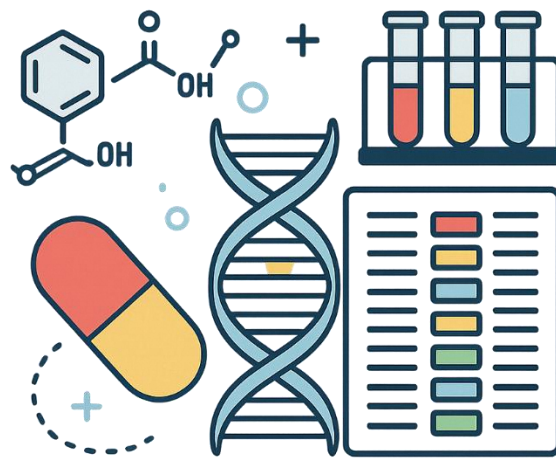


Pharmacogenomics of Adverse Drug Reactions

What is Pharmacogenomics?

- Pharmacogenomics is the study of how genetic variations influence an individual's response to drugs, including:
 - Efficacy
 - Toxicity
 - Adverse drug reactions (ADRs)
- In pharmacovigilance, pharmacogenomics helps explain why certain individuals experience ADRs while others do not, even at the same dose.



PHARMACOGENOMICS

Pharmacokinetic Parameters Affected by Genetics

- Absorption:** Genetic variants in drug transporters (e.g., ABCB1) can influence how much drug is absorbed into systemic circulation.
- Distribution:** Variants in plasma protein-binding genes or transporters can affect how drugs are distributed to tissues.
- Metabolism:** This is the most well-studied area. Genes like CYP2D6, CYP2C9, and CYP2C19 encode enzymes that metabolize many drugs.
- Excretion:** Genes affecting renal transporters (e.g., SLC22A2) can influence the clearance of drugs.

Genetics-Related ADR Example

Codeine and CYP2D6 Polymorphism

Background

- Codeine is a prodrug that must be metabolized into morphine to be effective.

- This conversion is catalyzed by the CYP2D6 enzyme, which exhibits genetic polymorphisms, resulting in different metabolizer phenotypes:
 - **Poor Metabolizers (PMs):** Little or no CYP2D6 activity.
 - **Ultra-Rapid Metabolizers (UMs):** Multiple copies of the CYP2D6 gene → excessive enzyme activity.

Pharmacokinetic Impact:

- **PMs:** Inadequate conversion → low morphine levels → poor pain control.
- **UMs:** Excessive conversion → high morphine levels → risk of respiratory depression, especially in children.

Adverse Drug Reaction (ADR) Example

- Fatal respiratory depression has been reported in children who are UMs after receiving codeine, especially post-tonsillectomy.
- These incidents led to regulatory actions, including:
 - Black box warnings
 - Contraindications for codeine use in pediatric populations

Mechanism

- Codeine → (CYP2D6 in liver) → Morphine (active form)
- CYP2D6 polymorphism affects conversion:
 - Ultra-rapid metabolizers (UMs) have multiple copies of the gene → produce more morphine, leading to toxicity and respiratory depression.
 - Poor metabolizers (PMs) have non-functional alleles → produce little or no morphine, leading to ineffective pain relief.

Other Examples of PK-Related Genetic ADRs

Drug	Gene	Effect	ADR
Warfarin	CYP2C9	Slower metabolism	Increased bleeding risk
Irinotecan	UGT1A1*28	Reduced clearance	Severe neutropenia, diarrhea
Simvastatin	SLCO1B1	Impaired hepatic uptake	Statin-induced myopathy

Drug safety evaluation in special population

Paediatrics (Children and Infants)

Why Special Consideration?

- Children are not "small adults." Their developing organ systems affect how drugs are processed:
 - **Immature Liver and Kidneys:** Reduced drug clearance.
 - **Body Composition:** Higher water and lower fat content affects drug distribution.
 - **Enzyme Activity:** Changes with age, influencing metabolism.
 - **Developmental Physiology:** Impacts absorption, distribution, metabolism, and elimination.



PAEDIATRICS

Key Risks in Paediatrics

- **Higher Risk of ADRs:** Due to immature metabolic pathways; symptoms may differ (e.g., irritability instead of headache).
- **Off-label Use:** Common due to limited child-specific drug data.
- **Dosing Challenges:** Risk of overdose or underdose due to weight- or surface area-based dosing.
- **Limited Clinical Trial Data:** Most drugs are studied in adults, not children.

Challenges

- **Non-specific Symptoms:** Children may show vague signs like crying or vomiting.
- **Reporting Gaps:** Reliance on parents, caregivers, and pediatricians for ADR reporting.

Safety Measures

- **Post-marketing Surveillance:** Pediatric-specific registries and monitoring systems.
- **Pharmacovigilance Databases:** Includes pediatric subsets (e.g., EudraVigilance).



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