



Enzyme Polymorphisms: Genetic Variation Influencing Metabolism, Physiology and Drug Response

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DESCRIPTION

Enzyme polymorphisms are inherited differences in Deoxyribonucleic Acid (DNA) sequences that can alter the activity, quantity, stability, or function of enzymes. Enzymes are proteins that accelerate biochemical reactions throughout the body. They participate in nutrient metabolism, hormone production, DNA processing, cellular signaling, detoxification and drug metabolism. Genetic differences within enzyme-coding genes can therefore contribute to variation in physiological processes and medication responses among individuals.

A polymorphism may involve a single nucleotide, a small insertion or deletion, or a larger change in DNA structure. Some variants produce an enzyme with altered amino acid composition, while others affect how much enzyme is produced by a cell. Certain variants have little measurable biological effect, whereas others can substantially change enzymatic activity. The consequences depend on the location of the genetic alteration, the affected enzyme and the biological pathway in which the enzyme functions. Cytochrome P450 enzymes provide important examples of enzyme polymorphisms with pharmacological relevance. Members of this enzyme family participate in the metabolism of numerous medicines. Genes such as *Cytochrome P450 2D6*, *CYP2C19*, *CYP2C9* and *CYP3A5* contain multiple allelic forms. These variants can result in differences in metabolic capacity. A person with reduced enzyme activity may process a particular medicine more slowly, whereas another individual may metabolize it more rapidly.

CYP2D6 is one of the most genetically variable drug-metabolizing enzymes. Several alleles produce reduced or absent enzyme activity, while some genetic arrangements can result in increased activity. These differences may affect the concentration of medicines processed through *CYP2D6*. Depending on the drug, slower metabolism can increase exposure, while faster metabolism may reduce exposure or modify the activation of a prodrug. *CYP2C19* polymorphisms can influence the metabolism

of several pharmaceutical compounds. Individuals may carry alleles associated with normal, reduced, or increased enzyme activity. This variation can be clinically relevant for medicines that require *CYP2C19*-mediated activation or elimination. Genotype information can assist medication decisions when validated clinical recommendations are available.

CYP2C9 also contains important functional variants. This enzyme participates in the metabolism of several medicines, including selected anticoagulant and anti-inflammatory agents. Reduced enzyme activity can increase the amount of some drugs remaining in circulation. Clinical factors such as age, liver function, diet, concurrent medicines and disease status can further influence the final response. Enzyme polymorphisms are not restricted to drug-metabolizing proteins. Genetic variation can affect enzymes involved in hormone synthesis, neurotransmitter metabolism, lipid processing, carbohydrate utilization and immune signaling. Differences in these enzymes may contribute to variation in disease susceptibility or physiological characteristics. For example, alterations in enzymes involved in lipid metabolism can influence circulating lipid concentrations and cardiovascular risk.

Enzyme activity can also be affected by variants located outside the protein-coding portion of a gene. Regulatory DNA sequences influence gene transcription and can determine how much enzyme is produced. A variant within such a region may increase or decrease gene expression without changing the amino acid sequence of the enzyme. Differences in messenger Ribonucleic Acid (RNA) processing can also affect the final amount of functional protein. Some polymorphisms influence enzyme stability. A genetic substitution may alter the three-dimensional structure of an enzyme, causing it to degrade more quickly or remain stable for a longer period. Changes in protein stability can affect the amount of functional enzyme available inside cells. This can influence the rate of biochemical reactions and may alter the concentration of downstream metabolites.

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Environmental factors can modify the effects of enzyme polymorphisms. Diet, smoking, alcohol exposure, inflammation, age, hormonal status and other medicines can change enzyme expression or activity. For example, one medicine may inhibit an enzyme, while another substance may increase its expression. Consequently, genotype alone cannot always predict the exact metabolic response of an individual. Pharmacogenetic testing can identify selected enzyme variants before or during treatment. Targeted genotyping methods examine specific DNA positions associated with known functional effects. DNA sequencing can provide information about multiple variants within one or more genes. Laboratory findings can then be translated into predicted metabolic categories when appropriate clinical guidelines and evidence are available.

Population diversity is important when interpreting enzyme polymorphisms. Allele frequencies vary among populations,

meaning that a genetic variant may be common in one group and uncommon in another. Genetic testing resources should account for this diversity to improve the identification of relevant variants across different populations. Clinical interpretation should also consider the population in which supporting evidence was obtained. Enzyme polymorphisms have particular importance in precision pharmacotherapy. Knowledge of an individual's metabolic genotype may assist with selecting medicines or doses for specific therapies. However, medication response also depends on kidney function, liver function, age, body composition, disease conditions, drug interactions, adherence and other factors. Genetic information is therefore most useful when integrated with clinical assessment.