GENERAL HEALTH

Pharmacogenomics: Genetic Variability and Its Clinical Relevance.

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Introduction:

Pharmacogenomics is a broad field that combines pharmacology (the scientific study of drugs) and genomics (the study of an organism?s genome). It is a study of how genetic differences affect the way the body responds to medications. These variations in drug responses are a global concern.

For a long time, physicians and researchers have observed that when the same drug at the same dosage is administered to a group of patients, the outcomes vary. Few recovered early, while others did not. While these differences were thought to be due to age and environmental factors, it is now understood that genes play an important role. Our genetic makeup affects how the body absorbs, transports, and metabolizes drugs. Traditional prescribing methods fail because they do not consider interindividual genetic differences. Pharmacogenomics can overcome this limitation. Integrating individual genetic knowledge with drug selection can improve drug efficacy.

Every year, many people are hospitalized due to the adverse effects of drugs, which can be life-threatening. Hence, tailoring the drug according to the individual?s genetic makeup can reduce this risk and improve overall public health by implementing this strategy globally. Idiosyncratic adverse drug reactions affect multiple organs, including the kidneys, liver, skin, muscles, and heart. In some cases, certain drugs trigger more generalized hypersensitivity responses (Daly, 2013).

Beyond clinical applications, pharmacogenomics has advanced in fields such as personalized medicine, pharmaceutical research, drug safety, oncology, cardiology, and other related fields. The use of pharmacogenomics is still limited, but it holds great potential.

Pharmacogenetic Testing

Through Pharmacogenetic tests, healthcare providers can decide on the right drug and dosage for a patient. It involves the use of genotyping assays to identify genetic variants that may affect a patient's response to a particular drug (Rogers, 2023). For the test, blood, saliva, or cells swabbed from the cheek are used. Through laboratory tests, specific genetic variations, such as copy number variations (CNVs), single nucleotide variants, and insertions/deletions, are determined. Using these findings, alleles can be determined, often allowing predictions about haplotypes or diplotypes. These alleles are then organized into diplotypes, which are used to predict phenotypes (McMillin, 2020).

Pharmacogenomics: Real-World Examples

HIV: Early HIV treatments used abacavir (Ziagen) and efavirenz (Sustiva). The researchers found that people with the HLA-B*57:01 gene variant were at a higher risk of developing a hypersensitivity reaction to abacavir. The metabolism of efavirenz is influenced by genetic variations in CYP2B6. In patients carrying certain variants of CYP2B6, the drug is metabolized more slowly. This leads to higher concentrations of efavirenz in the bloodstream and an increased risk of neuropsychiatric side effects (?The Evolution of PGx Testing,? 2024).

Caffeine Metabolism: The enzyme coded by CYP1A2 gene plays a key role in metabolizing caffeine. Individuals carrying a variant of this gene metabolize caffeine more slowly than others. As a result, the stimulant remains in their system for a longer duration (?The Evolution of PGx Testing,? 2024).

Warfarin: Warfarin is a widely used anticoagulant. The enzyme responsible for metabolizing warfarin is coded by CYP2C9. Warfarin targets VKORC1, which is involved in vitamin K recycling. CYP2C9 variants can affect drug metabolism by slowing it down. VKORC1 alters the sensitivity of enzymes to warfarin (Dean, 2018).

Clopidogrel (Plavix): It is used for patients with coronary artery disease and peripheral artery disease, especially following stent placement. As clopidogrel is a prodrug, it requires activation by the CYP2C19 enzyme. In individuals carrying a variation in the CYP2C19 gene, this results in insufficient conversion of clopidogrel to its active form. Therefore, patients are at a higher risk of serious cardiovascular events, such as stent thrombosis, stroke, and heart attack (Mirabbasi et al., 2017).

Antidepressants: CYP2D6 and CYP2C19 play key roles in the metabolism of drugs such as fluoxetine, venlafaxine, and amitriptyline. CYP2C19 is involved in metabolism of selective serotonin reuptake inhibitors (SSRIs) (Bousman et al., 2023). Some people with a variant of this gene cannot metabolize the drug efficiently, while others metabolize it too quickly. Slow metabolism leads to drug accumulation in the body, whereas ultra-rapid metabolism is too fast for the drug to have the intended effect.

ADHD: Methylphenidate (Ritalin) and amphetamine (Adderall) are common drugs prescribed for ADHD treatment. They are metabolized by enzymes in the cytochrome P450 system, such as CYP2D6. Genetic variations in CYP2D6 can lead to either poor or ultra-rapid drug metabolism (Bousman et al., 2023). Poor metabolizers are at risk of having higher concentrations of the drug in their system, leading to side effects such as difficulty sleeping and irritability. Ultrarapid metabolizers break down the drug too quickly for it to be effective.

Mood stabilizers: Valproic acid (VPA) and carbamazepine (CBZ) are widely prescribed mood stabilizers, mainly for the treatment of bipolar disorder. Patient responses to CBZ and VPA vary owing to inter-individual genetic differences. For example, Japanese women carrying CYP2C19*2 or CYP2C19*3 alleles are more prone to weight gain during valproate therapy.

Oncology: Anticancer drugs have a narrow therapeutic index; hence, it is important to use precise doses to maximize their benefits and prevent toxicity (Franczyk et al., 2022). 6-Mercaptopurine (6-MP) is a commonly used drug for treating acute lymphoblastic leukaemia (ALL). Thiopurine methyltransferase (TPMT) metabolizes 6-mercaptopurine into an inactive compound. This reduces the availability of the parent drug for the formation of thioguanine nucleotide (TGN) metabolites, which are both pharmacologically active and potentially toxic. Variant TPMT results in low enzyme activity and excessive accumulation of TGNs. Patients who inherit two loss-of-function alleles are at a higher risk of developing myelosuppression. (Carr et al., 2020).

Anthracycline-induced cardiotoxicity: 65% of patients receiving these drugs are affected by anthracycline-induced cardiotoxicity. The risk of congestive heart failure, especially in paediatric cancer patients undergoing anthracycline therapy, can be significantly reduced through pharmacogenomic interventions (Cacabelos et al., 2021).

Irinotecan (CPT-11): It is used in the treatment of advanced or metastatic colorectal cancer. It often leads to severe toxicities, such as neutropenia and diarrhea. The drug is converted into its active metabolite SN8 and further it is detoxified by uridine diphosphate-glucuronosyl transferases (UGT1A1). ABC transporters (ABCB1, ABCC1?ABCC6, and ABCG2) mediate drug efflux into bile and urine, and SLCO1B1 facilitates its uptake or influx from the bloodstream into hepatocytes. SNPs in these enzymes and transporters leads to toxicity and elevated levels of SN-38 (Cacabelos et al., 2021).

Antihistamines: The efficacy of antihistamines is largely influenced by gene polymorphisms. Antihistamines bind to histamine receptors, producing their anti-allergic effects. Absorption, distribution, metabolism, and

excretion of the drug are regulated by drug transporters and cytochrome P450 (CYP) enzymes. Mast cells are the primary histamine-releasing cells, and they express multiple receptors on their surface. Drug efficacy and adverse reactions could occur due to variations in genes encoding histamine receptors, enzymes, and drug transporters (Li et al., 2022).

Benefits of pharmacogenomics

Pharmacogenomics can help doctors choose the right drug and right dosage according to the patient?s genetic features. This reduces the risk of side effects caused by drugs. Doctors can determine whether a patient metabolizes the medication too quickly, too slowly, or at a normal rate. As a result, treatment becomes more effective compared to the traditional trial-and-error method. This tailored approach reduces the incidence of adverse drug reactions and improves the overall public health system. It decreases drug approval time, patient hospitalizations, and the length of medication use. Traditional clinical trials are expensive and require a lot of time, and a diverse population is tested to account for variability in drug responses. However, with pharmacogenomics, both cost and time are reduced, as testing specific genetic population groups is sufficient. Insights from genetic testing makes it possible to determine genetic markers associated with drug toxicity. This identification of the genetic markers allows for designing of safer drugs. Insights from genetic testing make it possible to determine genetic markers associated with drug toxicity. This identification of the genetic markers allows for the designing of safer drugs.

Pharmacogenomics is a core component of personalized medicine. The underlying idea is that the interindividual variability in drug response is due to the patient?s characteristics, environmental variables, genetics, and epigenomics. ?Omics? approach of pharmacogenomics has transformed our understanding of genetic susceptibility. It holds great potential in developing new treatment strategies (Qahwaji et al., 2024).

Conclusion:

Pharmacogenomics provides valuable insights to transform the traditional trial-and-error approach into a more personalized one. In current drug therapy practices, adverse drug reactions are frequent. However, many of these adverse drug reactions can be predicted and potentially prevented through pharmacogenomics. Beyond clinical applications and personalized care, it can also enhance the drug development process and therapeutic outcomes. Its integration with multi-omics technologies broadens the scope and impact of pharmacogenomics, despite challenges such as cost, accessibility, and awareness.

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Competing interests

The authors declare that they have no competing interests.

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