

Pharmacogenomics and Precision Medicine

Learning Outcomes

- Describe what is meant by the terms 'pharmacogenetics', 'pharmacogenomics' and 'personalised/precision medicine' more generally.
- Discuss generally how knowledge generated from these areas of study might lead to improvements in human/(animal) health.
- Describe how DNA polymorphisms and, in particular, SNPs can lead to changes in protein expression/function.
- Describe, using examples, how SNPs can change the Pharmacokinetic and Pharmacodynamic properties of drugs.
- Be aware of the ethical/economic considerations that the field of Pharmacogenetics/Pharmacogenomics raises.

Introduction to Pharmacogenomics

Pharmacogenomics plays a crucial role in precision medicine, moving away from a one-size-fits-all approach to therapeutics.

- Historically, compounds were modified to suit all patients, but with the understanding of human genome variations, it's clear that individual responses vary.
- Pharmacogenomics aims to identify genetic variations influencing drug efficacy and safety to personalise treatment.

Applications in Cancer Chemotherapy

Cancer chemotherapy has embraced pharmacogenomics for personalised and safer therapies.

- Genetic signatures of patients are used to tailor treatments for better outcomes.

Pharmacogenetics vs. Pharmacogenomics

Pharmacogenetics focuses on polymorphisms of single genes and their influence on drug response, while pharmacogenomics involves broader technology-driven approaches investigating multiple genes and variations.

Importance of Pharmacogenomics

Understanding patient variations in drug responses is crucial due to adverse reactions and lack of efficacy.

- Adverse drug reactions are costly and can be life-threatening, impacting both patients and healthcare systems.
- Lack of drug efficacy in certain patients can delay treatment, especially critical in conditions like cancer.

Impact of Genetic Variations

Polymorphisms in DNA can affect protein activity, drug metabolism, and drug interactions.

- Mutations can be germline or somatic
- Often SNPs
 - Examples of mutations like silent, conservative, and non-conservative mutations can impact protein structure and function.
- Polymorphisms can be direct, altering protein function or binding to drugs, or indirect, affecting gene expression levels.

Detection of Polymorphisms

Advancements in DNA sequencing have made identifying genetic variations more accessible and cost-effective.

- High-throughput DNA sequencing and microarray-based screening help detect single nucleotide polymorphisms linked to drug responses.
- Targeted approaches using chips with nucleotide sequences aid in analysing patient-specific genetic variations.

Pharmacokinetic Aspects

- Genetic polymorphisms in drug-metabolising enzymes can lead to altered drug levels in the body, affecting drug efficacy and adverse reactions.

Pharmacodynamic Aspects

- Proteins like receptors, ion channels, and enzymes can be influenced by genetic variations, impacting drug binding and activity.

Examples of Pharmacogenomics

- Example 1: Drug Metabolism - Suxamethonium metabolism variation due to polymorphic forms of plasma cholinesterase affecting muscle relaxation duration.
- Example 2: Drug Metabolism - Debrisoquine (anti-hypertensive) metabolism by cytochrome P450 enzyme showing varied effects on blood pressure due to enzyme polymorphisms.
- Example 3: Drug Metabolism - Thiopurine methyltransferase enzyme polymorphisms can affect deactivation of 6-mercaptopurine and lead to imbalance of active and inactive drugs, leading to potential adverse effects in leukaemia treatment
- Example 4: Genome-Wide Association Study - Polymorphism in SLC01B carrier protein reducing statin (blood cholesterol reducer) metabolism in the liver, leading to potential muscle damage.

Receptor Polymorphisms in Pharmacogenomics

- Example: Epidermal growth factor receptor (EGFR) polymorphism in lung cancer influences drug choice.
- Example: Enzyme polymorphisms affecting the activity of anticoagulant drug warfarin.
 - Warfarin inhibits clotting factors by targeting the Vitamin K reductase enzyme, but polymorphisms in enzymes like CYP2C9 can affect warfarin metabolism, leading to dosing challenges.
 - Individuals with enzyme polymorphisms may require personalised dosing of warfarin to balance clotting prevention and bleeding risks.

Role of Pharmacogenomics in Drug Therapy

- Current prescribing involves trial and error, but pharmacogenomics offers potential for more targeted drug selection.
- Cost and interpretation of genomic data remain challenges in implementing pharmacogenomics in practice.

Ethical and Economic Considerations

Pharmacogenomics raises ethical concerns regarding genetic screening, privacy, and access to tailored therapies based on genetic makeup.

Future of Pharmacogenomics

Pharmacogenomics is advancing precision medicine, but challenges remain in integrating genetic information into clinical practice effectively.

- Pharmaceutical companies are adapting to precision medicine models, focusing on tailored therapies.