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Original Article

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Insights on Pharmacogenetics and Pharmacogenomics: Advantages and Challenges for Healthcare Professionals

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Abstract:

Pharmacogenetics and pharmacogenomics (PGx) have revolutionized personalized medicine by studying DNA's role in drug response variability. While "pharmacogenetics" often relates to genes affecting drug metabolism, "pharmacogenomics" encompasses all genome-related drug responses. The distinction is arbitrary, and both terms are used interchangeably. PGx influences drug efficacy, safety, and dosage, allowing for personalized treatments. Its history dates back to 510 B.C., with Pythagoras noting differential reactions to fava beans. Despite international clinical guidelines, PGx research has gaps, especially in regions like Iraq, where genetic diversity and frequency data are lacking.

Drug responses result from both pharmacokinetic and pharmacodynamic factors, with GWAS aiding gene-drug interaction discovery. Genetic variations in PGx are prevalent, impacting over 50% of prescriptions in the USA and 58% in the UK. PGx influences drug dosages, exemplified by warfarin's sensitivity to CYP2C9 and VKORC1 variants. It also plays a role in adverse drug reactions (ADRs), with immune-mediated ADRs and HLA alleles studied extensively. Genotyping has significantly reduced ADRs, as seen with abacavir hypersensitivity.

Despite challenges, PGx is slowly integrating into clinical practice. Pre-emptive genotyping and panel-based testing hold promise, but validation is essential. PGx has also revolutionized drug development, doubling success rates by selecting genetically supported drug targets.

PGx's future involves addressing ethnic diversity gaps in genomics data and embracing polygenic risk scores. Its potential to shape healthcare and offer tailored therapies makes it a pivotal player in the future of medicine.

In conclusion, PGx is a transformative field that enhances drug therapy, drug development, and disease risk assessment. Overcoming challenges, particularly related to clinical implementation and genetic diversity, is essential to realize the full potential of PGx in shaping the future of healthcare globally.

Keywords: Pharmacogenetics, Pharmacogenomics, Personalized medicine, Drug response, Genetic variations, Genotyping, Adverse drug reactions, (ADRs), Drug development, Ethnic diversity, Polygenic risk scores.

Introduction

Pharmacogenetic and pharmacogenomic (PGx) is the study of the role of DNA sequence in interindividual differences in drug responses and has become an effective tool to fulfill the promise of personalized medicine (1). PGx has transformed our comprehension of the correlation between genes and drug reaction, spearheading enhanced therapeutic regimens in terms of effectiveness and safety. While the designation "pharmacogenetic" is predominantly employed for genes dictating drug metabolism, the term "pharmacogenomic" represents a wider concept that encompasses all genes in the genome that might influence drug response. Nevertheless, the differentiation is capricious and both terms can be interchanged (2).

The diversity in the genetic drug response can vary from poor therapeutic efficacy to severe, potentially fatal adverse drug events. The study of genomic information to enable the discovery and development of novel medicines, as well as the optimization of therapeutic dosage and choice in particular individuals to minimize toxicity and maximize efficacy, are broader definitions of precision medicine (Figure 1). Because of this, PGx is the component of clinical genomics that will almost probably experience the quickest and biggest clinical deployment, with the potential to eventually affect every patient's care worldwide (3).

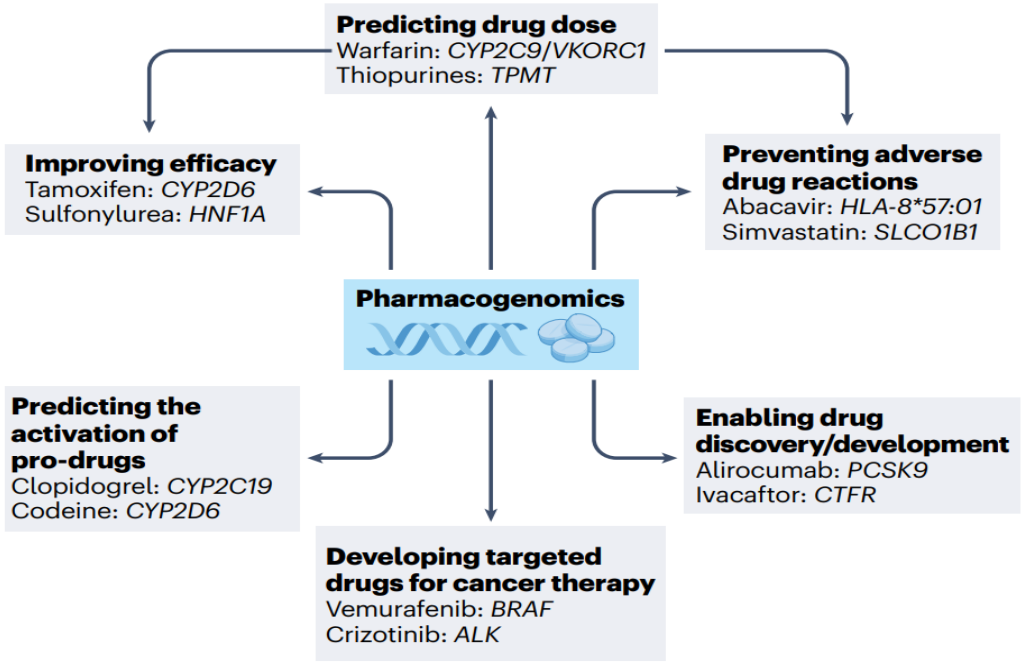

Fig. 1: The panorama of pharmacogenomics. PGxs are significant for expecting drug dose e. g. thiopurines dose (6-mercaptopurine depending difference in thiopurine methyltransferase (TPMT) gene), expecting pro drugs activation (codeine and clopidogrel into more active metabolites), enhancing drug efficacy e. g. sulfonylureas used in cases with sporadic mutations of HNF1A, and by prospectively genotyping individuals for at-risk alleles e.g. SLCO1B1 genotyping (prior to simvastatin treatment), side effects can be avoided. (4).

The first recorded mention of PGx dates back to 510 B.C., when Pythagoras observed that some, but not all, people experienced a possibly deadly reaction after consuming fava beans (5). Numerous turning points since then have altered this area of study and sparked the current wave of interest (6). Despite global efforts to create clinical recommendations for everyday use, the majority of research comes from the United States and Europe, frequently omitting or generalizing the Arabic community (7).

Scientific societies have recently worked to decrease this gap, but Iraq in particular faces special difficulties due to the country's extensive

genetic variety and differing frequencies or polymorphisms from other locations. Furthermore, the region lacks knowledge of frequency data and high-quality, population-focused studies on the links between genes and pharmacological responses. These elements work together to hinder the use of PGx in clinical settings in the Middle East. This review tries to focus on the PGx as a novel tool for enhancing prescription medication therapy in the future.

Basis of gene-drug associations

Drug responses are influenced by both pharmacokinetic and pharmacodynamic variables. We currently know more about drug-gene interactions than we do about pharmacodynamic interactions, which is a reflection of our greater understanding of drug pharmacokinetics than drug mechanisms of action (8). Significant progress has been made in the past 50 years in understanding how drug pharmacokinetics affect inter-individual variability in drug management. Metoprolol and torsemide pharmacokinetics in twin investigations showed heritability of 91% and 86%, respectively, indicating a considerable genetic contribution to drug pharmacokinetics (9). Genetic variants linked to drug response have been discovered thanks to developments in genotyping, sequencing, statistical genetics, and clinical trial designs, mostly through observational studies of different quality and scope (8).

Genome-wide association studies (GWAS) are a relatively inexpensive and objective way of determining gene-drug relations. They may be predominantly crucial for determining pharmacodynamic drug-gene interactions and for revealing new information about the mechanisms underlying toxicity or action. Nevertheless, only $1/10^{th}$ of the papers about the GWAS collection had examined pharmacological response as of yet. Furthermore, unlike the growth in records observed in complex-disease-GWAS (10), the population size for drug-response GWAS does not grown over time. This is most likely a result of challenges with reproducing results, defining a precise phenotype for pharmacogenomic revisions, and gathering sufficient population sample. GWAS has nevertheless revealed that compared to genetic variants linked to other dichotomous complex characteristics, pharmacogenomic variants have bigger effect sizes (11).

Variations of interindividual pharmacogenetics

Genetic variation in PGxs, affecting drug response, is common (12). In the USA, ~50% of prescriptions involve actionable germline PGxs (13), and in the UK, 58% of patients receive drugs influenced by pharmacogenetic polymorphisms (14). Elderly individuals, often requiring drug therapy, are exposed to pharmacogenomic-guided drugs (~90% of those over 70 years) (14). The Pharmacogenomics Knowledge Base (PharmGKB) provides current drug–gene information (14), while PharmVar offers high-quality pharmacogenetic data (15). The FDA lists 517 gene-drug associations in labels (16) and 121 drug-gene interactions (17). Nevertheless, global synchronization in PGx drug labeling remains challenging, impacting patient care. Some genetic interactions, like CYP2D6's impact on tamoxifen, are overlooked, affecting ~1 in 10 women with non-functional alleles (18).

Variations in gene dose association

Genetic variables have a role in dose determination, which affects a drug's efficacy and safety. The clearest example is the blood thinner warfarin, whose daily or weekly dose is determined by polymorphisms in the genes encoding the enzymes responsible for metabolizing it (CYP2C9) and the enzyme it inhibits (VKORC1). Reduced enzyme activity is linked to loss-of-function SNPs in these genes, necessitating lower warfarin doses to achieve therapeutic anticoagulation and prevent overexposure (19). With thiopurines, fluoropyrimidines, TPMT, NUDT15, DPYD, UGT1A1, as well as irinotecan polymorphisms, the germline polymorphisms have established a significant impact on how much anticancer medicine should be used (20).

In each of these circumstances, a polymorphism that either reduces or abolishes the activity of the relevant enzyme is linked to decreased metabolism of the anticancer drug, resulting in systemic overexposure and dose-dependent toxicity, which frequently causes severe diarrhea and/or bone marrow suppression (21).

Variations in gene adverse drug responses

Type A and type B adverse drug responses (ADRs) can both be influenced by hereditary variables, and they both be classified as ADRs. Over the past 2 decades, significant progress has been obtained in determining the inherited risk factors for ADRs. Type A adverse effects are an enhancement of a drug's pharmacologic effects and exhibit usual dose dependence, with a dose reduction resulting in an improvement in the ADR. Type B ADRs, also known as idiosyncratic reactions, are difficult to understand in light of the drug's known pharmacology, don't show a clear dose dependence, and frequently call for drug withdrawal to treat the ADR (22).

There are many immune-mediated ADRs. Significant advancements have been achieved, notably in the understanding of how HLA alleles contribute to these reactions.

Several of the relationships are comparable to Mendelian disorders with GWSA, such as associations with carbamazepine hypersensitivity hepatitis that were seen in 51 affected patients (23). Translational PGxs "poster child" is abacavir hypersensitivity. Anti-HIV medication has been associated with a severe hypersensitivity reaction that can have life-threatening consequences in HLA-B 57:01 (24). Before administration of abacavir, the use of HLA genotyping has virtually eliminated hypersensitivity observed in 5% of HIV cases treated with the abacavir before genotype's implementation. This is why genotyping is advised on drug labels everywhere (24).

Research into the pathways of immune-mediated ADRs has been extensively conducted as a result of advancements in HLA PGx. According to recent research, medications and their metabolites interact with particular that cause tissue damage (25).

Variations in gene Drug efficacy

Only 15% of medications are predicted to have genetic predictors of efficacy with an adequate impact size (26). The identification of heritable factors accounted for efficacy is challenging for the following causes: failure to take the placebo effect into account; poor study design making it difficult to describe drug benefit; the impact of medication non-adherence; insufficient statistical power, especially when efficacy is inhibited; and inadequate assessment of variation in disease phenotypes between different participants (4). As a result, this number may be underestimated. Contrary to all the other examples, the Olaparib link with the mutations of BRCA1 and BRCA2 was discovered before registering process.

Subjects with ischemic cardiac and cerebrovascular illness can benefit from the anti-platelet medication clopidogrel. A third of cases with decreased enzyme activity due to the loss-of-function polymorphisms of CYP2C19*2 or CYP2C19*3 (27) have the pro-drug clopidogrel, which is metabolized by CYP2C19 to its active component. Patients with these SNPs had significant platelet reactivity during treatment and were more likely to experience ischemic events (28). Clopidogrel use in those with coronary heart disease has been a subject of intense discussion and disagreement, but there is now general agreement that it should be used, especially in those having percutaneous coronary intervention.

In variations of CYP2C19 loss-of-function, the administration of an antiplatelet drug excluding clopidogrel decreased major atherothrombotic events by 44% (29). CYP2C19 loss-of-function as well, is linked with a higher risk of ischemic stroke after transient ischemia in intracranial atherosclerosis (30). The risk of stroke at 90 days was decreased by 23% 62 when ticagrelor was used in place of clopidogrel in such individuals. The pro-drug codeine, an opiate painkiller, is converted to morphine by the enzyme CYP2D6. The most extensively researched pharmacogene, CYP2D6, is extremely polymorphic; the PharmVar data repository lists over 133 CYP2D6 allelic variations (31). There are four categories of metabolizers: normal, poor, intermediate, and ultra-rapid.

Poor metabolizers without the CYP2D6 enzyme will have a diminished analgesic effect because morphine, not codeine, is the main source of this medication's analgesic efficacy (32, 33). Loss-of-function polymorphism frequencies range from 0% in West Africa to 12% in the UK 32, depending on the ethnic group. For instance, only 2% of people in the UK had ultra-rapid metabolisms, compared to 39.5% in Algeria (18). With 2 or more gene copies on the same chromosome, ultra-rapid metabolizers often need greater doses of active medications to have a

therapeutic impact. Pro-drugs, on the other hand, require smaller doses to have a therapeutic impact in ultra-rapid metabolizers, whilst using a regular dose can have harmful effects.

For instance, respiratory depression can result from enhanced codeine-to-morphine conversion (34). If they are ultra-rapid metabolizers, some children, such as those with obstructive sleep apnea, may be more susceptible to respiratory depression from codeine66. Codeine use post-tonsillectomy (in patients under the age of 18) and for the management of cough in those under the age of 12 is now universally contraindicated due to the lack of widespread availability of CYP2D6 genotyping.

Clinical implementation of PGxs

Pharmacogenomics has been slowly integrated into clinical practice, mostly at specialized facilities. The barriers to wider adoption include doubts regarding therapeutic value, difficulty accessing genotyping tests, cost-effectiveness questions, difficulties interpreting pharmacogenomic results, disturbance to standard clinical workflows, and worries about confidentiality. It's interesting to note that there appears to be a genetic type of exceptionalism, with acceptance of dose modifications based on pharmacokinetic modeling but resistance when the variation results from a genetic mutation with a comparable impact on drug exposure. Clinical usefulness must be demonstrated, although it may not always be possible to do so exclusively through resource-intensive randomized controlled trials (RCTs) (4, 35).

RCTs encounter challenges because of their high costs, poor generalizability, moral quandaries, and difficulties in designing trials that take into account polypharmacy and many gene-drug interactions. Low population allele frequencies are another problem for RCTs, making large sample sizes necessary (35). A thorough analysis of all evidence kinds is required to enable clinical application. To optimize patient outcomes, implementation processes must be constantly monitored in the actual world (36, 37).

To assist the introduction of pharmacogenomic research in the British National Health Service (NHS), the Physicians of the Royal College and the UK Pharmacology Society have made proposals that include pre-emptive genotyping (38). As shown in certain US settings (4), this strategy entails genotyping individuals using a pharmacogenomics panel and archiving data in electronic health records for later use. Genotype-guided therapy decreased adverse drug reactions (ADRs) by 30%, according to prospective research by the European Ubiquitous Pharmacogenomics project, providing randomized support for panel-based pharmacogenomic testing (39, 40).

Pharmacogenomic guidelines have been developed by several organizations. These recommendations should, however, also cover test eligibility requirements. Given that pharmacogenomic testing depends on variant allele frequencies, determining its cost-effectiveness is crucial (41, 42). In Asian, but not in European people, genotyping for HLA-B*58:01 to avert ADRs with allopurinol is cost-effective (43). Such a strategy might bring about disparities based on racial differences in allele frequencies between nations.

Variations in gene Drug bio-techno-pharmacology

Drug development is highly expensive and fraught with risk, with a failure rate exceeding 96% and a staggering estimated cost of approximately $1.3 billion per drug (44). Genomic data have emerged as powerful tools to enhance success rates in drug development. Notably, the selection of genetically supported drug targets has doubled the successful rate, particularly in phases of clinical development (41). In 2021, approximately 2/3rd of FDA-approved medications, mainly in oncology, were grounded in human genomic evidence. An open-access database, “Open Targets”, aids in detecting and prioritizing genetically supported drug targets.

Sequencing technologies in oncology have identified driver mutations in somatic cancer genes, leading to drugs targeting these mutations and improving patient prognosis (45). Examples include Vemurafenib and Crizotinib, which have demonstrated success in inhibiting BRAF and ALK, respectively. Tyrosine kinase inhibitors like imatinib, targeting the BCR/ABL1 fusion gene in chronic myeloid leukemia, have dramatically improved patient life expectancy (46). In solid tumors, challenges persist in finding optimal

combination therapies for sustained progression-free and overall survival.

Germline genetic variation can predict drug toxicity, reducing clinical development risks. For example, the DGAT1 inhibitor AZD7687 led to severe diarrhea in a phase I trial, reflecting DGAT1 mutations' effects in a specific population (47). Genetic insights can potentially modify or prevent the development of drugs with known phenotypic consequences. Statins like simvastatin have been associated with cataracts, with genetic analysis revealing that low-activity yypes of the HMG-CoA reductase gene variation are associated with Parkinson's disease (48).

Future perspectives

Population biobanks with associated genomics data offer a cost-effective opportunity for pharmacogenomics research due to their potential for larger sample sizes compared to traditional studies. For instance, BioVu demonstrated a significant cost advantage, with biobank studies costing approximately $77,000 compared to traditional studies exceeding $1.3 million, although biobank data may have coding accuracy and superficial phenotype limitations. While biobanks provide advantages, both biobank and traditional studies remain complementary rather than competitive for diverse phenotypes (41, 49).

Pharmacogenetics of rare variants

The heritability of drug response remains largely unknown. In at least one or more communities, 65 drug-response related alleles that are thought of as minor (variants) in the general population are existing as major alleles (incidence rate ≥0.5) (50). Rare variants, prevalent in pharmacogene (10.8% of putative functional variants), might contribute to the missing heritability (4). Incorporating rare variants into clinical implementation requires large, well-curated biobanks and novel study designs. Predicting rare variant functionality through in silico methods, including AI, is promising (51).

Pharmacogenomics and Polygenic Risk scores

The use of polygenic scores for pharmacogenomics, stratification, and disease risk assessment is becoming more popular (52). Warfarin dosage algorithms with RCT support are among the applications. Clopidogrel, beta-blockers, and drug-induced liver damage all offer potential for polygenic scores, but replication is necessary. Large sample sizes are necessary, maybe from biobank data. Early intervention may be made possible by disease risk classification using polygenic scores (4). Implementation is reliant on affordability, predictability, and healthcare environments, which face the same difficulties as pharmacogenomics integration.

Pharmacogenomics and genetic diversity

Ethnic health disparities have been exacerbated by the prominent focus on European ancestry in genomic studies and polygenic scores (53). With warfarin dosing algorithms based on European-specific SNPs, pharmacogenomic research likewise lacks variety. African-specific genes impacting medication metabolism are rarely taken into account while writing drug labels (53). Similar to this, European variations are primarily targeted by DPYD genotyping for anticancer drugs (54). Programs like Qatar-Genome-Program, H3 Africa, and All of the US Research Programs are making progress in attempting to diversify genomics data, however, there are still difficulties in correlating ethnic-specific variations with pharmacogenomic results (4). Building capacities across nations is essential for addressing these discrepancies.

Conclusion

Pharmacogenetics and pharmacogenomics (PGx) have emerged as powerful tools in the realm of personalized medicine. These disciplines often used interchangeably, have significantly deepened our understanding of how genetic variations influence individual responses to drugs. PGx has not only enhanced the efficacy and safety of drug regimens but has also opened new avenues in drug development and disease risk assessment.

The journey of PGx dates back to ancient times when observations of differential responses to substances like fava beans hinted at underlying genetic factors. Today, we stand on the cusp of transformative healthcare driven by genomics. Nevertheless, the road to comprehensive integration of PGx into clinical practice remains fraught with challenges. Clinical implementation hinges on demonstrating therapeutic value, expanding accessibility to genotyping tests, ensuring cost-effectiveness, and overcoming

interpretational complexities. Pre-emptive genotyping and panel-based testing have shown promise but require further validation.

PGx is not limited to clinical applications alone; it has revolutionized drug discovery by identifying genetically supported drug targets and enabling precision medicine in cancer treatment. Genetic insights have illuminated pathways for drug toxicity prediction and prompted the reevaluation of drugs with known phenotypic consequences.

To realize the full potential of PGx, addressing ethnic diversity gaps is paramount. Global efforts to diversify genomics data, bolster biobanks, and improve clinical implementation must persist. Collaboration, capacity building, and ongoing research are essential to ensuring equitable access to personalized medicine for all populations. In the coming years, PGx will continue to shape the future of healthcare, providing tailored therapies and advancing drug development, ultimately benefitting patients worldwide.

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