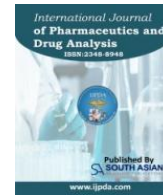




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PHARMACOGENOMICS

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Abstract

Pharmacogenomics represents a cutting-edge fusion of pharmacology, the intricate science of drugs, and genomics, the study of genes. This innovative discipline aims to craft personalized and secure medications, custom-tailored to an individual's unique genetic composition. Within the context of the burgeoning paradigm of personalized medicine (PM), the application of pharmacogenetics and pharmacogenomics (PGx) assumes an escalating significance. In the realm of clinical trials, the incorporation of PGx represents an adjunctive tool meriting consideration, fostering an enhanced comprehension of the efficacy and safety profiles of novel pharmaceutical entities. Foreseeing the near future, pharmacogenomics holds the promise of facilitating the formulation of tailor-made therapeutics to address pervasive health challenges such as neurodegenerative disorders, cardiovascular ailments, HIV, cancer, asthma, and other conditions. This review article covers the overall Pharmacogenomics.

Keywords: Pharmacogenomics, genomics, Applications, Pharmacology.

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Introduction

The terms pharmacogenomics and pharmacogenetics are frequently employed interchangeably, with the initial usage of the former dating back to the year 1997[1]. The regulatory criteria for accreditation set forth by the Canadian Council for Accreditation of Pharmacy Programs and the Accreditation Council for Pharmacy Education in the United States encompass the domain of "Pharmacogenomics." While pharmacy students exhibit a favorable disposition towards pharmacogenomic testing, their self-assurance in applying this knowledge in professional practice is notably diminished. This hesitancy stems, in part, from disparities in the instructional content and methodologies employed in their educational programs [2]. Given the inherent variability in individual responses to drug therapy, accurately forecasting the level of efficacy a medication may have for a specific patient poses a formidable challenge [3]. In addition to the aforementioned clinical determinants, certain pharmacological variables exert a significant influence, encompassing distinctions in metabolism, drug distribution, and

the proteins targeted by drugs [4,5]. Lately, significant sources of variability among individuals have been elucidated, stemming from genetic variances in the encoding of cytochrome P450 (CYP) and other metabolizing enzymes, leading to fluctuations in the plasma concentrations of certain drugs [6,7].

While pharmacogenomics encompasses the entirety of genes associated with determining drug effectiveness and safety, pharmacogenetics specifically denotes monogenetic variants that modify responses to drugs [8,9].

The discipline of pharmacogenomics can be delineated as the examination of genes and their influence on an individual's response to administered drugs. It represents a nascent field that amalgamates elements from both pharmacology (the scientific study of drugs) and genomics (the scientific study of genes) with the aim of formulating precise doses and secure medications customized to the genetic makeup of each individual patient [11].

In this context, the term pharmacogenomics is employed to denote the examination of inter-individual disparities in DNA sequence that contribute to variations in drug response, efficacy, or toxicity. In a broader sense, it encompasses genome-wide variances and potential intricate interactions, along with alterations in expression and post-translational modifications associated with drug responses. The overarching objective is to devise rational approaches for optimizing medication therapy by considering patients' genotypes, thereby augmenting drug efficacy and mitigating adverse effects [12]. Essentially, the

notion of pharmacogenetics remained elusive for over five decades. This investigation delves into the molecular mechanisms responsible for the variability in responses to drugs attributed to inherited traits and the drug development process [13]

Indeed, the implementation of personalized or individualized drug therapy poses a complex undertaking, requiring multifaceted considerations. Challenges arise due to potential gaps in information pertaining to drug actions and genomic factors relevant to critical aspects of disease pathogenesis, particularly in the context of intricate diseases. Additionally, the execution of extensive clinical studies on a large scale can present formidable challenges for researchers [14].

The integration of pharmacogenomics and cancer would broaden the spectrum of specific anticancer drugs, leading to enhanced chemotherapeutic outcomes. [15,3]. Prominent instances within recent clinical and pharmaceutical constraints illustrate scenarios where molecular-based mechanisms contribute to diverse drug responses among patients diagnosed with similar diseases[16,3]. Furthermore, the presence of diverse polymorphisms at the genetic level in genes has been identified to be associated with modifications in drug responses and the incidence rate of adverse drug reactions (ADRs) in human populations [17].

The human genome is estimated to encompass between 19,000 to 21,000 protein-coding genes. Among these genes, various forms of genetic variations can manifest, including single nucleotide polymorphisms (SNPs), indels (small insertion/deletions), and larger structural rearrangements, with SNPs being the most prevalent. Pharmacokinetics (PK) pertains to "what the body does to a drug," while pharmacodynamics (PD) concerns "what a drug does to the body." Genomic variations in genes associated with a drug's absorption, distribution, metabolism, and elimination, such as drug-metabolizing enzymes or transporters, have the potential to modify the drug's PK profile. This, in turn, can influence systemic exposure and lead to alterations in drug response, thereby impacting downstream pharmacodynamics [18].

Ultimately, the advancement of drug development and its regulatory framework through pharmacogenomics holds the promise of facilitating the emergence of novel and precisely targeted drugs. This advancement aims to bolster safe, effective, and economically viable drug therapy for individual patients [19].

Pharmacogenetics delves into the examination of how an individual's genetic makeup influences their response to a drug. This field, intricately linked with genomics, involves genetic-level investigations coupled with functional studies and pharmacology, encompassing both pharmacokinetics and pharmacodynamics. The collaborative integration of these branches contributes collectively to the advancement of medications that are not only safe and effective but also customized in terms of dosage to align with an individual's unique genetic composition [3,20–22].

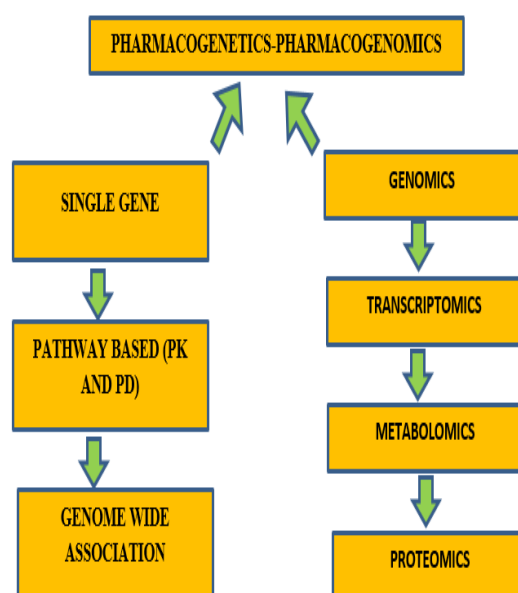


Figure 1: Pharmacogenomics and Pharmacogenetics Development

Instances wherein an individual's reactions to specific drugs are encompassed are represented by conditions such as Stevens-Johnson syndrome or epidermal toxic necrolysis, resistance to clopidogrel, malignant hyperthermia, sensitivity and resistance to warfarin, and deficiency in thiopurine S-methyltransferase [23]. While the integration of pharmacogenomics into clinical practice is progressively expanding, a notable absence persists in terms of an established genetic or any other clinical biomarker that could consistently forecast an individual's response to a chosen Multiple Sclerosis (MS) therapy. Nevertheless, amidst the burgeoning array of approved treatment modalities for MS patients in recent times and the swift strides observed in genomic technologies, the prospect for personalized medicine emerges as a promising avenue to enhance the optimization of treatment for individual patients [24].

Prospective Engagements of Pharmacists in the Clinical Integration of Pharmacogenomics [2].

- (1) Pharmacists should demonstrate competence in providing personalized consultations on pharmacogenomics test results to individual patients.
- (2) Pharmacists should employ pharmacogenomic testing judiciously for suitable patient cases, utilizing the test results to optimize medication therapy.
- (3) Pharmacists should serve as the primary point of contact for patients and healthcare professionals, offering interpretation services for pharmacogenomic test results and disseminating educational resources.
- (4) Pharmacists ought to assume a leadership role in the clinical integration of pharmacogenomics, serving as experts in drug-gene interactions.
- (5) Pharmacists should actively participate in pharmacogenomics research endeavors and contribute to the development of clinical practice guidelines.

Application

- Numerous prevalent diseases, characterized by elevated morbidity and mortality rates, are currently recognized to possess firmly established genetic components. The extent of the genetic influence has been extrapolated for conditions such as obesity and diabetes through meticulous sibling analyses. Similarly, certain uncommon gene mutations offer insights into the intricacies of more sophisticated biological processes [3, 25].
- As an illustration, in cases where individuals exhibit markedly elevated levels of high-density lipoprotein (HDL) in their bloodstream, the demonstrable impact of cholesteryl ester transfer protein (CETP) on HDL levels becomes evident. The proficient implementation and judicious utilization of pharmacogenomic testing across diverse clinical scenarios hinge upon the collaborative efforts of pharmacists and prescribers [26, 27, 3].
- In an alternative scenario, an individual harboring inactivating mutations attributable to the Janus kinase 3 (JAK3) gene manifests a pronounced manifestation of immune-deficient syndrome. This arises from the anticipated impact of JAK3 inhibition on human immune suppression[28,29]. Consequently, this prompted a novel inquiry into pharmaceutical agents featuring cholesteryl ester transfer protein (CETP) inhibition and Janus kinase 3 (JAK3) inhibition facilitated by the principles of pharmacogenetics[30].
- The application of a comprehensive Clinical Decision Support (CDS) system is advocated to aid in the explication of results and provide guidance in the selection of medications and dosages[31]. Moreover, the emergence of pharmacogenomics has facilitated the elucidation of the intricate associations between disease states and human genes, culminating in the judicious selection of therapeutic targets. Presently, a multitude of academic institutions and pharmaceutical enterprises are actively directing their efforts towards probing the intricate connections between disease phenotypes and genetic variations. This initiative aims to refine the classification of diseases for more targeted therapeutic interventions[32,33]
- The aggregation of medical phenotypes correlated with DNA samples offers a significant avenue for scrutinizing the genetic variations present in patients. The exploration of genetic variations entails the collection of DNA from specific patients, as exemplified in a study where the genetic material from an individual participating in lipid-lowering trials swiftly revealed associations between novel phenotypic features of the lipase gene family and HDL levels. The mentioned studies, as corroborated by existing literature, are underpinned by a robust hypothesis intertwined with the judicious selection of biologically relevant candidate genes. This methodology facilitates the seamless juxtaposition of genome selection, exclusively predicated on phenotypic criteria[13,34].
- These phases have replaced approximately 300,000 Single Nucleotide Polymorphisms (SNPs) throughout the genome, leveraging only a select few haplotype-defining SNPs. Perlegen Sciences has pioneered novel genotyping technologies, demonstrating the capacity to genotype numerous markers, ranging from hundreds to thousands, through high-density oligonucleotide arrays coupled with restriction enzyme-based genomic reduction.[3,35].
- The genomic approach, free from the constraints of candidate gene selection, offers enhanced efficiency in comprehending intricate diseases like psychiatric or cardiovascular conditions. Certain scholars posit that expanded insights into Linkage Disequilibrium (LD) coverage, alongside considerations of human genome intricacies and Single Nucleotide Polymorphism (SNP) density, will illuminate a substantial expanse of the genomic landscape and its interplay with phenotypic expressions[36,37].
- To appraise the efficacy of the Perlegen Sciences chip-based array platform and substantiate the utility of the haplotype tagging approach in discerning genetic associations, a total of 7,283 Single Nucleotide Polymorphisms (SNPs) spanning 17.1 megabases (Mb) of DNA were subjected to genotyping for the identification of linkages with High-Density Lipoprotein (HDL) levels. Notably, SNPs affiliated with the 50 CETP haploblock gene emerged as the most consequential associations within the dataset. Entities such as Perlegen Sciences and initiatives like the HapMap project have recently affirmed their commitment to disseminating their SNP markers to public domains, thereby fostering an expanded foundation for subsequent experiments within the scientific community[3,38].
- Conventional cancer treatments, involving surgery and intensive cytotoxic chemotherapies, are linked to notable adverse effects. The pursuit of molecularly targeted therapies, which commenced in the 1980s, entails treatments guided by molecular genetic markers and biological consequences, such as pathway activation or protein overexpression. In the initial stages of discovering molecular cancer biomarkers, proteins or genes with amplification, translocation, or overexpression were evaluated in tumors using techniques like immunohistochemistry (IHC), fluorescent in situ hybridization, or karyotyping.[39]
- Pharmacogenetics constitutes a pivotal augmentation in therapeutic outcomes and drug utilization. Prescribing medications in conservative doses, coupled with vigilant monitoring, is a viable strategy for patients genetically predisposed to adverse events. This approach proves particularly beneficial for drugs characterized by a narrow therapeutic index, such as warfarin, wherein gradual initiation may be instituted for individuals possessing the VKORC1 genotype associated with heightened warfarin sensitivity[3,40].
- Conversely, clinicians possess the potential to attenuate potential adverse effects through the

application of genetic information, thereby aligning appropriate drugs with suitable patients at optimal doses. In the context of hypertension management, the conventional approach involves iterative trials of various anti-hypertensive drugs until the desired blood pressure is achieved with acceptable drug tolerability. [3,41]

- The utilization of Next-Generation Sequencing (NGS) in the examination of clinical trial specimens facilitates a thorough genomic assessment of participants, enabling an expansive exploration of Pharmacogenomics (PGx) analysis that encompasses both prevalent and uncommon genetic variations.[49]

Case Studies for Pharmacogenomics

- Abacavir therapy and HLA testing Abacavir, an antiretroviral drug used in HIV/AIDS treatment, is generally well-tolerated but can cause severe side effects, including lactic acidosis and hypersensitivity reactions. Approximately 5% of HIV-infected individuals may experience severe hypersensitivity reactions to abacavir, presenting life-threatening symptoms. Studies indicate that the human leukocyte antigen (HLA) B5701 allele is a significant factor in hypersensitivity, with its presence indicating an elevated risk. An Australian cohort study reported a 114-fold increase in hypersensitivity reactions among individuals with the HLA-B5701 allele, while an industry-sponsored study found a 24-fold higher likelihood of such reactions. Genetic testing, incorporating pharmacogenetics into clinical practice, is proposed as a potential solution, considering the global distribution of the HLA-B5701 allele. [42,43,10,3].

➤ Opioid analgesic

Codeine and tramadol, weak opioid analgesics, are commonly prescribed for mild to moderate pain. Codeine, an inactive prodrug, undergoes CYP2D6-mediated O-demethylation to form morphine, which has a 200-fold greater affinity for the μ -opioid receptor than codeine. Tramadol, similarly, is metabolized to O-desmethyltramadol with a higher receptor affinity. In normal metabolizers (EM), about 80% of codeine is inactive, with 5–10% becoming morphine. Ultra-rapid metabolizers (UMs) have increased morphine conversion, leading to opiate toxicity. Poor metabolizers (PMs) experience minimal conversion, deriving little therapeutic benefit from codeine [18].

- Muscle relaxant succinylcholine and antitubercular drug, INH In the context of pharmacogenetics, genetic variations influencing enzymatic metabolism, particularly enzymatic hydrolysis and acetylation, act as monogenic traits and contribute to inherited variations in pharmacokinetics (PK). An illustrative example involves succinylcholine treatment, where patients exhibited prolonged muscle paralysis due to an inherited "atypical" butyryl cholinesterase enzyme (BCHE), attributed to a nonsynonymous coding single nucleotide polymorphism (SNP), G209 > A. This

SNP induces alterations in the enzyme's active sites, diminishing its capacity to catalyze succinylcholine hydrolysis and resist dibucaine compound inhibition. The challenges posed by tuberculosis are addressed through investigations indicating that polymorphisms in N-acetyl transferase 2 (NAT-2), CYP2E1, and glutathione S transferase (GST-1) can impact the concentration of liver-toxic isoniazid metabolites in plasma.[3,44,45].

➤ Warfarin

Warfarin, a crucial anticoagulant used for treating conditions like pulmonary embolism and deep vein thrombosis, has a narrow therapeutic index, leading to complex adverse reactions involving coagulation and hemorrhage. The S-form of warfarin is more potent and metabolized primarily by the genetically polymorphic CYP2C9 isoform. CYP2C9 exhibits common polymorphic forms, CYP2C9*2 and CYP2C9*3, with frequencies around 12% and 5% in Caucasians, respectively. Patients with these polymorphisms, identified in 1999, require a lower warfarin dose and face an increased risk of hemorrhage. The cloning of the VKORC1 gene in 2004 revealed that patients with specific haplotypes required lower warfarin doses, with maintenance doses nearly halved for those associated with high-dose maintenance. The combined influence of VKORC1 haplotyping and CYP2C9 genotyping explains about 25% of the dose variance in warfarin.



Figure: Warfarin pharmacogenomics.

VKORC1 haplotypes have a threefold greater impact on an individual's warfarin dose than CYP2C9, making them crucial in estimating the therapeutic dose based on individual genetic properties. In August 2007, the FDA approved a labeling change, recommending lower starting doses for warfarin in patients with specific genetic alterations in VKORC1 and CYP2C9, emphasizing the importance of personalized dosing guided by pharmacogenetic insights [3,46,47].

Challenges

- Global guidelines advise incorporating DNA collection for Pharmacogenomics (PGx) in clinical development. However, diverse international legal frameworks, regulations, and Institutional Review Boards/Independent Ethics Committees (IRB/IEC) often impede DNA acquisition or impose restrictions in PGx

research. Countries like China and Brazil have specific laws governing genetic research, DNA procurement, and biobanking, each impacting multinational trials. Stringent regulations in China, reinforced in 2019 and intensified by the 2019 Biosecurity Law, pose obstacles to sampling, testing, and intellectual property sharing. Similarly, Brazil's regulations and Israel's directives on genetic components in clinical trials add complexity to global pharmacogenomic research. Biobanking laws in many countries also affect a company's preservation of genetic specimens for research.[49]

Outlook for Future

Concurrently, in the European landscape, the Ubiquitous Pharmacogenomics Consortium (U-PGx) is embarking on the inaugural expansive, global implementation initiative aimed at assessing the ramifications of pre-emptive testing on the incidence, gravity, and consequential expenses associated with Adverse Drug Reactions (ADRs) [1].

These instances substantiate the potential efficacy of enhancing patient care through the implementation of pharmacogenetic approaches. However, it is crucial to meticulously define the allelic occurrences of gene alterations within the studied subjects. None of the aforementioned cases holds absolute certainty, necessitating the execution of sensitivity analyses to fortify conclusions against variations in probabilities. Moving forward, paramount attention must be devoted to maintaining the potential cost-effectiveness highlighted in recently published pharmacogenetic-associated reports. For instance, the consideration of vitamin K epoxide reductase gene variants in anticipating the warfarin response underscores the significance of this approach. Lastly, the simultaneous collection of pharmacoeconomic and pharmacogenetic data during industry-funded clinical trials is pivotal for the judicious development of cost-effective theragnostic approaches in a pragmatic manner [3,48].

Conclusion

In the realm of pharmacogenomics, the pursuit of individualized therapeutics, or tailor-made therapy, is a primary objective. Beyond genetic factors, diverse elements contribute to individual responses to drug administration. Recent progress in pharmacology and genomics has empowered physicians to approach the realization of individualized therapeutics. These advances provide avenues for establishing a comprehensive foundation to tailor specific drugs for individual patients, facilitating tailor-made therapy.

Advancements in pharmacogenomics have led to the emergence of fields like pharmacoproteomics, pharmacotranscriptomics, and pharmacometabolomics. These developing branches of science hold the potential to treat each patient as a unique and complex individual.

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Conflicts of Interests

There are no conflicts of interest.

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Authors Contributions

All the authors have contributed equally.

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