolizer (***Figure 3***) The psychiatrist prescribed bupropion, which is metabolized by the 2B6 enzyme rather than the 2D6 enzyme.

Conclusion. To introduce the concept of genotypic testing, this review has focused on simple illustrations of variations in a single gene. However, many genes in the P-450 family play important roles in metabolizing psychotropics. In the future, genotyping of panels of these genes will likely provide more-specific guidance than can be achieved by simply testing one gene at a time.

Related resources

- Lerer B (ed). Pharmacogenetics of psychotropic drugs. Cambridge, UK: Cambridge University Press, 2002.
- Kirchheiner J, Borsen K, Dahl ML, et al. CYP2D6 and CYP2C19 genotype-based dose recommendations for antidepressants: a first step towards subpopulation-specific dosages. *Acta Psychiatr Scand* 2001;103(3):173-92.
- Indiana University School of Medicine, Division of Clinical Pharmacology. Drug Interactions—Defining Genetic Influences on Pharmacologic Responses. **http://medicine.iupui.edu/flockhart**.

Drug brand names

Acetaminophen w/codeine phosphate • Tylenol w/codeine
Atomoxetine • Strattera
Benztropine mesylate • Cogentin
Bupropion • Wellbutrin
Desipramine • Norpramin
Fluoxetine • Prozac
Fluphenazine • Prolixin
Haloperidol • Haldol
Nortriptyline • Aventyl, Pamelor
Oxycodone • Oxycontin
Paroxetine • Paxil
Perphenazine • Trilafon
Risperidone • Risperdal
Sertraline • Zoloft
Thioridazine • Mellaril
Venlafaxine • Effexor

Disclosure

Dr. Mrazek reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

References

1. Mrazek DA. Clinical genomic testing.In: Wiener J, Dulcan M (eds). *Textbook of child and adolescent psychiatry (3rd ed)*. Washington, DC: American Psychiatric Publishing, Inc.,2001;193–203.
2. Mrazek DA. Pharmacogenomic screening for depressed children and adolescents (scientific proceedings).Miami Beach, FL: American Academy of Child and Adolescent Psychiatry annual meeting,2003;159.
3. Phillips KA, Veenstra DL, Oren E, et al. Potential role of pharmacogenomics in reducing adverse drug reactions. *JAMA* 2001;286(18):2270–9.
4. Shi MM, Mehrens D, Dacus K. Pharmacogenomics: Changing the health care paradigm. *Modern Drug Discovery* 2001;4(7):27–32.
5. Kirchheiner J, Brosen K, Dahl ML, et al. CYP2D6 and CYP2C19 genotype-based dose recommendations for antidepressants: a first step towards subpopulation-specific dosages. *Acta Psychiatr Scand* 2001;104:173–92.
6. Masimirembwa CM, Hasler JA. Genetic polymorphism of drug metabolising enzymes in African populations: implications for the use of neuroleptics and antidepressants. *Brain Res Bull* 1997;44(5):561–71.
7. 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(1):27–34.
8. Gaedigk A, Gotschall RR, Forbes NS, et al. Optimization of cytochrome P4502D6 (CYP2D6) phenotype assignment using a genotyping algorithm based on allele frequency data. *Pharmacogenetics* 1999;9(6):669–82.