EURASIAN EXPERIMENT JOURNAL OF PUBLIC HEALTH (EEJPH)

ISSN: 2992-4081 ©EEJPH Publications

Volume 7 Issue 1 2025

Pharmacogenomics: Tailoring Drug Therapies to Individual Genetics

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ABSTRACT

Pharmacogenomics, the study of how an individual's genetic makeup influences their response to drugs, represents a frontier in personalized medicine. By identifying genetic variations that affect drug metabolism, efficacy, and safety, pharmacogenomics aims to optimize therapeutic strategies, minimize adverse reactions, and improve clinical outcomes. This review investigates the fundamental principles of genetics in drug response, highlighting key genes and variants implicated in pharmacogenomics, such as the cytochrome P450 enzyme family. It also examines clinical applications across diverse conditions, ethical challenges, and regulatory considerations. Despite significant advancements, barriers such as the complexity of genetic data interpretation, ethical concerns, and accessibility issues persist. Addressing these challenges through research, education, and policy will be crucial in integrating pharmacogenomics into routine clinical practice and ensuring equitable access to its benefits.

Keywords: Pharmacogenomics, Personalized medicine, Genetic variations, Drug metabolism, Cytochrome P450, Clinical applications.

INTRODUCTION

Human genetics codes for differences in the anatomy and function of proteins in the body. Given that drug molecules are a form of 'keys' to unlock the door of protein 'locks,' it is logical that a person's genetic makeup can significantly influence the response to drug therapy. The goal of pharmacogenomics is to develop rational means to optimize drug therapy by identifying patients who are likely to respond to certain efficacious drugs with a minimum risk for side effects. In many ways, pharmacogenomics grew out of the historical discipline of pharmacology itself, which aims to optimize drug response by understanding principles of drug action and interpreting dose-response relationships. Research to date supports the view that genetic variation directly or indirectly contributes to response variation to most of the commonly used drugs [1, 2]. Pharmacogenomics is the study of the role of the genome in drug response. It aims to set the stage for the imminent arrival of genetics both in diagnosis and in guiding rational drug choice. The term pharmacogenomics can be considered somewhat of a misnomer: while pharmacogenetics implies genetic abnormalities that result either in drug response or drug metabolism, the term pharmacogenomics is applied more widely and also encompasses abnormalities that occur at the protein level, associated with global gene interaction and environmental exposure. Other core terminologies in this area include genetics and pharmacology. The current era is one moving towards 'post-genomic' science where we are no longer focused on cataloging genetic function, but instead are translating this knowledge into new clinical applications. It has become evident that the translation of these fields into the clinics represents a greater challenge than previously thought, which is now increasingly becoming the focus of the 'post-genomic' era. Although there are multiple exciting possibilities, the integration of genomics into clinical practice represents only an incremental advancement for the medical field and not a revolutionary new approach. Nevertheless, the clinical and ethical implications of the knowledge about genetic polymorphism variation in the gene coding for drug-metabolizing enzymes and transporters of relevance to the individualization of drug therapy are truly exciting. New developments in the basic

understanding of these areas provide a myriad of opportunities and challenges for pharmacogenomics [3, 4].

Fundamentals of Genetics in Drug Response

Genetics underpin physical and chemical differences in organisms. In drug response, these differences contribute to the variability in response within a population of individuals. Genetic information can be inherited, provide a blueprint for gene expression, and contain sequences responsible for drug metabolism, drug action, and end-organ actions of drugs. Genetics describes the inheritance of traits from generation to generation. For an individual, the genetic makeup accounts for the inherited potential for drug response as 'who we are.' Therefore, drug response emerges from the interaction of our inherited genetics controlling gene expression (the 'who we are' genetics) with the environmental influence on gene expression. Genetic information is coiled within 46 chromosomes compartmentalized in the nuclei; within the chromosomes, the gene is the basic unit within which instructions for building and maintaining cells, tissues, and organs are stored. Alleles are terms used to describe gene variations that determine aspects where gene function results in the synthesis of one or more proteins, which in turn contributes to the metabolizing of drugs. In general, alleles code for proteins non-functional in metabolism or reduced activity proteins; some alleles, however, may result in enhanced active metabolism. Environmental factors such as diet, age, and concurrent drugs can interact with alleles to modulate gene expression and therefore drug response. Pharmacokinetics and pharmacodynamics are two crucial concepts in understanding how drugs act and result in clinical effects. Single nucleotide polymorphisms are responsible for inter-individual variability in drug responses. Genetic markers are used to predict drug response and to prescribe individualized doses of drugs to optimize clinical outcomes [5, 6].

Key Genes and Variants in Pharmacogenomics

Human genetic variability results in different drug responses and phenotypes in terms of efficacy and adverse reactions. Several genes and variants modify drug pharmacokinetics and pharmacodynamics. One of the more studied gene families is the cytochrome P450, which is related to Phase I oxidation processes of metabolism. Another well-described important gene in this phase of metabolism is thiopurine S-methyltransferase, which is associated with high hematological toxicity from thiopurines. Moreover, allele carriers are at increased risk for adverse events due to mycophenolate [7, 8]. In addition, NAT2, CYP450 2D6, and UGT1A1 are pharmacogenetic genes that are critical for metabolizing several drugs. The UGT1A28 variant causes a decrease in the glucuronidation of MPA. GGM6 leads to a decrease in the elimination of MPA. These genetic factors, when combined with a mycophenolate regimen, can increase the risk of leukopenia or other bacterial infections. Carrier ranges are valuable to reinforce patient follow-up. Genetic testing for UGT1A1 variants is not necessary to determine mycophenolate treatment, but a dose adjustment should be considered if the patient experiences diarrhea, as influenced by UGT1A1, a gene that glucuronidates bilirubin, which leads to reduced UGT activity. Established guidelines for the use of pharmacogenomics; the principal goal of personalized genomic research is to determine which compounds are intrinsically prone to cause adverse effects. An institutional drug that requires a reduced starting dose, based on the patient's genetic profile, is clopidogrel. In contrast to CYP enzymes, UGT enzymes are not overexpressed in tumor cells. Some genes affect pharmacokinetic factors, while others influence the drug's effectiveness and toxicity by encoding membrane transporter receptors and enzymes [1, 9].

Clinical Applications of Pharmacogenomics

The practical application of pharmacogenomics involves the mindful use of genetic information to inform drug choice or dose to achieve better outcomes. Informed interpretation and clinical use of genotype-based drug recommendations may prevent adverse reactions and improve clinical outcomes. Some of the most common conditions in which pharmacogenomics is applied to clinical care include the treatment of cancer, depression, attention-deficit hyperactivity disorder, pain, cardiovascular and gastrointestinal conditions, as well as transplant-related care. Examples also exist in treating patients for elevated cholesterol, schizophrenia, and seizures. Further examples expand concepts surrounding anesthetic and critical care, and the increasing focus on an individual's tolerance to certain drug metabolites for more personalized medication regimens. Depending on the test being used, physicians, pharmacists, genetic counselors, or other healthcare practitioners provide patients with results and recommend future treatment options. Challenges in integrating behavioral, pharmacological, social, and medical care have prevented the widespread use of pharmacogenomic data as routine clinical information. Additionally, results from genetic testing may be challenging to interpret, particularly with the lack of standardization among interpretive results and the potential ease with which raw results are misinterpreted. Educating and preparing patients and healthcare providers to make informed decisions will require significant

resources, time, and effort. Ongoing pharmacogenomics research includes bench work, animal studies, or human subjects and can be seen in clinical trials or case studies. Many pharmacogenomic scientific results are based on small-scale studies to demonstrate the soundness and potential impact of novel approaches. Major research efforts are also working on large-scale genetic studies to investigate an association between the genetic makeup of a population and drug response. These associations are used to understand the contribution of genetics to variable drug response, to eventually support more targeted drug selection and dosage, thereby improving outcomes for specific populations [10, 11].

Ethical and Regulatory Considerations in Pharmacogenomics

Patient consent and privacy represent critical ethical considerations in pharmacogenomic research and practice. Patients' willingness to provide informed consent to having genetic information used in their clinical care is widely recognized as important given the potential psychological and social implications. One of the potential ethical dilemmas in pharmacogenomics is that normalizing variability in treatment response might facilitate genetic discrimination in clinical decision-making. The use of algorithms that incorporate genetic data in prescription decision-making could raise this problem as well. Another potential risk in pharmacogenomics is the risk of access and insurance-related discrimination. Ethical, legal, and social questions about access to genetic testing are also being raised. Some commentators have suggested that because current models of healthcare provision and reimbursement may limit access to genetic testing to certain groups, it is unjust for research to proceed on the basis that pharmacogenomic testing is a universal model of care [12, 13]. In the United States, all tests intended for clinical use, including pharmacogenomic tests, fall under the authority of the Food and Drug Administration. The Commercial Rule states that a "pharmacogenomic assessment" indicates whether the drug can increase the risk of adverse effects due to its metabolism and/or shows the risk for drug inefficacy. Although proteins can play a main role, in principle, the genetic makeup that makes the proteins can also be included in the test intended for clinical use. The Centers for Disease Control has also launched an awareness campaign on the issue of how advances in pharmacogenomics may create new ethical challenges for ensuring equitable access to appropriate medication for all population groups. Ethical and legal considerations cover the use of pharmacogenomics in everyday clinical practice, such as whether or not patients must consent to have their genetic information used to inform their care and how access to such tests is regulated to prevent "genetic discrimination" by insurance companies and employers. In 2011, a conference was held to identify some of the crucial regulatory, ethical, and social issues arising from the growth in the use and application of pharmacogenomics and to address and discuss these issues with a range of international experts. It was felt that the potential for the use of pharmacogenetics was dependent on whether additional regulatory advice was available and that most of the public needed to use either a common or generalist frame of ethical reference to make a judgment. The conference also concluded that there is a pressing need to hold a similar international, interdisciplinary policy dialogue describing and analyzing the key developments and issues in pharmacogenetics and global health and development. It was felt that attendees should include an even balance of researchers, patients, healthcare providers, civil society organizations, international organizations, policymakers, and industrial representatives in a three-day event designed as a high-level policy dialogue rather than a conventional, academic, or expert workshop [14, 15].

CONCLUSION

Pharmacogenomics stands as a promising innovation in the quest for personalized medicine, offering pathways to optimize drug therapies by tailoring them to individual genetic profiles. By understanding the interplay of genetic variations, pharmacokinetics, and pharmacodynamics, clinicians can mitigate adverse drug reactions and enhance treatment efficacy. While the potential of pharmacogenomics is undeniable, its integration into routine healthcare faces challenges, including ethical dilemmas, regulatory hurdles, and disparities in access. Overcoming these barriers requires collaboration across disciplines, robust research, and inclusive policy-making to realize the full potential of pharmacogenomics in transforming medical practice. By fostering awareness, education, and equitable access, the healthcare community can ensure this scientific advancement translates into meaningful improvements in patient care.

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CITE AS: Tugonza Akiro F. (2025). Pharmacogenomics: Tailoring Drug Therapies to Individual Genetics. EURASIAN EXPERIMENT JOURNAL OF PUBLIC HEALTH, 7(1):95-98