Pharmacogenomics from Bench to Bedside: A Comprehensive Review

Aftab Ullah[1*], Mudassir Khattak[2], Rameen Matloob[3], Sundas Taimour[3], Muhammad Hasnain[1], Suhail Ahmad[4] ,Mehmood-ur-Rehman[5], Haseen Ullah[1], Zaki Ullah[1]

[1]Department of Pharmacy, University of Peshawar, Peshawar, Pakistan

[2]Department of Pharmacy, Abasyn University Peshawar, Pakistan

[3]Department of Pharmacy, COMSATS University Islamabad, Pakistan

[4]North-West General and Research Hospital Peshawar, Pakistan

[5]Kabir Medical College Peshawar, Pakistan

*Correspondence:

Aftab Ullah

Abstract:

Pharmacogenomics investigates how interindividual genetic differences impact on drug response, marking a significant merging of pharmacology and genomics. This review thoroughly examined how genetic susceptibility influences complicated diseases and drug responses, especially in the realm of customized medicine. The Human Genome Project's completion has increased data on genetic variations, leading to progress in medicine discovery and patient care. The importance of genetic indicators like HLA-B*58:01 in predicting adverse medication reactions and improving treatment effectiveness is emphasized in the key findings. In clinical practice, integrating pharmacogenomic data offers a paradigm shift towards tailored treatment strategies that enhance drug safety and efficacy while minimizing adverse reactions. Challenges in translating pharmacogenomics into routine clinical practice include regulatory considerations, standardized validation guidelines, and ethical concerns. Collaborative efforts between healthcare professionals and scientists are essential to navigating these challenges and realizing the full potential of genomic medicine. The future of pharmacogenomics holds many promising aspects to

revolutionize healthcare delivery and improve patient outcomes. Governments can play a pivotal role in reducing healthcare disparities by incorporating pharmacogenomic testing into publicly funded healthcare systems. Education and awareness initiatives are crucial for empowering healthcare providers and the general public to navigate the evolving landscape of personalized medicine.

By embracing international perspectives, technological advancements, and interdisciplinary collaboration, pharmacogenomics has been poised to shape the future of medicine. This review encapsulates the transformative potential of pharmacogenomics in individualizing drug therapies, advancing research, and ultimately enhancing the quality of patient care in the era of precision medicine.

1. Introduction

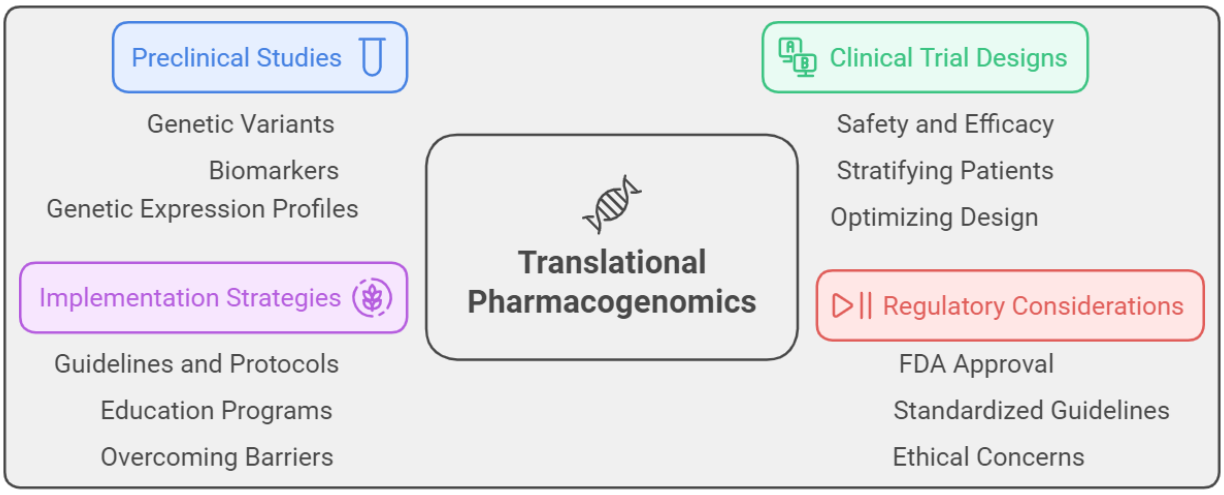
Pharmacogenomics studies genes and how they affect an individual's response to drugs. It is an emerging new field with a combination of both genomics and pharmacology, that aims to develop safe and effective drugs tailored to patient genetic makeup.[1]In the last decade, after the completion of the Human Genome Project, genetic variability in drug response and genetic susceptibility to complex diseases has been observed.[2] Genomics is a crucial aspect of drug development that helps pharmaceutical companies identify novel targets and patient subpopulations. However, transforming this into clinical practice remains a major problem as physicians and patients are not informed about the benefits of Pharmacogenomics. For precision medicine to be effective pharmacogenomics must be completely integrated into the approaches for finding the best drug for prevention, diagnosis, and treatment of disease. Demographic factors (age, sex, body mass) and drug-drug interactions need to be considered. Pharmacogenomics can provide critical insights to improve the process of decision-making for the treatment of choice.[3] The primary aim of pharmacogenomics is to leverage the individual's genetic makeup in optimizing targeted drug interventions, delineating between responsive and non-responsive individuals, thereby amplifying therapeutic efficacy while mitigating the occurrence of adverse reactions. [4] We briefly review the development of pharmacogenomics and the challenges in translating it from the research laboratory to the bedside with aim of personalizing drug therapy.

2. Basics of Pharmacogenomics

❖ DNA, Chromosomes, and Genes

Stretches of DNA, called genes, control the size, shape, and makeup of proteins in living organisms. Drug receptors, enzymes, drug transporters, cellular structural elements, and peptide hormones depend on proteins as shown in **Fig-1**. Their structure has a major impact on their function. Except for red blood cells and platelets, every human cell has chromosomes that contain DNA, which is the basic source of heredity. Some DNA sequences function as recipes and codes that can be translated into protein. These sequences are called genes. The number of nitrogenous nucleotide pairs a gene carries indicates its size. [5]

Fig-1 Molecular Pathway from DNA to Proteins and Their Functional Roles in Drug Response



❖ Genetic variations and drug response

Pharmacogenomics has aided in the prediction of pharmaceutical side effects. The FDA has recommended pharmacogenetic warning labels for many medications in the USA and the European Medicines Agency has followed it. The effectiveness, safety and therapeutic effects of drugs may be influenced by interindividual changes in the pharmacokinetics and pharmacodynamics of drugs due to genetic variations in the metabolism, enzymes and carriers of drugs. Interindividual changes in drug pharmacokinetics and pharmacodynamics may be influenced by the interindividual genetic variability in drug metabolism, enzymes and transporters,

influencing drug efficacy, safety, and treatment results. One example of such a difference is the VKORC1 gene polymorphism seen in the Ashkenazi Jewish community.[6]

❖ Key genes involved in pharmacogenomics

Very Important Pharmacogene (VIP) summaries provide a synopsis of a key gene related to drug response or metabolism. They frequently include variations that exacerbate adverse medication reactions. Tier 1 (genes with strong evidence), Tier 2 (genes with little evidence), and Tier 3 (genes relevant to tumor pharmacogenomics) comprise the three categories based on which PharmGKB classifies the list of VIPs. As new genes are connected to the CPIC clinical criteria, they are added to Tier 1. Tumor pharmacogenomics-related genes are included in the Cancer Genome list.[7]

❖ Techniques used in pharmacogenomic research

Pharmacogenomic research employs a range of laboratory techniques to ascertain an individual's genetic composition. To confirm that the PCR amplification was successful, gel electrophoresis was the next best step after DNA extraction. Pyrosequencing is an automated genotyping method, whereas PCR-RFLP analysis is a traditional method. Denaturing high-performance liquid chromatography (DHPLC) separates variant and non-variant alleles, whereas mass spectrometry separates the DNA molecules. Sanger sequencing, Next-Generation Sequencing (NGS), which may be Whole Genome Sequencing (WGS), Whole Exome Sequencing (WES), Long-Read Sequencing, and Targeted Sequencing. These techniques target protein-coding regions and offer a thorough understanding of a person's genetic composition. They can also aid in the detection of new variants. Pharmacogenomics can benefit from targeted sequencing techniques that selectively enrich particular genomic areas or genes of interest, such as amplicon sequencing or hybrid capture.[8],[9]

❖ Pharmacogenomic databases and resources

Pharmacogenomic databases and resources, such as DrugBank, PharmGKB, CPIC, SCAN, and PACdb, provide information on genetic varia, different drug pathways, and their relationship with drug response. Databases and resources of Pharmacogenomics such as PharmGKB, CPIC, SCAN, PACdb and DrugBank provide information about the genetic variant, drug pathways, and their

relationship with the drug. These resources are crucial for clinical doctors and translational researchers, and offer detailed guidelines of gene/drug clinical practice, evidence-based guidelines of drug targets, interactions, metabolic enzymes, and drug-drug interactions. These resources help advance pharmacogenomic research and aid clinicians in personalized medicine approaches.[10]

3. Translational Pharmacogenomics

❖ Preclinical studies: Bridging bench to bedside

Translational Pharmacogenomics involves the research and development of new drugs, starting with laboratory experiments and progressing to clinical applications. Preclinical research includes the identification of genetic variants, biomarkers, and genetic expression profiles to predict the response or toxicity of drugs as shown in **Fig-1**. This data helps drug developers make informed decisions about which compounds to advance to clinical trials.[11]

❖ Clinical trial designs integrating pharmacogenomic data

To assess the safety and efficacy of new drugs or therapeutic interventions, clinical trial are crucial. Integrating pharmacogenomic data into trial helps researchers assess genetic factors influencing drug response in specific populations, stratifying patients into subgroups with different response profiles, optimizing trial design, and personalizing treatment approaches.[11]

❖ Regulatory considerations and challenges

Translational Pharmacogenomics faces regulatory challenges, including FDA approval for the clinical utility and analytical validity of tests, establishing standardized validation guidelines, ensuring test accuracy and reproducibility, and addressing ethical and privacy concerns. In addition, determining the appropriate level of evidence for the clinical implementation of pharmacogenomic interventions is crucial. [11]

❖ Implementation strategies in clinical practice

Translational Pharmacogenomics involves the integration of pharmacogenomic testing and interventions into clinical practice. Implementation strategies include developing guidelines, protocols, and decision-support tools for healthcare providers. Education and training programs

are crucial for healthcare professionals to apply pharmacogenomic principles. Overcoming barriers like cost, infrastructure, and limited evidence is crucial for successful implementation.[11]

4. Clinical Applications of Pharmacogenomics

Individuals respond differently to medications, which can lead to therapy failure or adverse reactions. This variability is influenced by factors such as individual characteristics, clinical factors, environmental exposure, and genetics. Pharmacogenomics studies the impact of genetic mutations on the response of drugs to improve safe and effective treatment. Changes in the human genome can affect the absorption, distribution, metabolism, and elimination of drugs, which can affect the effectiveness or tolerability/safety of a drug as summarized in **Table-1 [12].**

Table 1 Pharmacogenomic Variants and Their Clinical Implications Across Common Therapeutic Drugs

Drug	Gene/Polymorphism	Effect on Therapy
Antidepressants	CYP2D6*4	Poor metabolizers experience side effects; recommend low doses of SSRIs* and TCAs*.
Antidepressants	CYP2C19	EMs* of sertraline and citalopram; patients on PGx-guided* therapy have better outcomes.
Codeine	CYP2D6	UMs* risk opioid toxicity; PMs* have no therapeutic effect.
Tramadol	CYP2D6	UMs* risk toxicity; PMs* show little therapeutic effect
Statins	SLCO1B1 (521T > C)	Associated with myopathy, especially at higher doses of simvastatin and atorvastatin

Clopidogrel	CYP2D6 (ROF alleles)	Reduced active metabolite formation, leading to higher platelet reactivity and adverse events.
Warfarin	VKORC1 (rs9923231)	Variations explain differences in dose requirements
Warfarin	CYP2C9 (ROF mutations)	Decreased WSD* due to altered metabolism of S-warfarin

***Abbreviations** SSRI (Selective Re-uptake Inhibitors), TCAs (Tricyclic Antidepressants), PGx (Pharmacogenomics), EM (Extensive Metabolizers), UMs (Ultra-Rapid Metabolizers), PMs (Poor Metabolizers), WSD (Warfarin stable dosage)

❖ **Pharmacogenomics in antidepressant and antipsychotic therapy**

Antidepressants are increasing each year, with more than 50% of them being selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and atypical antidepressants. [13] In the human genome, there are 57 potentially functioning CYP genes in which approximately 12 are responsible for the metabolism of one-third of all drugs in clinical practice. CYP-450 enzyme systems are mostly used for the metabolism of antidepressants along with CYP2D6 and CYP2C19.[13] CYP2D6 with more than 100 allelic variants is highly polymorphic, and CYP2D*4 is the most non-functioning variant having the highest frequency in the Caucasian Population. Studies have shown a correlation between venlafaxine with side effects in poor metabolizers of CYP2D6*4, such patients should take a low doses of SSRI and TCAs[14] CYP2C19 is highly polymorphic with more than 2000 variants with 34-star alleles, It extensively metabolizes sertraline and citalopram. A recent meta-analysis study showed that patients taking according to PGx guidelines were 1.71 times more effective for major depressive disorder (MDD) than those on the conventional dose.[15] PGx information has multiple benefits for selecting antidepressant treatments. It can circumvent certain risks associated with polypharmacy.[16] PGx information in psychosis and depression is significant for financial saving by reducing the number of non-useful drug.[17]

❖ Opioid Analgesics

Codeine and tramadol, are the opioid analgesic mostly prescribed for non-neuropathic pain. Codeine is activated to morphine through O-demethylation, while tramadol undergoes CYP2D6-mediated O-demethylation to form O-desmethyl tramadol. In extensive metabolizer (EM) of CYP2D6, approximately 80% of codeine metabolism results in inactive metabolites, and only 5-10% is transformed actively into morphine. In ultra-rapid metabolizers (UMs) of CYP2D6, increased biotransformation of codeine, even with low doses can result in opioid toxicity. Poor metabolizers (PMs) of CYP2D6 have little or no therapeutic effect. Infant opiate toxicity due to the high level of breast milk morphine in the ultra-rapid metabolizers (UMs) mothers has been reported and got international attention for the PGx of codeine.[18],[19]

❖ Statins:

Statins are drugs that lowers lipids and are used to prevent cardiovascular related problem, however they are linked to a higher chance of developing type-2 diabetes and myopathy. The diseases vary from muscle pain to myopathy. Risk of variables include simvastatin dosage, ethnicity, gender, age, weight, diabetes, and the concurrent use of specific medications. The correlation between SLCO1B1 and myotoxicity became stronger with higher doses of the 521C allele, simvastatin, and severity of myopathy. There is uncertainty regarding the relation of SLCO1B1 521T > C and other statins, while some research indicates that 521T might have a stronger impact on people taking high-dose atorvastatin. SLCO1B1 521T > C is linked to various forms of muscle toxicity, except IMNM. Clinical recommendations have been established for simvastatin-SLCO1B1 and atorvastatin-SLCO1B1. [20],[21]

❖ Clopidogrel:

An antiplatelet drug clopidogrel is indicated for different condition such as acute coronary syndrome, percutaneous coronary intervention (PCI), stroke, ischemic heart attack, atrial fibrillation.It is a prodrug, and CYP2C19 is the sole CYP enzyme used in both oxidative stages.ROF alleles of CYP2C19 are associated with reduced amounts of active clopidogrel metabolites in the bloodstream and heightened platelet reactivity under therapy. Two significant randomized clinical trials examined whether therapies utilizing CYP2C19 ROF alleles enhance

clinical results. Recent research indicates that ROF alleles are associated with risk of recurrent stroke, major adverse cardiovascular events (MACE), and greater restenosis in individuals having peripheral artery disease (PAD). Clinical guidelines have been developed for clopidogrel-CYP2C19, advising alternative antiplatelet therapy for individual having CYP2C19 ROF alleles.[22],[23]

❖ **Warfarin:**

An oral anticoagulant inhibits vitamin K, used for the prevention and treatment of venous thromboembolism (VTE), thromboembolism in atrial fibrillation (AF), and after mechanical heart valve replacement. This drug has a wide range of stable dose requirements among individuals, with a 30-fold difference, due to its narrow therapeutic index it is the third most common drug causing hospitalization. Genetic variables accounted for most of the differences in warfarin stable dose requirements, with rs9923231 (-1639G > A) in VKORC1 explaining 6-25% of the variation. CYP2C9 metabolizes the stronger S-warfarin enantiomer, while CYP2C9 ROF mutations decrease the need of WSD (Warfarin Stable Dosage). Multiple randomized controlled trials (RCTs) have investigated the use of genetic-guided warfarin dosing algorithms. Implementing point-of-care genotype-guided warfarin dosing has been proven to notably increases Time in Therapeutic Range (TTR) in real-world anticoagulation clinics. Yet, the utilization of direct oral anticoagulants (DOACs) is on the rise, and additional study is needed to establish the effectiveness of warfarin pharmacogenomics in particular circumstances.[24],[25],[26].

❖ **Metoprolol:**

Metoprolol is a chiral compound used to selectively block β1-adrenoreceptors and used to treat hypertension, heart failure, angina pectoris, arrhythmias, and prevent migraines. Almost 70% of the oral dosage is inactivated by CYP2D, and its poor metabolizers (PMs) are marked with elevated plasma concentrations of metoprolol compared to extensive metabolizers (EMs). Metoprolol lowers cardiac output, decreases heart rate, and raises the risk of bradycardia. The DPWG (Dutch Pharmacogenomics Working Groups) guideline recommends a reduction of dose for patients classified as CYP2D6 PM (Poor Metabolizers) and IM (Intermediate Metabolizers). In some cases, it may be necessary to consider using an alternative β-blocker.[27]

❖ **Allopurinol:**

A xanthine oxidase inhibitor, allopurinol commonly prescribed for gout prophylaxis or hyperuricemia. But there are certain severe cutaneous adverse reactions (SCARs) associated with this drug like Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS). SCARs have high rates of morbidity and mortality. HLA-B expression follows a co-dominant pattern, where patients are at greater risk of severe cutaneous adverse reactions (SCARs) by carrying just one copy of HLA-B*58:01.[28]

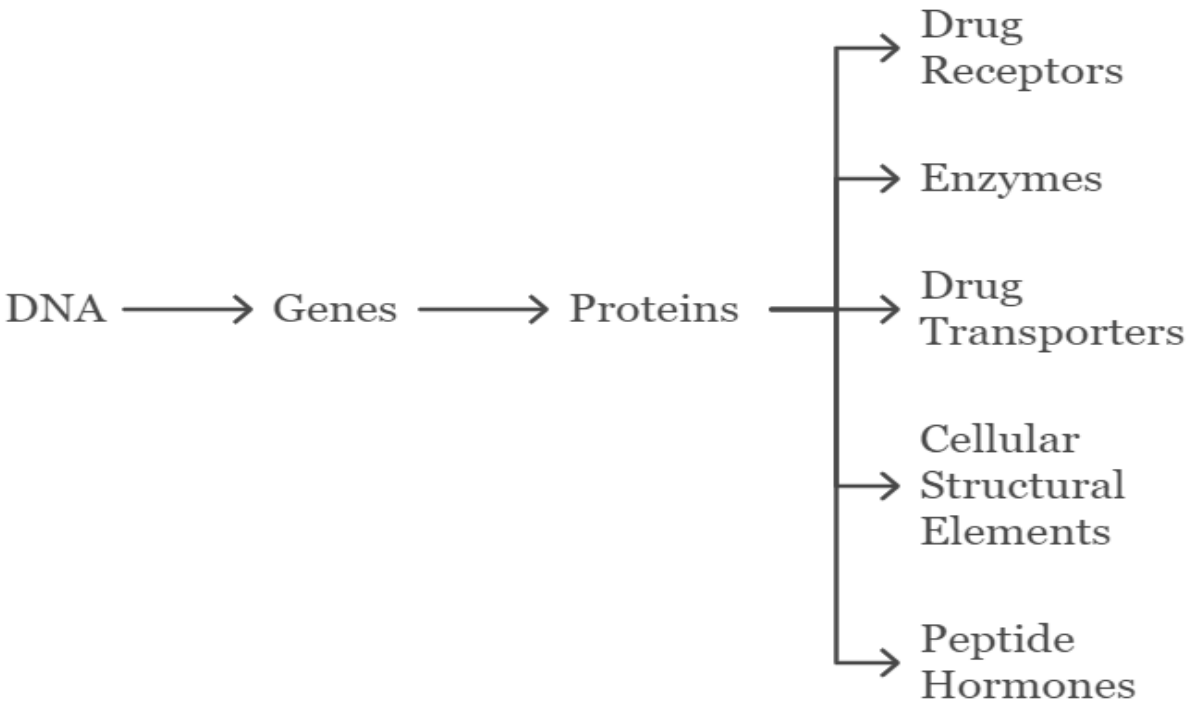


Fig-2 Key components of translational pharmacogenomics

5. Challenges and Future Directions

A treatment idea known as Pharmacogenomics examines how genes affect the reaction of the body to drugs. Owing to interindividual variations in therapeutic responses, despite its potential, its

application in routine practice is difficult. The integration of pharmacogenomics into clinical practice faces challenges, such as genetic variability, enzyme complexity, detection limitations, and factors influencing drug efficacy. Standardization of genomic testing and clinical laboratory processes is also a challenge. Inadequate training and education in this field can hinder confidence in pharmacogenomics. Additionally, the cost and accessibility of pharmacologically oriented diagnoses and treatments contribute to healthcare disparities. Addressing these issues is crucial for maximizing personalized medicine benefits.[29]

❖ Ethical, legal, and social implications of pharmacogenomics

Pharmacogenomics research and implementation must address ethical considerations such as informed consent, privacy, and genetic discrimination. Establishing regulations for genetic testing, data protection, and healthcare use is crucial for ethical practices. Understanding how pharmacogenomics impacts societal perceptions of health, disease, and individual responsibility is essential for successful integration into healthcare systems.[30]

❖ Overcoming barriers to widespread adoption

Barriers to the widespread adoption of genomics testing can be overcome by establishing standardized protocols, addressing reimbursement challenges, and providing adequate training and education to healthcare professionals. These measures can enhance the consistency and reliability of pharmacogenomic results, make these services more accessible to patients and healthcare providers, and increase their confidence in incorporating genetic information into clinical decision-making.[31] Such studies may be extend to the published studies as discussed. [32-41]

❖ Advances in technology and their impact on pharmacogenomic research

Advancements in genomic technologies, such as next-generation sequencing and bioinformatics, have enabled the comprehensive analysis of genetic variations and their clinical implications. Data integration with electronic health records and decision support systems can facilitate personalized treatment strategies based on genetic information. The convergence of pharmacogenomics with other omics disciplines offers a holistic approach to personalized medicine.[42]

❖ Prospects and potential breakthroughs

Collaboration between healthcare professionals and scientists is crucial for genomic medicine as each expert has unique training and expertise. To avoid misinterpretation, experts should collaborate and translate their work to the next recipient of the healthcare network. Governments can make pharmacogenomic testing a part of publicly funded health care, reducing health care disparities. Educating the general public on pharmacogenomics is need of the time, as this field is still being explored. Different countries have different guideline and perspectives for integrating pharmacogenomics into clinical practice. Learning from other countries' approaches and strategies through international summits or panel discussions is worthwhile.[43]

6. Conclusion:

Pharmacogenomics focuses on understanding how genetic variations affect individual responses to medications. Genes such as HLA-B*58:01 associated with severe adverse drug reactions have been identified, highlighting the importance of personalized medicine in optimizing treatment outcomes. Advances in technology, such as next-generation sequencing and bioinformatics, have revolutionized the field, enabling the comprehensive analysis of genetic variations and tailoring treatment strategies. Pharmacogenomics has profound implications for clinical practice and research as it allows healthcare providers to personalize treatment approaches, optimize drug efficacy, and minimize adverse reactions. Standardized protocols, adequate training for healthcare professionals, and decision-support tools are crucial for successful implementation. Collaboration between healthcare professionals and scientists is essential to unlock the full potential of genomic medicine. Governments can reduce healthcare disparities by incorporating pharmacogenomic testing into publicly funded healthcare systems.

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