JOURNAL OF TROPICAL PHARMACY AND CHEMISTRY
https://jtpc.ff.unmul.ac.id

Volume 10.2

Review Article

CYP450 Gene Variations and Their Implications for Drug Response: A Pharmacogenomic Review

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Abstract

The Human Genome Project (HGP) has significantly advanced our understanding of how human genetic variation affects drug response, particularly through metabolic enzymes such as Cytochrome P450 (CYP450). This study aimed to explore the impact of genetic variation on drug metabolism and its consequences for precision medicine therapies. This approach involved a literature review of various scientific articles discussing pharmacogenomics, CYP450 enzymes, and their clinical applications. The findings indicate that CYP450 enzymes are crucial in drug metabolism, especially during phase I reactions, such as oxidation, and their activity is heavily influenced by genetic polymorphisms, including those in CYP2C19. These genetic differences lead to variations in the ability of individuals to activate or eliminate drugs, thereby affecting the effectiveness of therapy and the likelihood of side effects. In addition to genetic factors, drug interactions, environmental influences, and the microbiome also play a role in drug response. For instance, genetic variation in the use of clopidogrel can result in therapeutic failure or a heightened risk of clinical events. Ultimately, integrating genomic data from the HGP with CYP450 enzyme profiles provides a vital basis for implementing precision medicine, allowing for more accurate drug and dosage selection, thereby enhancing therapeutic effectiveness and reducing the risk of side effects in patients.

Keywords: cytochrome P450; genetic variation; pharmacogenomic; phenoconversion; precision medicine

Accepted: 5 June 2026
Approved: 25 July 2026
Publication: 31 July 2026

Citation : I. F. Sakinah, K. Tosuli, A. Azzura, A. E. F. Siahaan, Sabrina, N. Febriani, M. B. O. Purek, K. Aileen, S. S. Billa, T. F. Puteri, and J. F. Suparningtyas, "CYP50 Gene Variations and Their Implications for Drug Response: A Pharmacogenomic Review", Journal of Tropical Pharmacy and Chemistry, vol. 10, no. 2, pp. 73–79, Jul. 2026, doi: 10.30872/jtpc.v10i2.434

Doi: 10.30872/jtpc.v10i2.434

1 Introduction

Advances in modern biomedicine have highlighted the growing importance of personalized treatment, known as precision medicine. This approach customizes drug administration based on the genetic traits, metabolism, and physiological responses of each patient. Genetic differences can influence how drugs are absorbed, distributed, metabolized, and eliminated, affecting their effectiveness and the risk of side effects [1]. In clinical settings, this presents a challenge because standard drug doses may not be suitable for every patient. Thus, understanding the genetic factors is crucial for enhancing the safety and success of therapy. The Human Genome Project (HGP), an international research initiative that started in 1990 and was completed in 2003, aimed to map the entire human genome by identifying genes and their variations. The success of this project laid the groundwork for understanding the links between genes, diseases, and drug responses, paving the way for precision medicine.

Genomic data from the HGP helps identify genetic polymorphisms affecting drug metabolism, predict patient responses to therapies, and develop pharmacogenomic databases for tailoring drug therapy to individual genetic profiles [1], [2]. One application of HGP data is studying the Cytochrome P450 (CYP450) enzyme, crucial for drug metabolism in the liver. This enzyme handles drug oxidation, reduction, and hydrolysis, influencing active drug levels in the body. Genetic variations found through the HGP allow categorization of patients by their drug metabolism capacity, such as poor, intermediate, extensive, and ultra-rapid metabolizers. Key genes like CYP2D6, CYP2C9, CYP2C19, CYP2B6, CYP3A4 and CYP3A5 are often studied for their role in metabolizing drugs like analgesics, antidepressants, and chemotherapy agents [3], [4], [5].

This knowledge helps healthcare providers to adjust drug dosages for safer and more effective treatment. In addition to affecting pharmacokinetics, genetic variations in CYP450 identified through the HGP also impact pharmacodynamics or how drugs work in the body. Genetic polymorphisms can change drug interactions with receptors, target enzymes, or cellular pathways, leading to different therapeutic responses even with the same dose [6]. For instance, rapid metabolism might reduce drug effectiveness, while slow metabolism could raise toxicity risk. Therefore, combining HGP genomic data and CYP450 profiles is a key strategy for predicting drug responses, minimizing side effects, and supporting safer, more effective precision medicine [2], [5].

The significant progress in elucidating genetic influences on drug metabolism through the Human Genome Project (HGP) and Cytochrome P450 (CYP450) enzyme polymorphisms has advanced precision medicine considerably. However, a critical gap persists in translating these molecular and genomic insights into standardized, evidence-based clinical protocols for personalized drug dosing. Addressing this gap requires bridging the foundational genomic knowledge with the development of practical guidelines, decision-support tools, and validation studies that enable clinicians to tailor drug therapies effectively in heterogeneous real-world clinical settings.

2 Method

2.1 Study Design

This study employs a narrative review design to systematically synthesize and critically analyze existing literature regarding CYP450 genetic variations and their influence on drug responses. This design allows for a structured qualitative integration of diverse research findings without statistical aggregation.

2.2 Literature Research Strategy

A comprehensive literature search was conducted using PubMed, Scopus, and Web of Science to improve literature coverage and reduce database-related selection bias. The search strategy combined controlled vocabulary and free-text terms with Boolean operators: (("CYP450" OR "Cytochrome P450" OR CYP2C19 OR CYP2D6 OR CYP2C9 OR CYP3A4 OR CYP3A5) AND (pharmacogenomic* OR pharmacogenetic*) AND ("drug response" OR "drug metabolism" OR "therapeutic outcome") AND ("genetic variation" OR polymorphism OR SNP)). The search was limited to peer-reviewed articles

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published between 2015 and 2025 in English, with emphasis on clinically relevant human studies and full-text availability whenever possible.

2.3 Eligibility Criteria

Studies were selected based on explicit inclusion and exclusion criteria to ensure the review's clinical relevance and focus.

- Inclusion Criteria:
  1. Review articles or literature reviews published between 2015 and 2025.
  2. Selected original clinical or epidemiological studies (e.g., cohort, case-control, cross-sectional, or clinical trials) up to a maximum of 1–2 articles, provided they contain comprehensive introduction and discussion sections explaining underlying mechanisms in non-technical laboratory language.
  3. Studies focusing on CYP450 genetic variations and their specific effects on drug responses.
  4. Studies providing specific drug examples (e.g., warfarin, clopidogrel).
  5. Publications in peer-reviewed scientific journals specializing in pharmacy, genetics, or clinical medicine.
  6. Availability of a full abstract, with full-text availability highly preferred.

- Exclusion Criteria
  1. Articles solely discussing general drug pharmacology without addressing genetics.
  2. Studies discussing gene variations for genetic diseases unrelated to pharmacogenomics or drug response.
  3. Overly technical papers containing raw Genome-Wide Association Studies (GWAS) data without clinical interpretation.
  4. Publications dated prior to 2015.
  5. Absence of an abstract or studies published only as conference abstracts.
  6. Pharmacogenomic topics focused on animal or veterinary models without direct human relevance.
  7. Purely laboratory-based original studies (e.g., PCR, Western blot, gene sequencing, CRISPR) lacking clinical context or dominated by unexplained technical data tables/graphs.

2.4 Synthesis Approach

The study selection followed a structured multi-step screening process. After removal of duplicates, titles and abstracts were screened for relevance to CYP450 variation, pharmacogenomics, and clinically meaningful drug-response outcomes. Potentially eligible records then underwent full-text assessment against the predefined inclusion and exclusion criteria. To strengthen scientific rigor, original studies were prioritized over secondary narrative sources when similar clinical topics were available. In addition, each included article was critically appraised for methodological clarity, relevance of the study population, outcome validity, and risk of interpretive bias before thematic synthesis.

2.5 Data Extraction and Synthesis Approach

A standardized data extraction protocol was implemented to capture author details, publication year, study design, population characteristics, specific CYP450 genes or variants investigated, implicated drugs, clinical outcomes, and the direction of pharmacogenomic effect. The findings were synthesized narratively into clinically oriented themes, with explicit attention to convergent findings, conflicting evidence, methodological limitations, and the translational implications for pharmacy practice.

3 Result and Discussion

After broadening the search strategy and databases, a larger body of literature was identified and screened to improve representativeness. Studies were then grouped according to design and clinical contribution, with greater emphasis placed on primary human studies and clinically interpretable pharmacogenomic evidence. The final synthesis therefore included both foundational review papers and

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original studies that directly informed CYP450-related variability in therapeutic response, adverse events, phenoconversion, and implementation challenges in precision medicine. The extracted findings were critically compared and summarized in Table 1.

Table 1 Summary of Main Findings and Pharmacy Relevancies of Included Studies

No	Study	Main Findings	Pharmacy Relevancies
1	**Zhao et. al. (2021)** [7]	CYP450 enzymes play a critical role in drug metabolism in humans; CYP450 enzymes are involved in phase I reactions such as oxidation; These enzymes influence drug elimination and bioavailability; There is variation in enzyme activity between individuals; This variation is influenced by genetic and environmental factors.	In the pharmaceutical field, understanding CYP450 enzymes helps in determining drug dosages, preventing interactions, and improving therapeutic safety.
2	**Hassan et. al. (2021)** [8]	Drug response is dually controlled by host genetics and gut microbiota; Gut microbes can alter the chemical structure of drugs (activation/toxicity); Genetic variation leads to differences in the expression of metabolic enzymes between individuals; Integration of genomic and microbiome data is key to personalized medicine.	Supporting the transition to precision medicine through understanding genetic variation and drug biotransformation by the microbiome to optimize therapeutic efficacy.
3	**Deodhar et.al. (2020)** [9]	CYP450 enzymes are the primary pathway for the metabolism of the majority of clinical drugs; The mechanism of MBI causes irreversible (permanent) enzyme inhibition; Polypharmacy increases the risk of drug-drug interactions (DDIs) via the CYP450 pathway; Enzyme inhibition triggers adverse drug events.	To provide a scientific basis for mitigating the risk of drug-drug interactions (DDIs) and preventing toxicity due to irreversible inhibition of metabolic enzymes.
4	**Oates & Lopez (2018)** [10]	Genetic factors contribute up to 95% to differences in the body's response to drugs; Cytochrome P450 (CYP450) enzymes play a crucial role in drug metabolism and elimination; Genetic variations, such as SNPs, can alter drug pharmacokinetics and pharmacodynamics, for example in the use of Warfarin, Clopidogrel, and Carbamazepine; The FDA has included pharmacogenomic information on the labels of more	It is crucial to assist pharmacists and healthcare professionals in determining safe and effective therapy, preventing serious side effects, and adjusting dosages based on the patient's genetic condition.

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No	Study	Main Findings	Pharmacy Relevancies
		than 100 drugs to ensure safe use; The application of pharmacogenetics aims to select the right drug, the right dose, and minimize side effects.	
5	**Brown & Pereira (2018)** [11]	The genetic variation in the CYP2C19 enzyme is important for the liver's two-step process that changes the prodrug clopidogrel into its active form; There are two groups of variants from CYP2C19 polymorphisms: Loss-of-Function (LOF) and Gain-of-Function (GOF); CYP2C19*2 and CYP2C19*3 lower the concentration of the drug's active form in the blood, reduce platelet inhibition, and raise the risk of adverse cardiovascular events like stent thrombosis; CYP2C19*17 is a gain-of-function variant that boosts the enzyme's activity, increasing clopidogrel bioactivation and has been linked to a higher bleeding risk in some studies; There are variability by Ethnicity	Understanding CYP2C19 pharmacogenomics enables pharmacists to optimize antiplatelet efficacy and patient safety by applying clinical guidelines to select alternative therapies, mitigating high-risk drug interactions with proton pump inhibitors, and managing compounding clinical variables like adherence and comorbidities.

3.1 Human Genome Project & Its Scientific Legacy

The Human Genome Project (HGP), conducted from 1990 to 2003, established the modern genomic framework that enabled systematic identification of human genetic variation, including polymorphisms relevant to drug metabolism. Beyond mapping genes, the HGP shifted biomedical research toward large-scale data integration and laid the foundation for precision medicine by linking genomic variability with disease susceptibility and treatment response. Although early clinical translation progressed gradually, the HGP remains a pivotal scientific platform for contemporary pharmacogenomics and individualized therapy.

3.2 Pharmacogenomics Basics: SNPs & Gene Variations

SNP (Single Nucleotide Polymorphism) is a change in a single nucleotide base in DNA that occurs among individuals and serves as a marker of genetic variation. This variation can be used to understand genetic differences that influence drug response. SNPs are a form of genetic polymorphism in genes, including genes that encode metabolic enzymes such as CYP450, and thus can affect enzyme activity, drug metabolism processes, and increase or decrease the risk of side effects or therapeutic failure [8]. Genetic variations in cytochrome P450 enzymes such as CYP2D6, CYP2C9, and CYP2C19 cause differences in the body's ability to metabolize drugs, resulting in varied therapeutic responses. These genetic variations can cause enzyme activity to become slower, so that drugs are processed more slowly in the body and their concentrations increase, raising the risk of side effects. Conversely, genetic variations can also increase enzyme activity, causing drugs to be metabolized more quickly and their concentrations to decrease, which may lead to suboptimal therapeutic effects. Based on the rate of metabolism, several types can be distinguished: poor metabolizer, which is very slow; intermediate metabolizer, which is somewhat slow; extensive metabolizer, which is normal; and ultra-rapid metabolizer, which is very fast. These differences cause the same drug dose to produce different outcomes—for example, poor

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metabolizers experience drug accumulation, whereas in ultra-rapid metabolizers the drug is eliminated quickly, making therapy potentially less effective [7].

3.3 Pharmacogenomics Case Study

The clinical adoption of pharmacogenetics highlights how inherited genetic variations directly dictate individual drug responses, particularly for medications with narrow therapeutic indexes. A quintessential example is Warfarin, where minor dosing deviations can trigger catastrophic therapeutic failures or toxic bleeding; its clearance is modulated by CYP2C9 polymorphisms, while downstream pharmacodynamic sensitivity is governed by VKORC1 variations. Integrating these genetic variants allows clinicians to calculate safer, highly individualized initial dosages. Similarly, Codeine efficacy relies entirely on bioactivation into morphine via the CYP2D6 enzyme, placing ultra-rapid metabolizers at risk of fatal opioid toxicity, while poor metabolizers derive virtually no analgesic benefit. Beyond cytochrome P450 enzymes, this genetic determinism extends to idiosyncratic hypersensitivity reactions, as seen with the antiretroviral Abacavir and its strong association with the HLA-B*5701 allele. Pre-treatment screening for this allele has successfully standardized safer alternative selection. Where genetic testing remains inaccessible, clinical risks must be circumvented through conventional empirical strategies, such as low-dose initiation and rigorous biomarkers monitoring (e.g., International Normalized Ratio [INR] assessments in Warfarin therapy) [10].

These examples show individual genetic or clinical risks, but the real complexity of personalized medicine is best seen in antiplatelet therapy. Here, genetic differences and drug interactions come together in one metabolic pathway. Brown & Pereira (2018) [11] noted that about 30% of patients with stents have a poor response to Clopidogrel because of loss-of-function changes in the liver enzyme CYP2C19 (*2 and *3 alleles). This genetic issue greatly reduces the drug's activation, leading to weak platelet inhibition and higher risks of stent thrombosis and heart attacks. On the other hand, those with the *17 allele have faster drug activation and increased bleeding risks. This balance is further complicated in real-world situations where multiple drugs are used. Deodhar et al. (2020) [9] found that Omeprazole, often given to prevent gastrointestinal bleeding, irreversibly inhibits CYP2C19. This drug interaction mimics a genetic poor metabolizer state, lowering active Clopidogrel levels and worsening heart problems. The FDA's strict Black Box Warnings highlight that just changing the timing of doses doesn't avoid this interaction because the enzyme is permanently inactivated. This stresses the need for doctors to use other antiplatelets like Prasugrel or Ticagrelor.

3.4 Implementation of Pharmacogenomics in Pharmacies/Clinics

The adoption of personalized medicine is undergoing a significant conceptual transformation, moving beyond host pharmacogenomics (PGx) to integrate the critical role of the human gut microbiome, or pharmacomicrobiomics, in drug metabolism. However, as noted by Hassan et al. (2021), this multi-layered biological complexity introduces a dual bottleneck: the severe underrepresentation of diverse, non-European populations in current genomic databases, and a critical scarcity of advanced multi-omics computational tools required to predict combined host-microbiome interactions in routine clinical settings [8].

A concrete example of pharmacomicrobiomics is digoxin, whose metabolism can be altered by the gut bacterium Eggerthella lenta through biotransformation of the drug into less active metabolites. This example illustrates that gut microbes do not merely coexist with host pharmacogenomic pathways, but can directly modify drug chemical structures, bioavailability, and clinical response, thereby adding another layer of variability that pharmacists should consider when interpreting therapeutic outcomes.

While the study of host-microbiome interactions is advancing, current medical practices face significant challenges due to metabolic issues, especially the economic and accessibility problems related to managing CYP450 enzyme inhibition and induction. In older adults with chronic diseases, polypharmacy frequently increases the risk of clinically important drug-drug interactions and phenoconversion, in which comedications functionally shift a patient from one metabolizer phenotype to another. Besides omeprazole-mediated CYP2C19 inhibition that can reduce clopidogrel activation,

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fluoxetine is a well-recognized CYP2D6 inhibitor that may increase exposure to susceptible substrates, whereas rifampin is a potent inducer of CYP3A4 and other enzymes that can reduce drug concentrations and compromise therapeutic efficacy. These interaction-driven changes can obscure the relationship between genotype and observed phenotype, making pharmacokinetic interpretation and real-world dose individualization more challenging in routine care.

Addressing these immediate practical gaps is key to advancing the future of medicine, which will depend on converting detailed genetic data into personalized treatment plans. The immediate focus is on improving clinical understanding of pharmacogenetics and increasing the use of established clinical databases, like CPIC, for high-risk drugs such as warfarin, codeine, and allopurinol. With rapid progress in genome sequencing, the treatment approach will shift from fixed, standard dosing to flexible strategies tailored to an individual's specific DNA profile, thus enhancing treatment success and systematically reducing preventable toxicities [10].

4 Conclusion

Inherited genetic variations in CYP450 enzymes significantly determine interindividual variability in drug response, efficacy, and toxicity risk (as in the case of warfarin, clopidogrel, and codeine). However, a critical gap exists in translating this basic genomic knowledge into standardized, evidence-based, real-world clinical protocols due to the complexity of phenoconversion phenomena, which is exacerbated by economic constraints, accessibility, and limited accurate predictive tools in healthcare facilities. Therefore, there is a need to formulate a comprehensive risk management strategy through the integration of clinical databases (such as CPIC) and optimize the role of pharmacists/clinicians in evaluating polypharmacy, thereby bridging theoretical genomics knowledge with the practical, safe, and effective implementation of personalized medicine dosing guidelines in everyday clinical settings.

5 Declarations

5.1 Acknowledgements

Thank you to the Faculty of Pharmacy, Universitas Mulawarman, for their invaluable institutional support in facilitating access to scientific database and academic resources essential for the competion of this reviewed

5.2 Author contributions

Isti Faiza Sakinah, Khairani Tosuli, and Ayla Azzura performed the primary literature analysis, drafted the main discussion sections, and authored the initial manuscript. Anastasya Esther Fiorelina Siahaan and Sabrina conducted the comprehensive literature search and article screening. Nanda Febriani and Maria Beatrix Ose Purek were responsible for data extraction, formulating the pharmacy relevancies, and drafting the study conclusion. Salwa Salsa Billa and Tasya Falda Puteri compiled the additional references and organized the data synthesis tables. Kaylila Aileen handled the manuscript formatting and technical editing. Juniza Firdha Suparningtyas designed the study framework, supervised the conceptual development, led the drafting and critical revision of the manuscript, and served as the corresponding author. All authors have read and agreed to the published version of the manuscript.

5.3 Ethics

Ethical approval was not required

5.4 Conflict of Interest

The authors declare that there are no conflicts of interest associated with this publication.

5.5 Funding Statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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