

Research Article

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The Impact of Drug Metabolism Enzyme Gene Polymorphism on Drug Response

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Abstract The genetic polymorphism of drug metabolism enzymes is a highly concerned research direction in the field of drug therapy, and has made significant progress in medicine and clinical practice. The polymorphism of drug metabolism enzyme genes has broad clinical importance for drug response, and its research goal is to understand how patient genotype information shapes their response to specific drugs, so that doctors can better formulate personalized treatment plans. This not only helps to improve the safety and success rate of patients' treatment, but also provides important clues for the development of new drugs to create safer and more effective treatment methods, further promoting the development of the medical field. This study provides an in-depth understanding of how genetic polymorphisms affect individuals' metabolic rate of drugs and the individualization of drug therapy. It explores the close relationship between phenotypic polymorphisms and drug response, and combines specific case studies of drug therapy to provide new insights into improving medical outcomes.

Keywords Drug metabolizing enzymes; Genetic polymorphism; Drug response; Personalized medicine; Case study

In modern medicine, personalized therapy has gradually become a highly focused area of research. Individualization of drug therapy refers to tailoring the most suitable treatment plan for patients based on their genotype and phenotype characteristics. The polymorphism of drug-metabolizing enzyme genes, as a crucial aspect of individual differences, has drawn considerable attention from researchers and clinicians. Drug-metabolizing enzyme gene polymorphism refers to the occurrence of different genotypes among individuals, and these distinct genotypes can influence the expression and activity of drug-metabolizing enzymes. Drug-metabolizing enzymes are proteins that mediate the metabolism and degradation of drugs in the body, including the cytochrome P450 (CYP) family, uridine diphosphate-glucuronosyltransferase (UGT) family, and N-acetyltransferase (NAT) family, among others. The function of these metabolic enzymes is to convert drugs into active metabolites or inactive metabolites, thereby affecting the efficacy and toxicity of drugs (Xu et al., 2018).

Differences in drug-metabolizing enzyme genotypes among individuals can result in significant variations in drug effects. Some individuals may metabolize a certain drug more rapidly due to their genotype, requiring higher doses to achieve therapeutic effects. On the other hand, other individuals may metabolize the same drug more slowly due to their genotype, leading to drug accumulation and adverse reactions. Therefore, understanding an individual's drug-metabolizing enzyme genotype is of crucial importance. Doctors can select appropriate drugs and adjust dosages based on the patient's genetic characteristics to ensure the safety and effectiveness of treatment. This personalized approach can maximize the success rate of drug therapy while minimizing unnecessary risks and adverse reactions (Dev et al., 2019).

The importance of studying drug-metabolizing enzyme gene polymorphism lies in its ability to provide clinicians with powerful tools to better predict patients' responses to specific drugs. This aids in reducing unnecessary adverse drug reactions, enhancing treatment success rates, and saving healthcare resources. Additionally, understanding drug-metabolizing enzyme gene polymorphism provides crucial insights for the development and design of drugs, enabling the creation of safer and more effective medications. By optimizing the structure and

metabolic pathways of drugs, researchers can lower the potential for adverse reactions, improve therapeutic outcomes, and thereby create more competitive drugs. This not only contributes to enhancing the patient's treatment experience but also drives progress in the field of medicine.

This study aims to investigate how drug-metabolizing enzyme gene polymorphism affects drug responses and explore its potential applications in personalized medicine. By presenting some clinical case studies demonstrating the impact of genetic polymorphism on actual treatments, we hope to contribute to the advancement of the medical field, ultimately providing patients with safer and more effective treatment options.

1 Drug-Metabolizing Enzyme Gene Polymorphism

1.1 Role of drug-metabolizing enzymes

Drug-metabolizing enzymes constitute a specific class of proteins that play a crucial role in the human body. Their primary function is to convert exogenous compounds, particularly drugs, into metabolites that are more easily excreted. This intricate biochemical process occurs in various organs, including the liver, small intestine, kidneys, and lungs. Drug-metabolizing enzymes have a direct impact on the efficacy, toxicity, and duration of drugs within the body (Pe et al., 2020). Due to genetic and phenotypic differences among individuals, the activity and efficiency of drug-metabolizing enzymes may vary. These individual variances are one of the reasons why people may respond differently to the same drug. Therefore, understanding the function of drug-metabolizing enzymes and individual differences is crucial for the rational use of drugs, minimizing adverse reactions, and formulating personalized treatment plans.

Drug-metabolizing enzymes initially break down drugs into simpler molecules, typically metabolites, through a series of biochemical reactions. This helps to reduce the concentration of drugs in the body and maintain the duration of drugs within the effective range of treatment. Drug-metabolizing enzymes also have the ability to convert certain drugs into their active forms, contributing to therapeutic effects. This implies that some drugs may not possess inherent activity but need to be metabolized into active metabolites within the body to exert therapeutic efficacy.

On the other hand, drug-metabolizing enzymes also have the capability to convert drugs or their metabolites into harmless or low-toxicity substances, reducing their harmful impact on the body. This contributes to lowering the overall toxicity of drugs. Enzymes not only break down drugs but also further metabolize the resulting products in preparation for excretion. This is a crucial step in ensuring that metabolites do not accumulate in the body, preventing potential toxicity. Drug-metabolizing enzymes also play a significant role in drug interactions. Some drugs can influence the activity of these enzymes, subsequently affecting the metabolic rate of other drugs and potentially leading to drug interactions.

1.2 Definition of genetic polymorphism

Genetic polymorphism, as a crucial concept in the field of genetics, describes the phenomenon of having multiple different alleles at a specific gene locus within human or other biological populations. These diverse alleles represent variants of DNA sequences at a particular gene locus, and they can result in genetic variations among individuals. Genetic polymorphism is a significant manifestation of biological diversity, playing a critical role in natural selection and evolution.

The key feature of genetic polymorphism lies in the fact that a specific gene locus can possess two or more different alleles. This implies that distinct individuals may have different genetic sequences at the same gene locus. This genetic variation is often caused by single nucleotide polymorphisms (SNPs) or other genetic alterations at the gene locus. These diverse alleles can be passed down to offspring through genetic inheritance, thereby maintaining and increasing the genetic diversity within populations (Li et al., 2021).

Genetic polymorphism is not exclusive to humans but is widespread among various biological species. The frequency of different alleles may vary across different populations, suggesting that a particular allele might be

more prevalent in one population while being relatively rare in another. These variations can be attributed to factors such as geography, environment, and the genetic evolution of populations.

In the fields of medicine and biology, the study of genetic polymorphism is crucial for understanding genetic variations among individuals, susceptibility to diseases, drug metabolism, drug response, and other physiological characteristics. For instance, certain genetic polymorphisms may be associated with the risk of specific diseases, or they may influence an individual's metabolism rate and efficacy of certain drugs. Understanding these genetic variations can assist healthcare professionals in devising personalized treatment plans, maximizing treatment effectiveness, and reducing adverse reactions.

1.3 Types of genetic polymorphism in metabolic enzymes

Genetic polymorphism in metabolic enzymes typically involves multiple gene families, with the most critical and extensively studied being the Cytochrome P450 (CYP) family (Figure 1). In addition to the CYP family, there are other enzyme families and associated genetic polymorphisms.

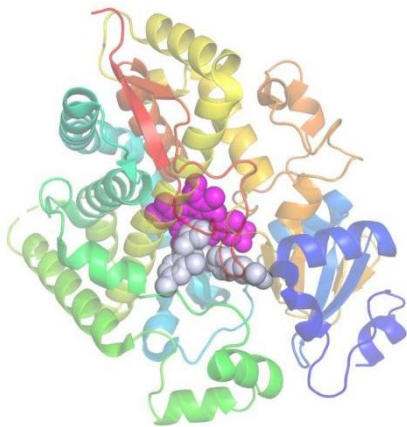


Figure 1 Cytochrome P450 metabolic enzyme

CYP enzymes are a widely distributed group of enzymes in the liver that participate in the metabolism of numerous drugs. The CYP gene family includes CYP1A1, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and others. Genetic polymorphism is highly prevalent in the CYP family, where different alleles can result in variations in drug metabolism rates, thereby influencing individual responses to medications.

The UGT family comprises multiple genes, such as *UGT1A1*, *UGT1A6*, *UGT2B7*, and others. These genes encode enzymes involved in the glucuronidation metabolism of drugs. Among them, *UGT1A1* is associated with medications crucial for conditions like bronze gallstones, cataracts, and drug metabolism, including drugs such as isoniazid.

The NAT family includes genes such as *NAT1* and *NAT2*. These genes encode enzymes involved in the N-acetylation metabolism of various drugs, such as the antituberculosis drug isoniazid. Genetic polymorphisms impact the activity of these enzymes, thereby influencing individual variations in drug metabolism and drug response. The diverse types of genetic polymorphisms in these metabolism enzyme genes cover various drug metabolic pathways, affecting the rate of drug metabolism and individual responses to drugs. Understanding these genetic polymorphisms is crucial for developing personalized treatment plans and predicting individual responses to medications.

The *Catechol-O-Methyltransferase (COMT)* gene encodes an enzyme involved in the breakdown of neurotransmitters such as dopamine. The polymorphism of the *COMT* gene is associated with the rate of dopamine degradation, making it crucial in certain mental disorders and drug treatments (Gao et al., 2023).

The Glutathione-S-Transferase (GST) family includes several genes such as *GSTM1*, *GSTT1*, and *GSTP1*. These genes encode enzymes involved in antioxidant defense and detoxification metabolism, influencing the metabolism

and excretion of toxic substances in the body. *GST* gene polymorphisms are associated with the exposure and metabolism of certain environmental toxins and drugs.

In addition to the aforementioned families, there are other metabolic enzymes and related genes such as acyl-CoA oxidase, alcohol dehydrogenase, renal transport proteins, etc. These also exhibit genetic polymorphisms that can influence drug metabolism and an individual's response to medications.

2 Genetic Polymorphism and Its Association with Drug Metabolism

2.1 Relationship between genotype and drug metabolism capacity

There is a close association between genotype and drug metabolism capacity, as an individual's genetic makeup can influence the activity and efficacy of their drug-metabolizing enzymes. This relationship is crucial for understanding individual responses to medications, formulating personalized treatment plans, and predicting the rate of drug metabolism.

Each individual's genome contains genes encoding drug-metabolizing enzymes. Variations in genotype among different individuals result in distinct alleles. These diverse alleles can influence the expression and activity of drug-metabolizing enzymes. Variations in alleles may lead to differences in the activity of drug-metabolizing enzymes (Figure 2). Some alleles may result in high enzyme activity, leading to faster drug metabolism, while others may lead to low enzyme activity, resulting in slower drug metabolism.

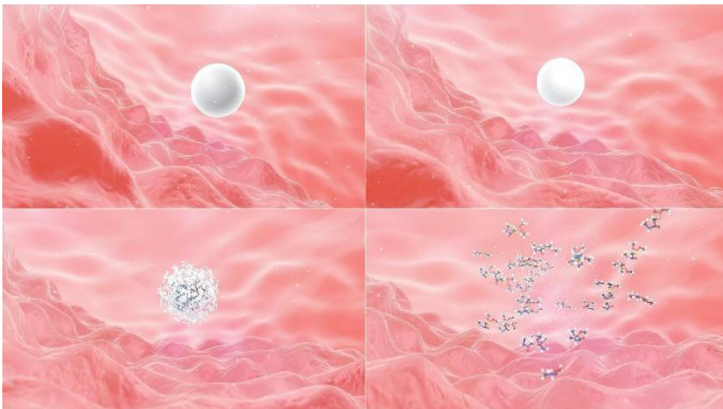


Figure 2 Drug decomposition

Individuals can be stratified into rapid metabolizers and slow metabolizers based on their genotypes. Rapid metabolizers typically carry highly active alleles, resulting in faster drug metabolism and clearance. In contrast, slow metabolizers usually possess low-activity alleles, leading to slower drug metabolism and higher drug concentrations in the body. Genotype directly influences an individual's metabolism rate for a specific drug. Rapid metabolizers may require higher drug doses to achieve therapeutic effects, while slow metabolizers may need lower doses. This stratification is crucial for developing personalized treatment plans.

Variations in drug metabolism capacity may result in diverse responses to the same drug among individuals, affecting both therapeutic efficacy and toxicity reactions. Rapid metabolizers may achieve therapeutic effects more easily but are also more susceptible to drug toxicity. Conversely, slow metabolizers exhibit the opposite pattern. Genotype can also influence an individual's susceptibility to drug interactions. Certain drugs may alter the activity of metabolic enzymes, subsequently modifying the metabolism rates of other drugs, leading to potential drug interactions (Cagin et al., 2022).

2.2 Relationship between phenotypic polymorphism and drug response

There is a close relationship between phenotypic polymorphism and drug response, as individual polymorphism variability can directly influence their responses to drugs. Phenotypic polymorphism refers to the differences among individuals in a population concerning specific traits or characteristics. These differences may encompass physiological features, metabolic capabilities, biochemical parameters, as well as susceptibility to diseases.

Phenotypic polymorphism is particularly crucial in the context of drug metabolism. The metabolic capabilities of different individuals can vary significantly, leading to differences in the rate at which drugs are metabolized in the body. This variability can influence the efficacy and toxicity of drugs, as excessively rapid or slow metabolism may alter drug concentrations and clearance rates. Phenotypic polymorphism is also associated with an individual's sensitivity to drugs. Some individuals may be more sensitive to a particular drug, requiring lower doses to achieve therapeutic effects, while others may be less responsive and need higher doses (Vyhlidalova et al., 2019).

Phenotypic polymorphism among individuals can lead to varied drug effects and adverse reactions. Some individuals may exhibit favorable therapeutic responses to drugs, while others may experience adverse reactions, potentially attributed to their physiological characteristics and metabolic capabilities. Phenotypic polymorphism also plays a role in disease susceptibility. Certain phenotypic traits may render individuals more prone to specific diseases, thereby influencing their treatment needs and responses.

2.3 Clinical significance and individual differences

There is a close connection between clinical significance and individual differences, as individual variations directly impact diagnosis, treatment, and health management in medical and clinical practices. The concept of personalized medicine has progressively become a cornerstone in modern medicine to better address the health needs of diverse individuals, enhance medical efficacy, and reduce adverse reactions.

Individual differences underscore the shift towards personalized treatment in the field of medicine. Each patient is unique, with variations in their genotype, physiological traits, metabolic capabilities, and disease risks. Therefore, devising personalized treatment plans is crucial to ensuring that patients achieve optimal therapeutic outcomes.

Individual differences play a crucial role in drug therapy. The metabolism rate and response to the same drug may vary among different individuals. Therefore, understanding an individual's drug metabolism capacity and sensitivity is paramount in determining the correct dosage and type of medication, aiming to maximize treatment efficacy and minimize adverse reactions. Individual differences also impact susceptibility to specific diseases. Some individuals may be more prone to certain diseases due to genetic, lifestyle, or environmental factors, necessitating personalized risk assessment and preventive measures.

Understanding individual differences can aid in early disease diagnosis and screening. For instance, based on individual genetic risk factors, early cancer screenings or disease risk assessments can be conducted to detect and intervene in potential health issues sooner. Clinicians can utilize information about individual differences to monitor a patient's response to treatment. This helps determine treatment effectiveness, the need for adjustments, and assists in devising more suitable treatment plans. Understanding individual differences contributes to better health management. This includes tailoring appropriate prevention and health maintenance plans for individuals based on their genetic traits and lifestyle factors, aiming to reduce potential health risks.

3 Clinical Case Study

3.1 *CYP2D6* gene polymorphism and antidepressant response

There exists a close relationship between *CYP2D6* gene polymorphism and the response to antidepressant drugs. *CYP2D6* is a cytochrome P450 enzyme responsible for metabolizing a variety of antidepressant medications (Figure 3). The polymorphism of this gene results in varying abilities of different individuals to metabolize drugs, thereby influencing the concentration and efficacy of the drugs within the body.

Individuals with different *CYP2D6* genotypes are categorized into different metabolic types, including rapid metabolizers, intermediate metabolizers, and poor metabolizers. Rapid metabolizers typically possess highly active *CYP2D6* alleles, resulting in faster drug metabolism. Conversely, poor metabolizers usually have low-activity alleles, leading to slower drug metabolism. These differences have a significant impact on the response to antidepressant medications (Ping et al., 2022).

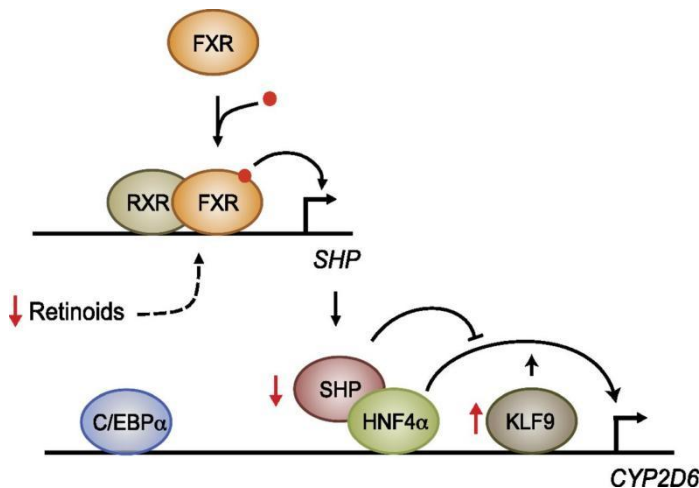


Figure 3 Transcriptional regulation of CYP2D6 expression

For rapid metabolizers, higher doses of antidepressant medications may be necessary to achieve efficacy because the drugs are rapidly metabolized in their bodies. In contrast, slow metabolizers may require lower drug doses to avoid potential drug toxicity. Therefore, understanding the patient's CYP2D6 genotype can assist doctors in better selecting appropriate antidepressant medications and determining the right dosage.

Furthermore, CYP2D6 gene polymorphism can also impact the adverse reactions of drugs. Rapid metabolizers may be more prone to experiencing adverse drug reactions due to higher drug concentrations in their bodies. In contrast, slow metabolizers may encounter fewer adverse reactions during drug therapy.

3.2 CYP2C9 and VKORC1 gene polymorphisms and their impact on warfarin therapy

CYP2C9 and VKORC1 gene polymorphisms have profound implications for warfarin treatment. These two genes play crucial roles in the metabolism and mechanism of action of warfarin (Figure 4). The genetic makeup of individual patients determines their rate of warfarin metabolism and sensitivity to the drug, directly influencing the therapeutic efficacy and safety of warfarin.

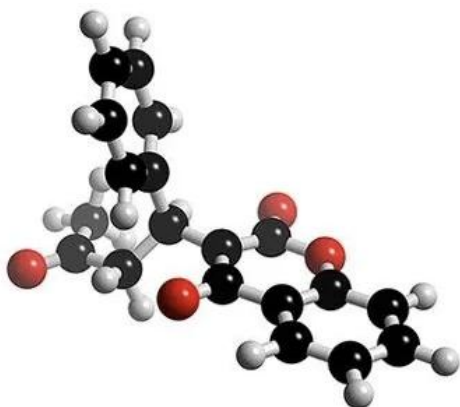


Figure 4 Warfarin molecule

CYP2C9 is a cytochrome P450 enzyme involved in the metabolism of warfarin. The CYP2C9 gene exhibits polymorphism, where different alleles encode varying enzyme activities. Individuals with alleles associated with lower CYP2C9 activity typically metabolize warfarin more slowly, requiring lower drug doses to achieve anticoagulation effects. Conversely, individuals with alleles linked to higher CYP2C9 activity usually require higher warfarin doses.

VKORC1 is the subunit 1 of the vitamin K epoxide reductase complex, serving as the target for warfarin action. VKORC1 gene polymorphism affects the sensitivity of warfarin towards VKORC1. Individuals with a sensitive

VKORC1 genotype typically require lower doses of warfarin to achieve therapeutic effects due to their heightened sensitivity to the anticoagulant effects of warfarin.

Understanding the CYP2C9 and VKORC1 genotypes of patients assists doctors in individualizing the dosage of warfarin. This ensures that patients maintain a stable anticoagulant state during treatment, reducing the risk of unnecessary bleeding or clotting events. Additionally, personalized dosage adjustments can enhance the effectiveness of warfarin therapy, ensuring patients achieve optimal treatment outcomes.

3.3 Relationship between *NAT2* gene polymorphism and isoniazid metabolism

There is a close association between *NAT2* gene polymorphism and the metabolism of isoniazid. *NAT2* is an enzyme involved in drug metabolism, playing a crucial role in the metabolism of isoniazid. The polymorphism in this gene results in variations among individuals in the metabolism rate and efficiency of isoniazid, directly influencing the efficacy and safety of the drug.

The *NAT2* gene comprises multiple alleles, and these alleles encode different levels of *NAT2* enzyme activity. Based on their *NAT2* genotype, individuals can be categorized into different metabolizer types, including rapid metabolizers, intermediate metabolizers, and slow metabolizers. These metabolizer types have a direct impact on the effectiveness of isoniazid therapy.

Individuals with highly active *NAT2* alleles typically fall into the category of rapid metabolizers. They can metabolize isoniazid more quickly, meaning that isoniazid is metabolized rapidly in their bodies. As a result, they usually require higher drug doses to maintain therapeutic effectiveness. Intermediate metabolizers have *NAT2* genotypes that lie between those of rapid and slow metabolizers. Their isoniazid metabolism rate is moderate, usually requiring moderate drug doses. Slow metabolizers typically carry low-activity *NAT2* alleles, resulting in a slower metabolism of isoniazid. This implies that they may experience stronger therapeutic effects with the same dose of isoniazid but also increases the risk of adverse reactions (Xu et al., 2022).

NAT2 gene polymorphism plays a significant role in the metabolism of isoniazid. The genotype of individual patients determines their metabolism rate of isoniazid, directly influencing the therapeutic effectiveness and safety of the drug. This underscores the importance of personalized medicine in drug treatment to meet the unique needs of different patients.

4 Summary and Outlook

Research on genetic polymorphism in drug-metabolizing enzymes has had profound implications in medicine and clinical practice, emphasizing its crucial role in personalized healthcare. The impact of genetic polymorphism in drug-metabolizing enzyme genes on drug metabolism rate and effects cannot be ignored. Individuals with different genotypes may require varying drug doses to achieve therapeutic effects, a phenomenon particularly notable in the treatment of drugs like warfarin. Understanding a patient's genotype can assist healthcare professionals in optimizing drug dosage, ensuring both the effectiveness and safety of the treatment.

Genetic polymorphism in drug-metabolizing enzyme genes directly influences the safety and occurrence of adverse reactions to medications. An individual's genotype can determine whether they are more prone to experiencing toxic reactions to drugs. Therefore, personalized dosage adjustments not only contribute to improving treatment efficacy but also help mitigate the risk of adverse reactions, providing patients with safer healthcare. Additionally, understanding drug-metabolizing enzyme gene polymorphism aids doctors in selecting medications that are better suited for individual patients. Based on a patient's genotype, physicians can opt for drugs unrelated to specific metabolic enzymes, ensuring treatment consistency. This offers patients better therapeutic options while reducing unnecessary trials and errors (Zhang and Cai, 2018).

Personalized medicine is currently entering an exciting era. With the continuous advancements in genetic sequencing technology, doctors will be able to understand patients' genotypes more accurately, leading to improved personalized treatment plans. This will make personalized medicine more routine, with widespread genetic testing and applications becoming a reality. As the cost decreases and technology improves, genetic

sequencing will be more widely applied in clinical practice, contributing to better-tailored treatment plans. Individualized drug therapy will become a more standard practice, allowing physicians to select and adjust drug dosages more effectively to meet the specific needs of patients and enhance treatment outcomes.

The prospects of research on drug metabolizing enzyme gene polymorphism are vast, offering new avenues for improved healthcare and more effective treatments. Future studies and clinical practices will continue to delve into the complex mechanisms of drug metabolizing enzyme gene polymorphism, providing further opportunities for personalized medicine. However, it is essential to ensure the feasibility and sustainability of personalized healthcare simultaneously.

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