



Genetic Determinants of Individual Drug Response

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DESCRIPTION

Pharmacogenetic architecture describes the collection of genetic factors that influence how an individual responds to medicines. Drug response is rarely determined by a single genetic difference. Instead, multiple genes, genetic variants, regulatory regions and biological pathways can contribute to differences in drug absorption, distribution, metabolism, target interaction, therapeutic activity and adverse reactions. Understanding this genetic architecture provides a framework for explaining why the same medicine and dose can produce different outcomes among individuals.

Human Deoxyribonucleic Acid (DNA) contains millions of genetic variations. Some occur within protein-coding regions, while others are located in promoters, enhancers, introns, untranslated regions and other regulatory segments. These variations can alter protein structure, enzyme activity, gene expression, or cellular signaling. When the affected biological process participates in drug handling or drug action, the genetic difference may influence treatment response. Pharmacogenetic architecture can be viewed at several levels. The first level involves genes responsible for drug metabolism. Cytochrome P450 enzymes are particularly important because they process numerous medicines. *Cytochrome P450 2D6*, *CYP2C19*, *CYP2C9* and *CYP3A5* contain genetic variants that can change enzyme activity. Depending on the medicine, reduced activity may increase drug exposure, while increased activity may lower exposure or alter the conversion of a prodrug into its active form.

CYP2D6 provides a useful example of genetic complexity. Numerous variants occur within this gene and some individuals carry multiple functional copies. Consequently, *CYP2D6* activity can vary substantially among individuals. Medicines processed through this pathway may therefore show different concentration profiles in people with different genetic backgrounds. Clinical interpretation requires consideration of the specific medicine and validated prescribing recommendations. *CYP2C19* is another important component of pharmacogenetic architecture. Several genetic variants can

reduce or alter enzyme activity. This can influence the processing of medicines such as selected antiplatelet agents and acid-suppressing drugs. For some prodrugs, enzyme activity affects the amount of active compound generated. Genetic information can therefore contribute to treatment selection when appropriate clinical guidance is available.

Drug transporters form another component of this architecture. Transport proteins control movement of pharmaceutical compounds across cellular membranes. They participate in intestinal absorption, tissue distribution, hepatic uptake, biliary secretion and renal elimination. Genetic variants within transporter genes may change protein expression or activity and consequently alter the concentration of a medicine in blood or specific tissues. Drug targets also contribute to pharmacogenetic variation. Receptors, ion channels, enzymes and signaling proteins may contain sequence differences that modify their structure or function. If a medicine acts on one of these molecules, the genetic variant may influence the strength or duration of its effect. Differences in target expression can also affect therapeutic response even when the drug concentration remains similar.

Immune-related genes represent another important part of pharmacogenetic architecture. Human leukocyte antigen variants can influence susceptibility to certain immune-mediated drug reactions. Specific Human Leukocyte Antigen (HLA) alleles have been associated with serious adverse reactions to selected medicines. When clinical recommendations support genetic screening, identifying a relevant allele before treatment can help clinicians select safer therapeutic options. Genetic effects can also interact with one another. One variant may alter drug metabolism, while another influences drug transport or target sensitivity. The combined effects can be greater, smaller, or different from the effect of either variant alone. This means that medication response cannot always be explained by examining one gene independently.

Gene regulation adds another layer of complexity. Variants in regulatory DNA can change the amount of an enzyme, receptor, or transporter produced by a cell. Epigenetic factors can further

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Received: 01-Dec-2025, Manuscript No. JPP-25-32641; **Editor assigned:** 03-Dec-2025, PreQC No. JPP-25-32641 (PQ); **Reviewed:** 17-Dec-2025, QC No. JPP-25-32641; **Revised:** 24-Dec-2025, Manuscript No. JPP-25-32641 (R); **Published:** 31-Dec-2025, DOI: 10.35248/2153-0645.25.16.154

Citation: Pereira L (2025). Genetic Determinants of Individual Drug Response. J Pharmacogenom Pharmacoproteomics. 16:154.

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influence gene activity without changing the DNA sequence. Age, nutrition, inflammation, smoking, disease conditions and other environmental influences may also modify gene expression. Pharmacogenetic architecture therefore exists within a broader biological environment. Population differences are relevant when interpreting pharmacogenetic variants. Allele frequencies can differ between populations because of ancestry, demographic history and other evolutionary factors. A variant that is relatively common in one population may be uncommon in another. Genetic testing platforms and clinical guidelines should therefore account for population diversity to reduce the possibility of missing relevant variants.

Genomic technologies have expanded the ability to identify pharmacogenetic variation. Targeted genotyping can detect

selected variants, while DNA sequencing can examine multiple genes or larger genomic regions. Computational tools can classify variants according to their predicted or established effects. Clinical databases can connect genetic findings with medication recommendations, metabolic phenotypes and documented adverse reactions. Pharmacogenetic architecture is also relevant to drug development. Genetic information can help identify molecular factors associated with treatment response and toxicity. During medicine development, differences in genetic background can be considered when evaluating drug exposure and clinical outcomes. This can support the identification of patient groups that may require different doses or alternative treatments.