Preprescription Genotyping
Not Yet Ready for Prime Time, but Getting There

Dan M. Roden, MD; Nancy J. Brown, MD

There are few, if any, situations in medicine in which a clinician can predict with certainty an individual’s response to drug therapy. A host of factors can modulate this response: concomitant disease or drug therapy, sex, age, ethnicity, or dysfunction of excretory organs, to name but a few. Even when we correct for changes anticipated by such conditions, however, drug responses remain highly variable. It is an appealing concept, and one to which we subscribe, that some portion of this variability—and perhaps a great portion in many cases—is attributable to genetic factors. An increasingly sophisticated view of the genetic determinants of drug action in the context of complex diseases now raises the realistic expectation that this possibility can be addressed.

The Present Study
In this issue of Circulation, McNamara and colleagues present data that a common polymorphism in the ACE gene determines response to β-blocker therapy in ACE inhibitor–treated patients with congestive heart failure. The insertion/deletion (I/D) polymorphism in the ACE gene was first described in 1990, and it is clear that individuals homozygous (DD) for the D allele have consistently higher ACE activity. Interestingly, despite a decade of work, the mechanism whereby the I/D polymorphism affects ACE activity is uncertain. Moreover, although the physiological consequences of the polymorphism seem clear, its actual role in mediating important diseases such as hypertension, myocardial infarction, or heart failure is not totally settled. McNamara and colleagues followed up 328 patients with heart failure and found that the prognosis was worse in patients with the DD genotype. Previous smaller studies have also tended toward a similar result, but the conclusions have not been entirely consistent. The new and intriguing finding in the present study was that the poor prognosis conferred by the D allele was improved (to that seen in II and ID groups) in patients treated with β-blockers. Given the concept that activation of the renin-angiotensin-aldosterone system (RAAS) is enhanced in subjects with the D allele and that β-blockers suppress renin release, the results presented by McNamara et al are intuitively appealing: the reasoning is that addition of a β-blocker to the regimen of a patient with the DD allele would be predicted to exert a greater beneficial effect, given their greater RAAS activation. Should all patients with heart failure therefore undergo genotyping for the ACE gene I/D polymorphism?

As physiologically appealing as the results appear to be, there are a number of caveats to this interpretation. Renin and angiotensin concentrations are not reported. There are a number of small differences among patients with the II, ID, and DD genotypes (such as the percentage of patients with ischemic heart disease and the percentage of patients receiving angiotensin-receptor blockers). These differences, collectively, may make DD patients different from other groups in ways independent of genotype. Similarly, assignment to β-blockers was not randomized. The finding that the DD genotype confers a worse prognosis in heart failure has not been observed in other trials, particularly in Chinese subjects (in whom the DD genotype is less common); this finding and other studies suggest that other factors, including other polymorphisms, may contribute to the prognosis in heart failure. One could also argue that the present results, together with data indicating that the duration of ACE inhibition is shortened for individuals homozygous for the D allele, suggest that DD patients should simply receive higher doses of ACE inhibitor.

Genetic Mechanisms Underlying Variability in Drug Action
The concept that variability in drug metabolism might be a contributor to variability in drug action was advanced in the early 20th century. In the 1940s and 1950s, familial patterns of drug disposition, often associated with unusual drug actions, were described: notable examples were prolonged paralysis after succinylcholine due to familial pseudocholinesterase deficiency and enhanced isoniazid toxicity due to the rapid acetylation phenotype. The term “pharmacogenetics” was enshrined in a textbook of that name published in 1962. Thus, the concept of a familial component modulating drug action is not a new one. More recently, defects in other drug-metabolizing and drug transport pathways have been described as major contributors to variability in actions of commonly used drugs, such as codeine, propranolol, omeprazole, warfarin, cyclosporine, and digoxin. One of the most instructive examples was the description in the late 1970s of the debrisoquine 4-hydroxylase deficiency. This is now known to arise in individuals homozygous for loss of function alleles in the gene encoding a specific drug
metabolizing enzyme, cytochrome P450 (or CYP) 2D6. Indeed, the 2 most commonly used β-blockers in the study reported by McNamara et al, metoprolol and carvedilol, are both recognized as CYP2D6 substrates,\(^1,2\) with higher drug concentrations and enhanced β-blockade in subjects with deficient CYP2D6 activity.

**Drug-Target Interactions**

Not all genetically determined variability in drug action is attributable to changes in drug absorption, distribution, metabolism, or excretion that alter concentrations. Drugs exert their actions by interacting with specific macromolecular targets, most often proteins encoded by specific genes. Thus, altered sensitivity to a drug could arise as a consequence of a DNA variant in the gene encoding the drug target. Indeed, variable responses to ACE inhibitors, as a function of the I/D genotype, have been described,\(^6\) presumably arising through this mechanism. The drug-target interaction, however, almost never occurs in splendid isolation. Rather, these interactions occur in the context of a complex physiological system, so DNA variants that modulate function of the system as a whole may well modulate the extent to which a drug-target interaction exerts a physiological effect. In the case of the ACE polymorphism studied by McNamara et al, subjects with the DD allele would be predicted to have greater ACE activity and thus higher tissue angiotensin concentrations. The apparent genetic dependence of β-blocker activity in their patients therefore most likely reflects not a direct action of β-blockers on the ACE gene product but rather modulation of the effect of β-blockers in the setting of genetically determined variable RAAS activation.

**Pharmacogenetics and Pharmacogenomics**

Pseudocholinesterase deficiency arises as a consequence of a rare DNA variant, a “mutation.”\(^8\) The study of rare disease-associated mutations has provided tremendous benefits to our understanding of the physiology and rational treatment of such diseases as cystic fibrosis, sickle cell anemia, certain subsets of hypertension, etc. The other type of DNA variant, a polymorphism, is more common (generally defined as >1% prevalence in a given population) and may or may not have functional consequences.\(^21\) Most polymorphisms in the human genome occur at single nucleotide sites and have been designated “single-nucleotide polymorphisms” (or SNPs). Others, such as the I/D polymorphism, consist of changes in larger segments of DNA but are less common. Current estimates suggest that there are \(\geq 3\,000\,000\) SNPs in the human genome, but not all will turn out to have functional consequences. Given the extraordinary prevalence of DNA polymorphisms, the notion that variability in drug response will be attributable to a single polymorphism or even a handful of polymorphisms becomes less tenable. Polymorphisms in multiple other “candidate” genes might be postulated as contributing to variability in the response to β-blockers described by McNamara et al. Indeed, functionally important polymorphisms have been described in the genes encoding angiotensinogen,\(^22\) the AT\(_1\) angiotensin II receptor,\(^5,23\) and the β\(_2\) adrenergic receptor, and some have been implicated in the course of congestive heart failure.\(^24\)

also, recent studies suggest that combinations of SNPs that determine individual haplotypes may be a key to understanding genetically determined variability in drug action.\(^25\) CYP2D6 is another candidate for modulating response to β-blockers through a pharmacokinetic mechanism. Ultimately, the identification of genes that modulate response to drug therapies may require SNP-based or haplotype-based analysis of very large sets of patients with well-characterized responses to specific drug therapies. This will require close collaboration among geneticists, informatics specialists, and above all, clinician-investigators. A crucial first step is for clinicians to recognize this new opportunity for clinical investigation and to begin to develop clinical/DNA databases to address these issues. Given the potential complexities of the genetic determinants of drug action and the likely explosion in information derived from studies such as the one presented here, however, we believe that it is crucial that any proposed a priori test to segregate patients into potential responders or nonresponders be validated in prospective trials before being widely applied. McNamara and colleagues are to be congratulated for taking an important first step in this direction.

**References**


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