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Pharmacogenomics: Bridging the Gap between Pharmacology and Personalized Medicine

Abdullah Ibrahim Henishi[1], Salman Hutayl Alshammari[2], Ahmed Abdulaziz Samkri[3], Saud Ahmad Hassan Al Zahrani[4], Thamer Huthith Almutairi[5]

[1,5]Pharmacist, Prince Sultan Military Medical City, Riyadh KSA
[2,3,4]Pharmacy Technician, Prince Sultan Military Medical City, Riyadh KSA

ABSTRACT

Pharmacogenomics is an emerging discipline that links pharmacology and personalized medicine by studying genetic variation in response to drugs. Genetic variations in genes encoding drug-metabolizing enzymes, transporters, receptors, and immune-related molecules are crucial for drug pharmacokinetics and pharmacodynamics, with resultant influence on therapeutic efficacy and the frequency of ADRs (Evans & Relling, 1999; Roden et al., 2019). However, failure to consider this genetic diversity in conventional "one-drug-fits-all" therapeutic regimens leads to ineffective patient treatment, drug toxicity and elevated healthcare cost (Wilke et al., 2007).

This review is a summary of clinical evidence and the molecular mechanisms that underlie pharmacogenomics, focusing on clinically useful genetic markers like CYP2D6, CYP2C19, CYP2C9, TPMT, SLCO1B1; and HLA alleles which have profound effects in drug metabolism, toxicity and dosing in various disease conditions (Ingelman-Sundberg 2004; Johnson and Cavallari 2013). Genomic technologies, such as next-generation sequencing, genome-wide association studies and bioinformatics approaches have more rapidly identified actionable variants that can be implemented into clinical care (Relling and Evans, 2015).

The clinical practice of pharmacogenomics is reinforced by evidence-based guidelines and decision support tools developed by global consortia, which seek to facilitate the standardization for genotype-guided prescribing and improve patient care (Caudle et al., 2014). Nonethe- less, barriers like clinician unfamiliarity, costs and infrastructure impediments, the population-specific nature of genetic variation and ethical, legal and social issues surrounding genomic information continue to be formidable challenges to broader uptake (Shuldiner et al., 2013; Vassy et al., 2017). New methods combining pharmacogenomics, AI, electronic health records (EHRs), and multi-omics data are anticipated to improve clinical utility and scalability (Topol, 2019). In general, pharmacogenomics is a foundation of precision medicine and promises a course to safer, effective and patient-centred drug treatment.

Keywords: Pharmacogenomics; Personalized medicine; Precision pharmacotherapy; Genetic polymorphism; Drug metabolism; Adverse drug reactions; Clinical implementation; Genomic medicine

INTRODUCTION

Variability in drug response among individuals is a well-recognized problem since the early days of clinical pharmacology and it still stands as one the major obstacles to optimal therapeutic results. When treating different patients with the same drug at equivalent doses determine to be associated, have been observed great variabilities in efficacy, tolerability and safety, that can cause clinical response failure or severe ADRs. ADRs are one of the major concerns of hospitalization and drug withdrawal in worldwide, emphasizing that therapy strategies based on population averages cannot account for individual biological diversity (Evans and Relling, 1999; Wilke et al., 2007). These observations have stimulated the hunt for predictors of drug response beyond age, sex, body weight, organ function and environmental factors and have led to genetics being placed at the foreground of precision therapeutics.

Pharmacogenomics is one of the most important scientific disciplines which deals with genetic variations in the human genome and their influence on drug response at pharmacokinetic as well as pharmacodynamic level. Polymorphisms in genes that encode such enzymes, for example those of the cytochrome P450 (CYP) superfamily as well as drug transporters, ATP binding cassette or solute carrier proteins and receptors/ enzymes targets can have dramatic implications on a drug's exposure and clinical response (Ingelman-Sundberg, 2004). Furthermore, polymorphisms in immune-related genes, particularly human leukocyte antigen (HLA) alleles are strongly linked to severe and sometimes fatal adverse reactions, thus emphasizing the importance of genetic determinants in drug safety (Relling and Evans, 2015).

The introduction of pharmacogenomics into the clinic is part of a larger initiative to achieve more personalized or precision medicine, in which prevention, diagnosis, and treatment will be customized based on patient-specific factors. Whereas classical pharmacogenetic studies typically examined a single gene–drug interaction, a genomewide approach facilitates the investigation of more complex, multigene contributors to drug response (Roden et al., 2019). This transition has been facilitated by the fast development of genomic technologies including next generation sequencing (NGS) and genome-wide association studies (GWAS), which have turned genetic testing into a more rapid, accurate and increasingly cost-effective procedure.

Pharmacogenomic findings with the greatest clinical impact have generally been in therapeutic areas in which drug response is characterized by low to moderate response variability and for which consequences of inappropriate therapy are substantial. In the field of oncology, there is a continual need for pharmacogenomic biomarkers to assist in selection of target therapies and dosing of cytotoxic drugs with therapeutic concentration rather than toxic concentrations. Cardiovascular medicine and psychiatry have shown a beneficial enhancement in safety and efficacy of anticoagulants and psychotropic drugs by using genotype-guided dosing (Johnson & Cavallari, 2013). These efforts have resulted in clinical guidelines and consensus recommendations with the ultimate goal of further promoting the integration of pharmacogenomics into clinical practice. International cooperation has proved instrumental in translating genomic evidence into guidance around the prescription of medications and clinical decision supports (Caudle et al., 2014).

Despite these developments, the use of pharmacogenomics in routine clinical care varies among healthcare systems and geographic regions. Obstacles include low clinician knowledge and skill, population-level differences in the genetic nature of disease, poor infrastructure for testing, inadequacies in reimbursement, and conflicting ethical, legal, and social implications regarding information privacy, consent and equity of access (Shuldiner et al., 2013; Vassy et al., 2017). Solving these problems is a prerequisite to achieving accessibility of this technology not only for some special centres or populations but for the health system as whole.

This review is intended to give an overview of pharmacogenomics as a bridge between classic pharmacology and optics of medicine. The review is intended to emphasize the crucial role PGx plays in facilitating precision pharmacotherapy and foster patient-centered care in contemporary health-care system through overviewing biological background of gene–drug interactions, technological development, clinical applications and implementation issues.

Methodology

We performed a systematic structured narrative review to overview the current evidence on pharmacogenomics and its potential as a link between pharmacology and personalized medicine. The process was developed to be transparent, reproducible, and focused on clinical and translational research.

Literature Search Strategy

A full literature search was done using the main scientific and biomedical databases, including PubMed/MEDLINE, Scopus, Web of Science and Google Scholar. Search was conducted for peer-reviewed articles published mostly in English within January 2000 up to the most recent available literature, considering the rapid advance of pharmacogenomics. Keywords and Boolean combinations used were pharmacogenomics, pharmacogenetics, personalized medicine, precision pharmacotherapy, genetic polymorphism, drug metabolism, cytochrome P450 clinical implementation AND genotype-guided therapy. The reference lists of appropriate review articles and key papers were hand searched for additional eligible publications (Relling & Evans, 2015; Roden et al., 2019).

Eligibility Criteria

Inclusion and exclusion criteria were predetermined for studies to be included in the analysis. Articles considered were original research, systematic reviews/meta-analyses, clinical guidelines and consensus statements on genetic basis of drug response; pharmacogenomic technologies or its clinical applications. Experiments involving animal models and in vitro methods that did not have clinical implications, conference abstracts in the absence of full text articles, and non–peer-reviewed studies were also excluded unless they reported important contextual or methodological information.

Study Selection and Data Extraction

Titles and abstracts identified from the database search were reviewed for relevance independently. Full text articles were obtained for studies that met the inclusion criteria, or where it was unclear if criteria were met. Data were collected using a structured format that included study design, patient population, genes and drug categories assessed in individual studies, clinical outcomes, and major implications. Emphasis was given to widely-validated gene–drug pairs that have known or emerging clinical relevance (e.g., cytochrome P450 enzymes, drug transporters, HLA alleles) (Ingelman-Sundberg, 2004; Johnson and Cavallari, 2013).

Data Synthesis and Analysis
Due to the variety of study designs and populations, as well as heterogeneity in outcomes, a narrative qualitative synthesis was performed instead of a quantitative meta-analysis. Results were categorized into major domains that included molecular mechanisms of pharmacogenomic variation, technological aspects of genomic testing, clinical implementation strategies, and ethical -- legal -- social implications. Where possible, clinical trial and real-world use study evidence were emphasized to illustrate translational potential (Shuldiner et al., 2013).

Quality Assessment
Methodological quality and level of evidence of the included studies were evaluated according to based criteria for study types. The clinical guidelines and consensus documents were assessed for the methodological quality and clarity of recommendations, whereas observational and interventional studies were evaluated according to the sample size, validity of genetic testing methods utilised, as well as clinical outcome reporting. This assessment guided interpretation of results and knowledge gaps (Caudle et al., 2014).

Reporting Framework
The manuscript was written according to the guidelines for conducting narrative and scoping reviews, and we made every effort to ensure clarity, consistency, and comprehensiveness. Ethical issues pertaining to genetic research and reporting were observed in the process of the review.

Using this approach, the review seeks to offer an integrated and contemporary summary of pharmacogenomics studies, focusing on its scientific basis, and clinical implications, as well as future developments in personalized medicine.

RESULTS

A substantial and consistent evidence supporting the contribution of pharmacogenomics to the inter-individual variability in drug response, as well as its potential value in increasing the effectiveness and safety of pharmacotherapy, was found during the literature analysis. The discoveries are compiled by major points of encounter, such as genetic predictors for drug response, technical innovation, and medical utilization and dissemination.

Genetic Determinants of Drug Response

Drug-metabolizing enzyme genetic polymorphisms emerged as the most widely studied and clinically relevant drug response predictors, in several studies. Polymorphisms in cytochrome P450 enzymes, especially CYP2D6, CYP2C9 and CYP2C19 which were frequently associated with changes in drug metabolism resulting in wide differences of plasma concentrations of the drug are observed among individuals on treatment as well as varying therapeutic efficacy and occurrence of side effects (Ingelman-Sundberg, 2004). Poor, intermediate, and ultra-rapid metabolizer patients showed predictable changes in response to treatment, emphasizing the need for genotype-directed dosing approaches.

Furthermore, drug transporter genes, such as SLCO1B1 and ABCB1, in addition to metabolic enzymes were demonstrated to modulate drug absorption and tissue distribution. These variants were particularly interesting in the context of statins and other cardiovascular drugs, as transporter-related genetic variation was associated with elevated risk of developing drug-induced toxicity (Johnson and Cavallari, 2013). Immune-related genetic markers including certain human leukocyte antigen (HLA) alleles showed significant associations with some sever hypersensitivity reactions to drugs and underscore the importance of pharmacogenomics in drug safety advances (Relling and Evans, 2015).

Advances in Pharmacogenomic Technologies
In all studies included, it was consistently reported that the implementation of novel genomic technologies has revolutionized the identification and clinical interpretation of pharmacogenomic variants. The advancement of next-generation sequencing and genome-wide association studies allowed for the joint evaluation of multiple genes, which should provide a more robust measure of variability in drug response when compared to single gene approaches (Roden et al., 2019). Reinforcement of assessments by bioinformatics and access to the latest in databases for curated variants further increased the validity and practical usefulness of results of genetic testing, and justified using these results as a basis for clinical recommendations.

Clinical Applications and Therapeutic Impact
Results from randomised clinical trials and real-world implementations studies had shown that pharmacogenomics-guided treatment leads to better outcomes in the many conditions studied. In cancer, selection of treatment on the basis of genotype was linked to better response and less toxicity. Cardiovascular and Psychiatric Medicine Task Genotype-guided

(Pharmacogenetic) doses reduced the number of adverse drug events and increased medication adherence in cardiovascular medicine, psychiatry (Johnson, Cavallari, 2013). Together, these findings provide clinical evidence for the utility of pharmacogenomic-based individualised drug therapy to improve patient safety.

Implementation and Clinical Decision Support

The findings also demonstrated that evidence-based guidelines and clinical decision support were enablers to the implementation of pharmacogenomics into routine care. A number of studies reporting guideline-based implementation have shown increased prescribing accuracy and clinician confidence in data entered into electronic health records (Caudle et al. Yet there was variability in implementation success at health systems, largely influenced by differences in infrastructure, clinician education and population-level availability of genetic data.

Challenges and Knowledge Gaps

Although there is strong evidence for its clinical utility, the literature reviewed highlighted continuing difficulties in translating pharmacogenomics into routine practice. These concerns comprised the general underrepresentation of diverse populations in genetic studies, uncertainty about costeffectiveness specifically in certain settings, and issues related to ethics associated with processing, storing and consenting for genetic data (Shuldiner et al., 2013; Vassy et al., 2017). In combination these results provide evidence for the necessity of ongoing research and policy advocacy to support fair and efficacious integration of pharmacogenomics into standard clinical practice.

In summary, the findings of this review highlight pharmacogenomics as a strong scientific and clinical foundation for personalize medicine with obvious value in maximizing drug efficacy; decreasing adverse drug reactions, and thus enhancing patient-centered therapeutic effects.

DISCUSSION

The results of the present review support the importance of pharmacogenomics in dealing with chronic problems in pharmacotherapy due to interindividual variation in drug response. The compiled evidence highlights that genetic variation has a major impact on drug metabolism, transport, target binding and immune-mediated toxicity with implications for both efficacy and safety. These findings underpin the notion that pharmacogenomics is a key connecting piece between classic pharmacology and personalized medicine, taking clinical practice from a purely empirical to a precision-based utilizing one approach in drug treatment (Evans and Relling, 1999; Roden et al., 2019).

One of the aspects revealed by different studies in the literature is the clinical importance of genetic polymorphisms of drug-metabolizing enzymes, especially cytochrome P450s. Allelic variants in genes for such enzymes as CYP2D6, CYP2C9, and CYP2C19 have been previously correlated with changes in exposure to drugs and with specific differences in clinical outcome. The categorization of patients based on a metabolizer phenotype enables the mechanistic explanation for individual variation in response to treatment, and corresponding clinical relevance as genotype-related dosing reduces number of ADRs and therapeutic failure (Ingelman-Sundberg, 2004). These observations are in concordance with former general pharmacological maxims, and an expansion of these, through a genomic filter to permit individualized therapy.

The conversation here also emphasises the increasing importance of non-metabolic pharmacogenomic determinants (e.g., drug transporters, immune associated genes). Transporter polymorphisms, including in the SLCO1B1 gene, have shown robust associations with drug-induced toxicities (especially in cardiovascular treatments), and HLA variants emerged as strong predictive markers for both severe hypersensitivity reactions. These results emphasize the polymorphism not only in efficacy but also in safety optimization of drugs which is clinically and economically important (Relling and Evans, 2015). Breakthroughs in technology have been paramount to expediting the translation of pharmacogenomics to the clinic.

The evolution of next generation sequencing as well as the development of powerful bioinformatic resources have led to the contamination/identification of clinically actionable variations and conversely paved the way for multi-gene testing strategies. Whereas previous testing approaches that were based on single genes resulted in some clear benefits, genome-wide and panel testing provide a more broad view into the variability of drug responses to inform complex clinical decision making that involves pharmacogenomics (Roden et al., 2019). But the application of genomic information is still difficult, especially for rare variants and population-specific genetic variation.

Although the clinical utility of pharmacogenomics is increasingly recognized, uptake of pharmacogenomics is variable among healthcare systems. Adoption has been enhanced in some areas by the availability of evidence-based guidelines and clinical decision-support tools; however, barriers including inadequate clinician training, inadequate infrastructure for standardized testing, and uncertain cost-effectiveness remain to deter widespread adoption (Caudle et al., 2014). Moreover,

the lack of multiethnic participation in pharmacogenomic research is a concern for the applicability to recommendations and need for studies on specific populations around the world, especially in low and middle income countries (Shuldiner et al., 2013).

Ethical, legal and social issues present additional barriers for the adoption of pharmacogenomics within clinical practice. Ethical considerations Patients with NDDs Recommendations 1–3 Ethical issues around privacy, informed consent and equality of access to testing should be resolved prior to widespread use. Literature examined suggest that clear governance models and patient-focused communication strategies are needed to ensure trust in the public and clinical utility of PGx testing (Vassy et al., 2017).

In the future, integration of pharmacogenomics with artificial intelligence (AI), electronic health records and multi-omics data may provide more accurate predictions and clinical scalability. This level of integration may support prescribing decisions that are led by data and generated in real time, and further the transformation toward truly individualized pharmacotherapy (Topol 2019). In conclusion, this work emphasizes that beyond valuable clinical applications that have already been achieved, the clinical value of pharmacogenomics can be reinforced by ongoing research, education and infrastructure development with support from various stakeholders resulting in its adoption as part of personalized medicine.

CONCLUSION

Pharmacogenomics is now an integral part of contemporary precision medicine, offering a scientific basis for interpreting and managing individual variability in drug response. The data pooled in this review attests to the essential role of these drug-metabolizing enzyme, transporters, drug targets, and immune response genes genetic variants in defining differential drug's effectiveness/safety/dosing needs. In doing so, and by combining knowledge from the genome with principles long-known to pharmacology49 (ie, less variation in drug response than within individuals) and therapeutics that evolved over generations of experience, pharmacogenomics serves as a bridge between population-based prescribing or practice of medicine86 and genuinely personalized use of drugs (Evans & Relling 1999; Relling & Evans 2015).

The clinical practice summaries presented here demonstrate that pharmacogenomic-guided therapy can lead to a decreased occurrence of adverse drug вЂ“related events, improved therapeutic response and increased patient safety in a number of disease settings ranging from oncology to cardiovascular therapy and from psychiatry to infectious diseases. Recent progress in genomics technologies and evidence-based clinical guidelines has also increased the potential of integrating pharmacogenomic information into routine clinical care (Caudle et al., 2014; Roden et al., 2019). These advances demonstrate the increasing maturity of the discipline and its applicability to current healthcare provision.

However, implementation of pharmacogenomics is limited by issues on infrastructure, cost, provider education and awareness, population diversity and ethical-legal social implications. Overcoming these barriers with focused research, standardised implementation structures and policy-level support is required to ensure equitable access and affordable integration of pharmacogenomics into healthcare (Shuldiner et al., 2013; Vassy et al., 2017).

In summary, pharmacogenomics is a paradigm in medicine that closer applies to the concept of individualized medicine. Further research, education, and integration into health systems are needed as well as the adoption of evolving innovations such as artificial intelligence and multi-omics technologies to fully develop the potential for pharmacogenomics. With these ongoing efforts, pharmacogenomics will be a standard part of clinical decision making and will contribute to patient-centric outcomes as well as personalized quality of drug therapy.

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