WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

An overview of Pharmacogenomics: The genomics of drug response

M. SHALIMA[1], MRS.K. MALARVIZHI[2]

[1] B. PHARMACY
[2] B.PHARM., M.PHARM.,
PALLAVAN PHARMACY COLLEGE, KOLIVAKKAM, KANCHEEPURAM-631502

ABSTRACT:

The study of genetic variation in how people react to medication treatment is known as pharmacogenomics. It has a lengthy and diverse history as scientists have learned more about human genetic variability and how it might impact how people react to drugs and other substances. Though additional study is needed, it has the potential to enhance the healthcare system in the future significantly and is required right now to initiate this. Pharmacogenomics uses genetic and other "omic" data to assist in directing, educating, and customizing medication treatment. Despite being a relatively new field, pharmacogenomics is already making its way into clinical settings and assisting doctors and other healthcare professionals in making more precise and tailored treatment decisions.

Keywords: Pharmacogenomics, health care, human genetic,treatment

INTRODUCTION:

A deeper comprehension of drug response at the individual level will be possible through pharmacogenomics, and the application of genetic approaches to the study of pharmacological function, drug disposition, and drug activity. This serves as the primary foundation for the trend toward more individualized medicine, or "personalized medicine." A new study proposes the term "stratified medicine" to more accurately characterize the idea of applying pharmacogenomics to identify groupings (as opposed to individuals).
In the quickly developing subject of pharmacogenomics, the nomenclature is still being established. Understanding the language used in scientific literature and regulatory papers is crucial when thinking about incorporating pharmacogenomics into international drug development initiatives. Numerous studies have shown that personalized medicine is becoming more popular, and the general public's awareness of it is growing due to news and media coverage.
Basis of pharmacogenomics:
Alkaptonuria is a metabolic condition that was treated with the first pharmacogenomic-type medication. A genetic foundation was proposed as the fundamental reason in 1902. A particular enzyme was identified as the genetic variable during World War II after it was discovered that African-American troops had hemolysis more frequently as a result of antimalarial medication.
Genetic diversity in genes is the subject of pharmacogenetics, which adds to the idea of "many genomes, one drug," which suggests patient variety to get the intended outcome.

On the other hand, pharmacogenomics is predicated on the idea that different pharmacological molecules may be chosen for a particular genome, resulting in "many drugs, one genome. Both adjust to a person's medication metabolism and reaction to reduce adverse effects, but pharmacogenomics is a more comprehensive notion that may be used in the pharmaceutical business as a tool for compound selectivity.

Benefits in the short-term

Over 100,000 fatalities annually in the United States are attributed to adverse drug reactions (ADRs), which rank as the fourth or sixth largest cause of mortality out of the 3 billion prescriptions written each year, with an estimated 3 million of those prescriptions being inaccurate or ineffective.
Since medications are typically administered to treat illnesses, anyone with a propensity to such a condition might be prescribed a prescription without knowing how they would react. Only 40–60% of the general population responds well to a blockbuster medication, which is a commercially successful medication for the whole population.

Benefits in the long-term

A more efficient healthcare system is a predicted outcome of pharmacogenomics.

A doctor is more likely to make wise suggestions if they combine a patient's genetic predispositions with their clinical history. A patient's attitude regarding their health may improve if they have faith in the medical system. Nowadays, half of all patients stop taking their prescription drugs for chronic diseases within a year due to the large number of useless prescriptions.

Current clinical care implications of the combined findings:

Both germline and somatic genetic differences are taken into account in personalized medication treatment.

Remarkably, significant progress has been made in customizing medication for cancer therapies. This advancement is mostly due to the careful analysis of certain alterations in genes and growth receptors that are essential to the related signal transduction pathways. Somatic mutations in ten different pharmacogenes-ALK, ABL1, BCR, BRCA1, BRAF, EGFR, ERBB2, KIT, KRAS, and NRAS-are highly significant in predicting the efficacy of cancer treatment in this setting. ABCB1, CYP2D6, DPYD, NUDT15, MTHFR, TPMT, and TYMS are the seven essential genes whose germline variations are also crucial for the pharmacokinetics of anticancer drugs.
It is clear that a small group of genes-including CYP2C9, CYP2C19, CYP2D6, CYP3A5, DPYD, TPMT, SLCO1B1, and HLA-B took priority in clinical trials carried out between 2012 and 2020 in a variety of therapeutic domains, with a particular emphasis on certain gene-drug pair interactions. Surprisingly, the FDA now considers these genes, along with NAT2 and UGT1A1, to be significant in the pharmacogenomic domain, and the evidence supports treatment recommendations. The two most important genes to take into account when it comes to polymorphism genes influencing pharmacokinetics are CYP2C19 and CYP2D6. Therefore, it is important to note that the number of polymorphic genes with clinical significance has been minimal and mostly constant in recent years.

Confounding variables in studies using pharmacogenomics:

To successfully identify gene-drug interactions, suitable pharmacogenomic tests must be used in patient cohorts that are sufficiently large and well-characterized to provide statistically significant findings. Nonetheless, a large number of pharmacogenomic investigations have been carried out on diverse patient groups that lack thorough phenotypic stratification and fail to adequately take into account pathophysiological and environmental aspects, such as the liver and renal function of patients.

Numerous confounding variables provide significant obstacles to larger clinical studies in this field. In particular, closed-label trials are a major worry as they make it very challenging to blind doctors to the treatment circumstances. As demonstrated in the instance of treating mental depression with novel selective serotonin reuptake inhibitors (SSRIs), where placebos might account for up to 50% of the reported effects, the influence of placebo effects in randomized controlled trials (RCTs) is significant. Another significant factor is polypharmacy and the ensuing drug-drug interactions (DDIs), particularly in elderly patients who frequently need more than five concurrent drugs to treat their diseases.

Studies should be planned to include a significant percentage of patients with functional variations relevant to each medicine under investigation in the setting of the specific treatment intervention for comparison's sake. Since the genetic basis of up to 50% of hereditary variation in drug pharmacokinetics is still unclear, elucidating heritability presents another difficulty. Because classifications of response or adverse events might be more subjective, consideration should also be given to using hard quantitative endpoints, such as differences in drug concentrations in pharmacokinetic studies. The latest demonstrated the aforementioned difficulties, with individuals getting conventional treatment showing a similar decrease in side effects to those receiving genotype-guided medication therapy.

Genetic Factors Affecting Individual Differences in Drug Response:

Pharmacokinetic factors:

- Absorption
- Distribution
- Metabolism
- Elimination

Pharmacodynamic factors:

- Downstream signalling pathway differences
- Receptor variations
- Tissue-specific expression of drug targets
- Disease states impacting drug response
- The presence of genetic polymorphisms that alter the drug's ability to bind to or activate receptors

Receptor variations:
The genes that code for drug receptors might vary genetically in different people, resulting in variances in receptor affinity, sensitivity, or signaling pathways that affect how a medication interacts with the target tissue.

Signal transduction pathways:
Individuals may have different treatment results due to genetic changes in the signaling pathways downstream of a drug receptor, which can also affect the total medication response.

Tissue-specific expression:
Depending on the genetic composition of the individual, a medicine may have a greater effect on one tissue than another due to the fact that the expression level of a drug target gene might change between various tissues.

Disease state impact:
Changes in receptor expression or illness-related signaling pathways can affect the pharmacodynamic response to medication in specific disease conditions.

Genetic polymorphisms:
The total pharmacodynamic effect may be impacted by changes in drug binding, activation, or metabolism caused by variations in the genes encoding drug targets or associated proteins.

Examples of pharmacodynamic pharmacogenomic interactions:

Warfarin and VKORC1 gene:
The necessary dosage of the anticoagulant warfarin can be greatly impacted by variations in the VKORC1 gene, which codes for a protein involved in the metabolism of vitamin K.

Beta-blockers and ADRB1 gene:
The reaction to beta-blocker drugs can be influenced by genetic differences in the ADRB1 gene, which codes for the beta-1 adrenergic receptor.

Opioids and OPRM1 gene:
A person's susceptibility to opioid drugs may be impacted by variations in the OPRM1 gene, which codes for the mu-opioid receptor.

Pharmacogenomics' potential implications for medication development:

During the medication development process, the application of pharmacogenomics concepts has significantly improved drug targeting, lowered the dosage, and accelerated the rate of absorption.

1. Identification of target:
Currently, available medications act on less than 450 of the 1000 targets in the human proteome. Pharmacogenomics and pharmacogenetics techniques have significantly expanded the number of targets for medication therapy by:

- Finding novel proteins implicated in the illness process;
- Targeting the mechanism that causes the disease.

2. Preclinical medication development:
Pharmacogenomics has a significant influence on this stage of medication development. Only by identifying molecular defects-which vary from person to person-is in-vitro screening made practicable. For instance, the cytochrome P450 enzyme, which breaks down drugs, has been used to make progress. These are the most significant biological catalysts in charge of how various medications are metabolized. As a result, the drug's interaction with the P450 enzyme was evaluated.

3. Phase I–III research:
Regulatory approval to introduce a medication onto the market is granted at these stages of the clinical study. Phase I clinical trials usually cost around $7 million, whereas phase III clinical trials can cost up to $43 million. The pharmacogenomics concept, which emphasizes individual genotypes through pre-clinical testing, is used to refine the phase I trial. Early detection of the drug's flaw during phase I may result in the compound being dropped early on, which saves money and time throughout development. The pharmacogenetic factors of drug response may be further refined in phase II, which might yield data required for phase III study design. The overall result might be a smaller sample size.

4. Phase IV research:
This phase, sometimes referred to as post-marketing monitoring or pharmacovigilance, is the time frame during which licenses are issued to introduce medications onto the market. During this phase, several studies are conducted, including pharmacoepidemiologic research, hypothesis testing, reporting, and hypothesis generation studies. Pharmacogenomics can assist enhance marketing monitoring with less work than creating a single market and harmonizing the marketing authorization process.

Present-Day Pharmacogenomic Achievements:

Codeine:

Codeine (3-methyl morphine) is one of the most often used medications for treating mild to moderate pain in both adults and children. The pharmacologically active metabolite of codeine, morphine, is produced in the liver and is responsible for the analgesic action; it has an analgesic impact that is around 600 times greater than codeine's. Codeine-related toxicity has led to a recent decline in its use.

After consuming the mother's breast milk while taking a regular dosage of codeine for postpartum pain, the newborn has experienced severe or even deadly adverse responses.

Warfarin:

By blocking the enzyme vitamin K epoxide reductase, which is encoded in VKORC1, warfarin, an anticoagulant, prevents and treats venous thromboembolism by reducing the amount of vitamin K available for coagulation factor production. From patient to patient, the amount of warfarin needed to generate an anticoagulant effect varies by around 20 times.
Both clinical and genetic variables influence the warfarin dosage. Gamma-glutamyl carboxylase (GGCX) and cytochrome P450 4F2 (CYP4F2) are two more genes that affect the warfarin dosage.
Once the VKORC1 and CYP2C9 variants are taken into consideration, the influence of the genes on the variance in warfarin dosage is negligible. The VKORC/CYP2C9 genome and warfarin have a strong correlation in pediatric patients, according to a new study, indicating that the same genetic variations are crucial for children's warfarin dosage. Several pharmacogenetic-based dosing algorithms have been developed to estimate the precise dosage of warfarin.

Genetic testing's ramifications:

The first kind of genetic test would determine a person's medication intake, including its distribution, metabolism, excretion, and absorption. To increase efficacy, the second kind of test would concentrate on matching people to specific therapeutic molecules. Lastly, genetic testing would determine whether people are more susceptible to particular diseases.
A person can obtain predictive information about their health and susceptibility to specific diseases or ailments through genetic testing. People can determine their risk of developing a certain illness or condition by getting a particular section of the genetic code known to encode a given tendency. Some people are worried by the approach as the reaction to such information may either encourage or discourage behavior change, even when the result is independent of the surroundings.

Advantages of Pharmacogenomics:

- Drugs are more effective: Drugs may target particular disorders with fewer side effects than earlier medications since they are made especially for a person's protein, RNA molecule, and enzyme composition that are linked to their genes.
- Boost in vaccination efficacy: Vaccines that strengthen the immune system without increasing the danger of infection can be made using DNA and RNA.
- In contrast to the prior trial-and-error process, medications may be matched to a patient's genetic composition, meaning the patient will be provided the appropriate medication that has no negative effects.
- Because the medications were administered correctly, patients recover quickly.

Disadvantage of pharmacogenomics:

- Finding gene variants that impact medication responsiveness can be challenging. It's similar to trying to find a needle in a stack of needles while wearing a blindfold while trying to identify SNPs that influence medication response. Finding the right SNPs is a costly and time-consuming task since we don't fully understand which genes influence medication response. This could impede pharmacogenomics' advancement.
- Teaching medical professionals:
  The issue with pharmacogenomics is that, depending on your genetic makeup, there may be hundreds or even thousands of identical medications available on the market. This will make selecting and distributing medications much more difficult.
- Ethical Concerns: These will become "designer drugs," which will prevent many underprivileged individuals and nations from accessing the best possible care. This is the primary ethical concern.
  resulting in a wider gap between the rich and the poor. If the big pharmaceutical firms don't embrace the concept of pharmacogenomics, this might become a serious issue. The use of genetically engineered animals to produce necessary human medications, or "pharming," is the other significant ethical concern.

Application of Pharmacogenomic Approach at Different Phases of Drug Development:

Stage	Use of Pharmacogenomics
Drug target identification	Identifying and characterizing the gene that codes for the therapeutic target and evaluating its variability

Phase I clinical trial	Criteria for patient selection: inclusion/exclusion
Phase II clinical trial	Selection of dose range Modification of dosage
Phase III clinical trial	Analyzing trial outcomes using the findings of pharmacogenetics tests
Phase IV clinical trial	FDA analysis of adverse event reports using pharmacogenomics data throughout development
Regulatory affairs	FDA requirement that pharmacogenetic data be submitted during development
Patient's therapeutic	Customization of medication treatment. Pharmacogenetic information on medication labels. Respondents and non-respondents are identified. Finding the high-risk population for a negative occurrence

Conclusions:

Although the field of pharmacogenomics has made significant strides in the last ten years, these developments have not yet resulted in well-accepted therapeutic tools. Essentially, we find ourselves at a point in the evolution of this field that signifies the end of the beginning rather than the start of the end. Using a GWAS in a large cohort of 5.4 million participants, recent research showed that height and 12,111 independent SNVs in 7209 non-overlapping genomic segments-which make up around 21% of the genome-were significantly correlated. Although it is conceivable that the genetics of height are more complex than those of drug reaction, it seems impossible to achieve comparable drug response heritability saturation. Rapid advancements in sequencing techniques are encouraging, but confirming these genetic variations requires expensive and time-consuming clinical trials, which are sometimes hampered by a lack of financing.

REFERENCES:

1. 1.Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 1998: 279 (15): 1200–1205.
2. 2.Volpe D, McMahon Tobin G, Mellon R et al. Uniform assessment and ranking of opioid μ receptor binding constants for selected opioid drugs. Regul Toxicol Pharmacol 2011: 59 (3): 385–390.
3. 3.Somogyi A, Barratt D, Coller J. Pharmacogenetics of opioids. Clin Pharmacol Ther 2007: 81 (3): 429–444.
4. 4.Tremaine, L.; Brian, W.; DelMonte, T.; Francke, S.; Groenen, P.; Johnson, K.; Li, L.; Pearson, K.; Marshall, J.-C. The Role of ADME pharmacogenomics in early clinical Trials: Perspective of the Industry Pharmacogenomics Working Group (I-PWG). Pharmacogenomics 2015, 16, 2055–2067. [CrossRef] [PubMed]
5. 5.AACR Project Genie Consortium; André, F.; Arnedos, M.; Baras, A.S.; Baselga, J.; Zhang, H. AACR Project GENIE: Powering Precision Medicine through an International Consortium. Cancer Discov. 2017, 7, 818–831. [CrossRef]
6. 6.Arendt, D.; Musser, J.M.; Baker, C.V.H.; Bergman, A.; Cepko, C.; Erwin, D.H.; Pavlicev, M.; Schlosser, G.; Widder, S.; Laubichler, M.D.; et al. The origin and evolution of cell types. Nat. Rev. Genet. 2016, 17, 744–757. [CrossRef]
7. 7.Aneesh, T.P.; Sekhar, S.; Jose, A.; Chandran, L.; Zachariah, S.M. Pharmacogenomics: The right drug to the right person. J. Clin. Med. Res. 2009, 1, 191.
8. 8.Lindpaintner K., British Journal of Clinical Pharmacology, 2002; 54:221- 230.
9. 9.Pirazzoli, G. Recchia., Pharmacological Research,2004;49:357–361.
10. Young WP, Innocenti F, Ratain MJ., Clinical Pharmacology, 2006, 62:35- 46.
11. Pirmohamed M and Park BK., Trends in Pharmacological Sciences, 2001; 22: 298-305.