

Pharmacogenetics

Pharmacogenetics – An Overview

- Pharmacogenetics is the study of how an individual's genetic makeup affects their response to drugs.
- It aims to understand the genetic variations that lead to differences in drug metabolism, efficacy, and toxicity among individuals.
- Ultimately, pharmacogenetics contributes to personalized medicine, where therapy is tailored according to a patient's genetic profile.
- Pharmacogenetics focuses primarily on single gene variations and their effects on drug response.
- It is closely related to pharmacogenomics, which considers multiple genes or the whole genome.

The Areas of Focus in Pharmacogenetics Include:

1. Genetic polymorphisms in drug metabolism enzymes
2. Genetic polymorphisms in drug transporters and targets
3. Pharmacokinetic and pharmacodynamic implications of genetic variations

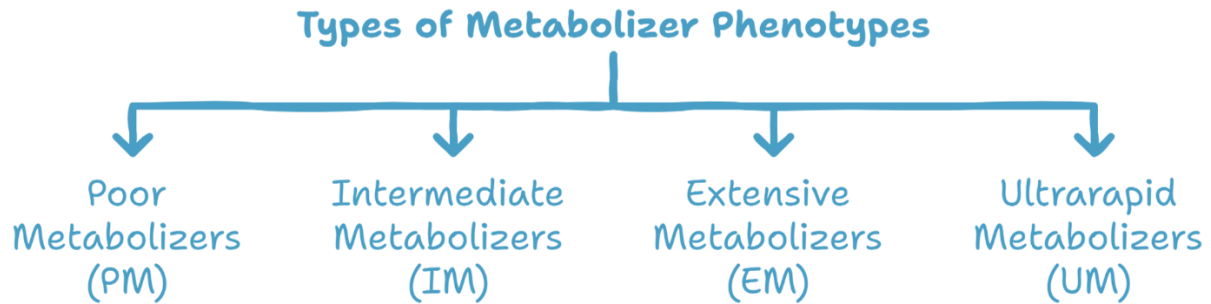
Genetic Polymorphism in Drug Metabolism: Cytochrome P-450 Isoenzymes

Overview

- The **CYP450 family** of enzymes is central to drug metabolism:
 - Primarily located in the **liver**.
 - Responsible for the **oxidation of xenobiotics**, including most pharmaceutical drugs.
 - Of the ~57 human CYP genes, only a few significantly impact drug metabolism:
 - **CYP3A4/5**
 - **CYP2D6**
 - **CYP2C9**
 - **CYP2C19**
 - **CYP1A2**
- These enzymes exhibit **genetic polymorphisms**—natural DNA variations that affect enzyme activity and, consequently, drug response.

Types of Metabolizer Phenotypes

- Based on polymorphisms in CYP genes, individuals can be classified into four general metabolizer types:



- A. **Poor Metabolizers (PM):** Have little or no functional enzyme activity.
- B. **Intermediate Metabolizers (IM):** Have reduced enzyme activity.
- C. **Extensive Metabolizers (EM):** Have normal enzyme activity (wild-type).
- D. **Ultrarapid Metabolizers (UM):** Have increased enzyme activity, often due to gene duplication.

Clinical Impact

A. Poor Metabolizers (PM):

- May accumulate higher levels of active drug → leading to toxicity.
- **Example:** CYP2D6 poor metabolizers may experience side effects with standard doses of antidepressants (e.g., nortriptyline).

B. Ultrarapid Metabolizers (UM):

- May metabolize drugs too quickly → leading to therapeutic failure.
- **Example:** CYP2D6 ultrarapid metabolizers may convert codeine to morphine rapidly → increasing the risk of morphine toxicity, especially in children.

Examples of CYP450 Polymorphisms

A. CYP2D6

- Polymorphic with over 100 known alleles.
- Affects metabolism of ~25% of commonly used drugs, such as antidepressants, antipsychotics, beta-blockers, and opioids.
- Gene duplications (e.g., CYP2D61xN*) can lead to ultrarapid metabolism.

B. CYP2C9

- Polymorphisms (e.g., *2, *3 alleles) lead to reduced enzyme activity.
- Affects metabolism of drugs like warfarin and phenytoin.
- Individuals with variant alleles may require lower doses of warfarin to avoid bleeding.

C. CYP2C19

- Poor metabolizer phenotype is more common in Asian populations.
- Influences metabolism of drugs like clopidogrel (a prodrug), proton pump inhibitors, and certain antidepressants.
- CYP2C19 poor metabolizers may not effectively activate clopidogrel → reduced antiplatelet effect → higher risk of cardiovascular events.

D. CYP3A4/5

- Involved in metabolism of the largest number of drugs.
- CYP3A5 expression is genetically controlled.
- For example, African populations more frequently express the active *CYP3A5** allele, influencing tacrolimus dosing.

Pharmacogenetic Testing

- Genetic tests are now available to identify CYP450 polymorphisms.
- Useful in tailoring drug therapy (precision medicine).
- Commonly used in oncology, psychiatry, cardiology, and pain management.

Importance of Genotyping

- Identifying a patient's CYP450 genotype helps clinicians:
 - Adjust drug dosages.
 - Choose alternative medications.
 - Avoid adverse drug reactions (ADRs).

Genetic Polymorphism in Drug Transport and Drug Targets

Overview

- Pharmacogenetics extends beyond drug metabolism to include **genetic variations** that affect:
 - **Drug transport** – how drugs are moved into and out of cells.
 - **Drug targets** – how drugs interact with receptors, enzymes, or proteins at their sites of action.
- These polymorphisms can significantly influence:
 - **Absorption**
 - **Distribution**
 - **Efficacy**
 - **Toxicity**

Clinical Significance and Application

- Understanding genetic polymorphisms in transporters and drug targets helps:
 - **Predict individual drug response.**
 - **Avoid adverse drug reactions (ADRs).**
 - **Tailor medication and dosing** for optimal efficacy.

Pharmacogenetic Integration

- Clinical guidelines (e.g., **CPIC**, **FDA drug labels**) now include recommendations based on:
 - **Transporter gene variants** (e.g., *SLCO1B1*)
 - **Target gene polymorphisms** (e.g., *VKORC1*, *ADRB1*)

Genetic Polymorphism in Drug Transport

Drug Transporters:

- Drug transporters are membrane proteins that mediate the influx and efflux of drugs across biological membranes.
- They are crucial in determining the pharmacokinetics (absorption, distribution, and elimination) of drugs.

Two major families:

- **ATP-Binding Cassette (ABC) Transporters** – mainly efflux transporters.
- **Solute Carrier (SLC) Transporters** – mainly influx transporters.

Notable Transporters and Polymorphisms

Drug Transporters and Polymorphisms

P-glycoprotein

Efflux transporter affecting drug bioavailability and distribution.



Breast Cancer Resistance Protein

Efflux transporter limiting oral bioavailability and brain penetration.



Organic Anion Transporting Polypeptides

Influx transporter for hepatic drug uptake, affected by polymorphisms.



A. P-glycoprotein (P-gp / MDR1)

- **Gene:** ABCB1
- **Function:** Efflux transporter located in the intestine, liver, kidneys, and blood-brain barrier
- **Polymorphism Example:** C3435T
 - Affects P-gp expression and activity
 - Alters bioavailability and drug distribution
- **Clinical Impact:**
 - **Drugs affected:** Digoxin, verapamil, certain chemotherapy agents

B. Breast Cancer Resistance Protein (BCRP)

- **Gene:** ABCG2
- **Function:** Efflux transporter
- **Role:** Limits oral bioavailability and brain penetration of drugs
- **Drugs affected:** Topotecan, rosuvastatin

C. Organic Anion Transporting Polypeptides (OATPs)

- **Gene:** SLCO1B1 (encodes OATP1B1)
- **Function:** Influx transporter for hepatic drug uptake
- **Polymorphism:** c.521T>C
 - Leads to reduced uptake of drugs like statins
 - Associated with statin-induced myopathy due to higher plasma concentrations

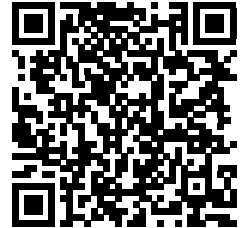


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