



Genetic Variation in Drug Metabolism, Transport, and Treatment Response

Ethan Williams*

Department of Pharmacogenomics, University of California, San Francisco, USA

DESCRIPTION

Genetic drug susceptibility refers to the influence of inherited genetic differences on an individual's response to medicines. People receiving the same medication and dose can experience different levels of therapeutic benefit, drug concentration, or unwanted effects. These differences may arise from variations in genes involved in drug metabolism, transport, receptor activity, immune recognition and cellular signaling. Understanding these genetic influences can support safer medication use and provide useful information for selecting appropriate therapies. Human genetic variation includes single-nucleotide polymorphisms, insertions, deletions, copy-number changes and other Deoxyribonucleic Acid (DNA) differences. Some variants have little measurable biological effect, whereas others can alter the amount or function of a protein. When the affected protein participates in the handling or action of a medicine, the genetic difference may influence treatment response. The effect of one variant can also depend on other genetic and clinical factors.

Drug metabolism is one of the most important areas associated with genetic susceptibility. Enzymes belonging to the cytochrome P450 family process many commonly used medicines. Genes such as *Cytochrome P450 2D6*, *CYP2C19*, *CYP2C9* and *CYP3A5* contain multiple variants that can alter enzyme activity. Individuals may therefore process the same medicine at different rates. Depending on the drug, slower metabolism may increase exposure, while faster metabolism may reduce exposure or alter the activation of a prodrug. *CYP2D6* provides an important example of genetic variation in drug processing. Numerous alleles have been identified and their combined effects can produce different levels of enzyme activity. A person with reduced *CYP2D6* activity may process certain medicines more slowly than someone with normal activity. In contrast, increased activity can cause faster conversion or elimination for particular drugs. Clinical interpretation depends on the medicine and the established relationship between genotype, metabolic phenotype and treatment outcome.

CYP2C19 variation can also affect medication response. Some alleles are associated with reduced enzyme activity, while others maintain normal function. This difference can influence medicines that depend on *CYP2C19* for activation or elimination. For selected therapies, genetic information may assist clinicians when deciding whether a particular medicine is suitable or whether another option should be considered. Drug transport represents another source of genetic susceptibility. Transport proteins regulate the movement of pharmaceutical compounds across cellular membranes. They influence intestinal absorption, distribution into tissues, hepatic uptake, biliary secretion and renal elimination. Genetic variants affecting transporter expression or activity can change the concentration of a medicine at its target site. The resulting clinical effect varies according to the drug and the specific transporter involved.

Genetic differences in drug targets can also influence treatment response. Receptors, enzymes, ion channels and signaling proteins are common targets for pharmaceutical compounds. A DNA variant can alter the structure, quantity, or activity of one of these proteins. When a medicine interacts with the affected target, the strength of the therapeutic response may differ from that observed in individuals carrying another allele. Immune-related genetic variation is particularly important for certain adverse drug reactions. Human leukocyte antigen genes contain variants associated with susceptibility to immune-mediated responses against specific medicines. Some of these reactions can be severe. When clinical recommendations support genetic screening before treatment, identifying a relevant allele can help healthcare professionals select an alternative medicine and reduce avoidable risk.

Genetic drug susceptibility is not determined by DNA alone. Age, body weight, kidney function, liver function, nutritional status, disease conditions, smoking, alcohol exposure and concurrent medicines can influence drug response. Enzyme activity may also change because of environmental factors or interactions with other medicines. Therefore, genetic information should be interpreted together with the patient's

Correspondence to: Ethan Williams, Department of Pharmacogenomics, University of California, San Francisco, USA, E-mail: ethan.williams@molpharm.us

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clinical characteristics. The effect of genetic variants can differ between populations. Allele frequencies are not identical across geographical and ancestral groups. A variant that is relatively frequent in one population may occur less frequently in another. This difference is important when developing genetic tests and interpreting pharmacogenetic findings. Broader representation of diverse populations can improve the usefulness of genetic information for different patient groups.

Genetic testing methods have developed considerably. Targeted genotyping can identify selected variants associated with specific medicines. DNA sequencing can examine multiple genes and detect a wider range of genetic changes. Bioinformatic tools can compare DNA sequences with reference databases and classify

variants according to available functional and clinical evidence. The interpretation of a genetic result requires attention to the particular medicine, allele combination and clinical recommendation. Genetic information can also contribute to medication safety by identifying people who may have an increased risk of toxicity. For some medicines, inherited differences in metabolism can cause unusually high drug exposure. For others, genetic changes may reduce activation and result in inadequate therapeutic activity. Identifying these differences can help clinicians consider dose modification, alternative medicines, or additional monitoring when supported by clinical guidance.