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Genes and the Response to Drugs

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The response to many drugs in common use varies greatly among patients. After the intake of identical doses of a given agent, some patients may have clinically significant adverse effects, whereas others may have no therapeutic response. Some of this diversity in rates of response can be ascribed to differences in the rate of drug metabolism, particularly by the cytochrome P-450 superfamily of enzymes. Ten isoforms of cytochrome P-450 are responsible for the oxidative metabolism of most drugs, each having selective yet overlapping substrate specificity. Variability among patients in the activity of these enzymes reflects a complex interaction between environmental factors and both genetic and non-genetic host factors. The effect of genetic polymorphisms on catalytic activity is most prominent for three isoforms — CYP2C9, CYP2C19, and CYP2D6 — which collectively account for about 40 percent of drug metabolism mediated by cytochrome P-450. The results of a recent meta-analysis demonstrating that adverse drug reactions are more likely for drugs metabolized by enzymes that have genetic polymorphisms¹ underscore the clinical relevance of these variations.

Among the various cytochrome P-450 enzymes, CYP2D6 has been most extensively studied. It is involved in the metabolism of about 100 drugs, including beta-blockers and antiarrhythmic, antidepressant, neuroleptic, and opioid agents. Pioneering studies in the 1970s revealed that some patients — classified as having “poor metabolism” of certain drugs — lack CYP2D6 activity.^{2,3} Patients who have some enzyme activity are classified into three subgroups: those with “normal” activity (or exten-

sive metabolism), those with reduced activity (intermediate metabolism), and those with markedly enhanced activity (ultrarapid metabolism). Figure 1 shows the relative frequency of these phenotypes

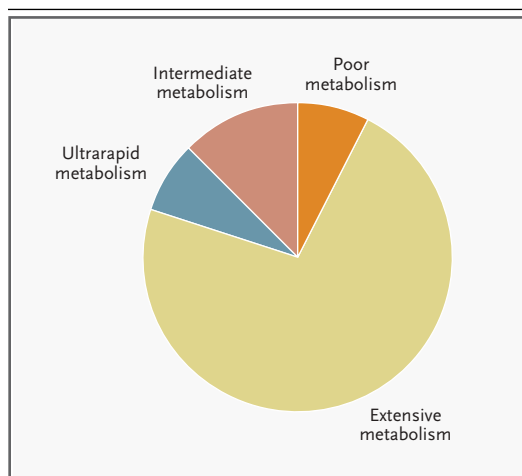


Figure 1. Frequency of CYP2D6 Phenotypes in White Populations.

The chart shows the proportions of whites who are classified as having CYP2D6 phenotypes associated with poor drug metabolism, extensive metabolism, intermediate metabolism, and ultrarapid metabolism. On the two ends of the continuum, poor metabolism is associated with an increase in adverse reactions induced by drugs that are inactivated by CYP2D6 and a decreased effect of prodrugs that are bioactivated by CYP2D6. Ultrarapid metabolism is associated with a decreased effect of drugs that are inactivated by CYP2D6 and an increased effect of prodrugs that are bioactivated by CYP2D6.

among whites. The distribution of CYP2D6 phenotypes varies with race. For example, the frequency of the phenotype associated with poor metabolism is 5 to 10 percent in white populations but only 1 percent in Chinese and Japanese populations.

Much of this phenotypic diversity is explained by the polymorphic nature of the gene encoding CYP2D6, which has more than 80 distinct allelic variants. (Data are available on the Web, at the home page of the CYP Allele Nomenclature Committee at <http://www.imm.ki.se/CYPalleles/cyp2d6.htm>.) Some alleles code for “normal” protein, whereas others code for an enzyme with reduced activity, an inactive enzyme, or a total absence of the enzyme. Furthermore, in 1 to 8 percent of whites (and in a much higher percentage of some other national groups, such as Saudi Arabians and Ethiopians), at least one additional copy of the *CYP2D6* gene is identified, the result of a process that is known as duplication or multiduplication. Despite the abundance of different allelic variants, most of these variants occur at low frequency in the population. Most of the time, patients with poor metabolism can be identified by testing only for the five most prevalent mutant alleles.⁴ However, the decision regarding which specific alleles to analyze depends on the racial and ethnic composition of the population, since the distribution of mutated alleles varies among racial and ethnic groups.

Genotyping to determine “metabolizer status” has the attraction of being a simple procedure that does not require the administration of a drug and is not influenced by concurrent drug intake. Nevertheless, genotyping has major drawbacks. For example, since gene duplication explains only a fraction of the phenotype associated with ultrarapid metabolism (up to about 40 percent of cases), knowing the genotype may not confer the needed phenotypic information. Furthermore, genotyping cannot distinguish among people who have various levels of catalytic activity within the group associated with extensive metabolism nor between people with extensive metabolism and those with intermediate metabolism. It is anticipated that the discovery of new allelic variants such as *CYP2D6*^{*41}, which appears to modulate gene expression,⁵ and *CYP2D6*^{*35}, which is associated with enhanced CYP2D6 activity,⁶ might improve the accuracy of genotyping in predicting the phenotype, but we are a long way from having complete correlations between genotype and phenotype.

Dosages for most drugs are commonly recom-

mended on the basis of their pharmacokinetic behavior in a group of healthy patients, most of whom have extensive metabolism of CYP2D6 substrates. For drugs that are inactivated by the CYP2D6 enzyme, such “average doses” are clearly too much for people with poor metabolism and too little for those with ultrarapid metabolism. Not surprisingly, multiple reports have attested to the clinical relevance of CYP2D6 polymorphisms, typically by describing toxic effects among patients with poor metabolism or a lack of therapeutic effect among those with ultrarapid metabolism who are treated with “normal” doses of various CYP2D6 substrates.

In a majority of cases, metabolism that is mediated by cytochrome P-450 represents a deactivation pathway. For some drugs, however, oxidation leads to conversion of a prodrug into an active compound. A prime example is codeine (metabolized by CYP2D6); other examples include clopidogrel (metabolized by CYP3A4), cyclophosphamide (metabolized by CYP2B6), and tamoxifen (metabolized by CYP2D6). The major metabolic pathway of codeine consists of glucuronidation and *N*-demethylation, whereas the CYP2D6-mediated *O*-demethylation to produce morphine is a minor reaction. Nevertheless, the latter is a crucial step in bioactivation, since the affinity of codeine for the μ -opioid receptor is only 1/200 to 1/3000 that of morphine.⁷ Previous studies have shown that the effects of codeine — analgesic, respiratory, psychomotor, and miotic — are markedly attenuated in people with poor metabolism of CYP2D6.⁸ On the other hand, people with ultrarapid metabolism, such as the patient described by Gasche et al.⁹ in this issue of the *Journal*, produce greater amounts of morphine from codeine and therefore may experience exaggerated pharmacologic effects in response to regular doses of codeine. Similar effects, albeit less dramatic, have been described in patients with ultrarapid metabolism of CYP2D6 in response to routine doses of hydrocodone or oxycodone, which are other opioids requiring CYP2D6-mediated activation.¹⁰ These reports clearly illustrate the effect of *CYP2D6* genetic polymorphisms on the action of codeine, ranging from virtually no effect in patients with poor metabolism to severe toxic effects in those with ultrarapid metabolism. To put these observations into perspective, these extremes of response might be relevant for some 10 to 20 percent of whites who have phenotypes associated with either poor metabolism or ultrarapid metabolism.

Despite the increasing evidence that genetic de-

terminants may mediate variability among persons in the response to a drug, genotyping or phenotyping before therapy is not a common practice. One hurdle for the application of genetic data in medicine is that the response to drugs is usually determined not by single-gene polymorphisms but, rather, by heterogeneity in multiple genes affecting drug metabolism, transport, or target proteins. In the case of codeine, polymorphisms in the gene encoding codeine glucuronidation (*UGT2B4* and *UGT2B7*) may determine the amount of codeine available for *O*-demethylation by *CYP2D6*.¹¹

In addition to the *CYP2D6* gene, the *CYP2D* locus consists of two homologous genes, *CYP2D7* and *CYP2D8*. Both are considered pseudogenes, since they normally contain disruptive mutations and therefore do not encode functional proteins. The recently discovered 138delT polymorphism in the *CYP2D7* gene generates an alternate splicing and converts the *CYP2D7* pseudogene into a functional gene.¹² This splice variant was isolated from brain tissue, and it is speculated that in subjects who carry this polymorphism, local production of morphine from codeine *in situ* may increase the effects of codeine. Furthermore, an A118G polymorphism in the μ -opioid receptor gene may also play a role in determining the response to opioids. Finally, as in the case described by Gasche et al., nongenetic host factors such as renal dysfunction or environmental influences such as the use of interacting drugs are also important.

Prospective studies are needed to evaluate whether the use of genetic and phenotypic data to guide drug selection and dosage will result in improved drug safety and efficacy. Although there are many hurdles still to be overcome, the incorporation of pharmacogenetics into clinical medicine is

likely to have a great effect on public health in the near future.

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