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Commentary Article

Genetic Variation in Drugs

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INTRODUCTION

Differences in genetic (inherited) makeup among individuals affect what the body does to a drug and what the drug does to the body. The study of genetic differences within the response to drugs is named pharmacogenetics.

Because of their genetic makeup, some people process drugs slowly. As a result, a drug may accumulate within the body, causing toxicity. Other people metabolize drugs so quickly that after they take a usual dose, drug levels within the blood never become high enough for the drug to be effective.

Genetic polymorphisms are identified for several drug-metabolizing enzymes, including the cytochrome P450 (CYP450) enzymes. This gives rise to distinct population phenotypes of persons who have metabolism capabilities starting from extremely poor to extremely fast.

VARIABLE DRUG ACTIONS AND SINGLE GENE VARIANTS

Large Effect Variants in Drug-Metabolizing Enzymes

In the 1950s, McKusick and Price-Evans described variable N-acetylation,3 a crucial contributor to variable isoniazid hepatotoxicity and therefore the lupus syndrome during treatment with procainamide and hydralazine. In the 1970s, two groups, studying different drugs (debrisoquine, an antihypertensive,36 and sparteine, being assessed as an antiarrhythmic37,38), reported a group of 5–10% of subjects with adverse effects due to apparent absence of a key enzyme mediating drug bioinactivation. The enzymes were initially termed debrisoquine 4-hydroxylase and sparteine N-oxidase, but subsequently it became clear that this was an equivalent defect, 39 now recognized to represent homozygosity for loss of function of a selected member of the cytochrome P450 (CYP) superfamily of drug metabolizing enzymes, CYP2D6.40 Dozens of variants have now been reported to scale back or eliminate CYP2D6 function

Coding region variants in other members of this superfamily, like CYP2C9 and CYP2C19, generate populations of "poor metabolizers" for substrates of every of those enzymes. Interestingly, CYP3A4, the enzyme most ordinarily implicated within the metabolism of clinically-used drugs,41 doesn't include common coding region polymorphisms that alter function; nevertheless, CYP3A4 activity varies widely across individuals, and at least some of this variability likely arises from genetic variation in the regulation of CYP3A4 gene expression.42 Another contributor to variability in CYP3A activity is a common intronic single nucleotide polymorphism in a closely-related gene, CYP3A5;20,43 the variant CYP3A5*3 allele alters mRNA by creating a new splice site.

The incidence of functionally-important CYP alleles can vary strikingly by ancestry. For example, poor metabolizers with absent CYP2D6 function are found in 5–10% of European and African populations, but are less common in Asian subjects. By contrast, CYP2C19 poor metabolizers are commoner in Asian subjects compared to the opposite two major ancestry groups, and therefore the frequency of the CYP3A5*3 variant is far higher in Caucasians (0.85) compared to African Americans (0.55), which correlates with higher hepatic CYP3A5 expression in African American subjects.

Genetic Makeup and Response to Drugs

Differences in genetic (inherited) makeup among individuals affect what the body does to a drug and what the drug does to the body. The study of genetic differences within the response to drugs is named pharmacogenetics. In some cases, the extent of an enzyme that metabolizes medications is often measured before starting the therapy. This should be considered before prescribing.

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In about half the people within the N-acetyltransferase, a liver enzyme that metabolizes certain drugs, works slowly. Such people are called slow acetylators. Drugs, like isoniazid (which is employed to treat tuberculosis), that are metabolized by this enzyme tend to succeed in higher blood levels and remain within the body longer in slow acetylators than they are doing in people in whom this enzyme metabolizes drugs rapidly (fast acetylators).

About 1 of 1,500 peoples has low levels of pseudocholinesterase, a blood enzyme that inactivates drugs like succinylcholine, which is usually given to temporarily relax muscles during surgical procedures. If succinylcholine isn't rapidly inactivated, muscle relaxation could also be prolonged, and other people might not be ready to breathe on their own as soon after surgery as is common. They may need a ventilator for an extended time.

About 10% of black men and fewer black women have a deficiency of glucose-6-phosphate dehydrogenase (G6PD), an enzyme that protects red blood cells from certain toxic chemicals. For example, in people with G6PD deficiency, some drugs (such as chloroquine and primaquine, which are wont to treat malaria) destroy red blood cells and cause haemolytic anaemia .

requires resources and vigilance as trials become approved for human use. Although the current ethical, legal and social issues include some educational projects, a distinct and expanded program should be launched that is aimed for students, the general public, clinicians and genetic counselors.

CONCLUSION

However, some important clinical issues will require being quickly and adequately resolved. The pharmacokinetic and pharmacodynamic parameters of gene delivery vectors are largely uncharacterized in humans. Estimation of risk-to-benefit ratio and actual healthcare costs for gene therapy isn't well documented. Undoubtedly, gene therapy won't be cheap, and