A Review of Future Scope - Pharmacogenomics

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Received: 12-11-2022; Revised: 16-12-2022; Accepted: 23-12-2022; Published on: 15-01-2023.

ABSTRACT
Pharmacogenomics is the study to identify the role of single gene in drug response. PGx testing is done in case-by-case to promote individualized medication. The Clinical Pharmacogenetics Implementation Consortium (CPIC), and the Dutch Pharmacogenetics Working Group (DPWG) have been advancing the translation of complex PGx. This is done in certain disease condition like depression, diabetes, major depressive disorder, kidney disease, hypertension etc. By using single nucleotide variant, next generation sequencing technologies, long read sequencing. Pharmacogenomics testing also prevent ADR by estimating the gene drug interaction. Its purpose is to unlock some of the difficulties, to use as many facts as possible to improve medicine, and thereby to help all human beings.

Keywords: Pharmacogenomics, Drug, Disease, Medicine.

INTRODUCTION
Pharmacogenomics is the study to identify the role of single gene in drug response. It focuses on the genetic variants that impact drug effects through changes in a drug’s pharmacokinetics or pharmacodynamics2. Incorporation of Pharmacogenomics (PGx) into clinical practice has been steadily increasing.

PGx testing is done in case-by-case to promote individualized medication it is done before drug administration in both as single gene and multiple gene. The efficacy and the toxicity of the drug get vary from person to person because of the variation in heterogeneity. So, by this pharmacogenomics testing, drug with the best efficacy safety profile can be identified. Tests such as blood work, which no need to be repeated. Since, germ line DNA does not change over the course of a person’s life, and thus the long-term benefits of pharmacogenomics results are applicable over the lifetime of the patient. Organisations like Clinical Pharmacogenetics Implementation Consortium (CPIC), the Dutch Pharmacogenetics Working Group (DPWG) have been advancing the translation of complex PGx information into actionable phenotypes that are useful for clinicians while research has focused on PGx integration within health systems, little has been done to facilitate the sharing of PGx results between family members and clinicians3.

History
In 1959, Friedrich Vogel was first to create the term “Pharmacogenetics”, however, the origins of pharmacogenomics were first traced back in 510 BC. Pythagoras confirmed that some individuals ingesting fava beans experienced potentially fatal haemolytic anaemia, whereas others did not. It was later found out that it was occurred due to inherited deficiency of glucose-6-phosphate dehydrogenase (G6PD).

Subsequent studies were performed to identify the pattern of inheritance for many drug effects, and in 1987 it was identified that CYP2D6, the first polymorphic human drug metabolizing gene to be cloned. With gene nomenclature, hundreds of CYP2D6 alleles have been identified. CYP2D6 is highly polymorphic; it accounts for 2–5% of the total hepatic P450 enzymes and it is involved in the metabolism of 25% of all drugs used in clinical practice.

Commonly used opioids, including codeine and tramadol are majorly metabolized by CYP2D6. The analgesic effect of codeine is exposed only by the conversion codeine to morphine; and this effect gets altered between individual to individual depending on metabolism enzymes that are coded by genes. Based on Individuals metabolism their gene alleles are classified into metabolic categories: ultrarapid metabolizer (UM), extensive metabolizer (EM), intermediate metabolizer (IM), and poor metabolizer (PM) ranges from the individual with extensive high metabolism to individual has little or no enzymatic action. This was fact behind patients whose effect varies for “universal” doses of opioids2.

Clinical Application
While pharmacogenetics focuses on a single or a few genes, pharmacogenomics examines genes in all...
chromosomes. Although pharmacogenetics and pharmacogenomics are used interchangeably, for purposes of this review, the preferred term will be pharmacogenomics\textsuperscript{26}. Pharmacogenomics of specific drug therapies psychiatric drugs, anticoagulant, pain killers highlights the limitations and challenges with clinical applications of pharmacogenomics testing. The therapeutic areas were recruited based on the level of evidence for testing recommended the role of pharmacogenomics testing and clinical utility. Clinical utility was based on the frequency of pharmacogenomic testing in the clinical setting. For example, with carbamazepine, the level of evidence of pharmacogenomic testing is high as well as its clinical utility\textsuperscript{26}.

**Personalised Medicine**

For clinical scenarios, genotype is clearly linked to important outcomes, direct genetic testing appear to obviate the need to use race as a surrogate for genetic predisposition in decision-making. However, pharmacogenomics research often involves race to stratify genetic risk: The assumption is that racial categories can sufficiently distinguish populations with high or low prevalence’s of certain genes, allowing clinicians to identify high-prevalence groups for testing\textsuperscript{1}.

Pharmacogenomics (PGx) studies, the optimization of drug efficacy and dosage, and the minimization of adverse drug reactions (ADRs) based on variations and alterations in the genome of each individual. The emergence of organisation has facilitated the development and enrichment of databases such as The Pharmacogenomics Knowledge Base (PharmGKB) and The Clinical Pharmacogenetics Implementation Consortium (CPIC).

These databases have not only organized pharmacogenomic information in a more systematic, standardized, and evidence-based manner, they have also provided clinical recommendations including gene-drug-disease relationships; all of which have fostered the transfer of pure pharmacogenomic knowledge into daily practices and contributed to the development of personalized medicine\textsuperscript{4}.

Genetic polymorphisms coequally impact the science of drug discovery, clinical trials, and dose fixing in therapies. Delivering optimal therapy minimizes trial and error prescribing, thereby avoiding the occurrence of adverse drug reactions (ADRs). This strategy of personalized medicine demands a revolutionary change from the process of drug discovery to the determination of patients who will receive the therapy. So, pharmacogenomics emphasized need for phase transfer, from general gene-based personalized medicine to patient-centric personalized medicine with the support of modern pharmaceuticals for the benefit of patients\textsuperscript{5}.

For example, Allopurinol can cause severe cutaneous adverse reactions (SCARs), which are potentially deadly. Researchers in Taiwan were the first to demonstrate the association of the HLA-B*5801 allele with allopurinol-induced SCARs. The American College of Rheumatology (ACR) recently recommended that people of Southeast Asian and African American descent should be tested for the HLA-B*5801 allele before initiation of allopurinol\textsuperscript{3}.

**Pharmacogenomics and Pregnancy:**

During pregnancy there are not only physiological changes that leads to drug-response variability but also the genes encoding proteins show variability involved in drug absorption, metabolism and elimination of drugs and thus, there are challenges for the safe and effective use of drugs.

Pharmacogenomics helps in understanding the impact of this variability in genes encoding proteins on drug responses and approaches towards the individualized treatment regimens for the pregnant women. This approach results in an effective treatment and lowers the risk of adverse drug reactions (ADRs) which a major cause of mortality\textsuperscript{7}.

**Drug Metabolism during Pregnancy**

Pregnant women are considered to represent a special population as they undergo substantial endocrine and physiological changes like –

- Hormonal shifts
- Expanded plasma volume
- Increased renal clearance
- Changes in protein binding
- Changes in hepatic metabolism\textsuperscript{7}.

Pregnancy is a very dynamic process. The physiological changes mentioned above begin after the conception process and the production of progesterone and oestrogen takes place. These hormones are produced in the ovaries initially and then in the placenta\textsuperscript{8}.

CYP450 enzymes are the major metabolic pathways for more than half of the approved drugs and has an increased activity during pregnancy.\textsuperscript{7} The major organ for the expression of CYP450s is the Liver and are also expressed in the Gastrointestinal Tract, Kidney and Brain\textsuperscript{8}.

CYP2D6 is involved in the metabolism of commonly prescribed drugs to pregnant women and its activity begins to rise in the second trimester and increases to the third trimester\textsuperscript{7}. These drugs include antidepressants, b-blockers and Analgesics and other opioids like oxycodone and tramadol are metabolized by CYP2D6 to their active metabolite oxymorphone and O-desmethyltramadol respectively\textsuperscript{8}. Women with CYP2D6 as extensive metabolizers have increased enzymatic activity during pregnancy and women with CYP2D6 as poor metabolizers have decreased enzymatic activity throughout the pregnancy\textsuperscript{7}.

CYP1A2 is essential for metabolizing psychiatric and asthma medications prescribed during pregnancy as well as caffeine\textsuperscript{7}. During the first trimester of pregnancy the activity of CYP1A2 decreases and have clinical impact for...
other CYP1A2 substrates, especially during the second and third trimester\(^8\).

CYP2E1 plays an important role in metabolizing paracetamol into the hepatotoxic NAPQI metabolite. Although Polymorphisms are identified in CYP2E1 gene, the importance of these variants is not clear. Therefore, predictive genotyping for CYP2E1 activity is not currently possible\(^8\).

Thus, there is genetic variability in drug responses for the medications metabolized by CYP systems and this may result in drug related adverse events. Genetic testing is available to identify every individual’s genotype of CYP genes. This pharmacogenomic information is to be clinically used and to properly interpret pharmacogenomics test results\(^7\).

**Applications of Pharmacogenomics in Pregnancy**

Understanding pharmacogenetic liability is especially important, given that medication use during pregnancy is common and increasing. Antibiotics, antiemetics, and medications used to treat chronic conditions such as asthma, depression, anxiety, hypothyroidism, and pain are among the most common prescription medications during pregnancy.\(^7\) FDA labelling is designed to alert clinicians to potential treatment concerns based on pharmacogenomics information and, in some instances, alert clinicians to when to obtain genetic testing prior to prescribing a medication.

CPIC guidelines are designed to help clinicians understand how to use available genetic information to maximize efficacy and decrease the likelihood of adverse events. At this time, there are no prescribing guidelines specific to pharmacogenomics and pregnancy\(^7\).

**Pharmacogenomics with Disease:**

**Diabetics:**

Monogenic diabetes are single gene defect that results in diabetes usually inherited in an autosomal dominant or receive fashion. Monogenic diabetic can be sub-classified into neonatal diabetes and maturity onset diabetes (MODY). Neonatal diabetes rarely affect 1 in 100000 births. MODY occurs in all cases of diabetes those diagnosed under age of 30 years. MODY cases are mutated by one of four gene are Transcription factors, Hepatocyte nuclear factor 1-alpha (HNF1A), 4-alpha (HNF4A), 1-beta (HNF1B). The biomarkers assisted for genetic testing are C-Peptide, Pancreatic auto-antibodies, Lipid profiles and high sensitivity C-reactive protein. Raising awareness of monogenic diabetes and developing high-quality, affordable genetic testing remain major challenges\(^5\).

The sulfonylureas are continue to cornerstone in type 2 diabetes treatment. The hypoglycaemic are the most common and serious adverse effect of sulfonylureas and it may result in significant morbidity. Sulfonylureas are primarily metabolised by CYP2C9 enzyme in the liver. With CYP2C9*1 as a predominant allele, CYP2C9 is a highly polymorphic gene. On CYP2C9*2 and CYP2C9*3, the common variation has poor metabolism and decreased function. The relationship between CYP2C9 and POR (P450 oxidoreductase) genes is influenced by the risk of sulfonylureas-induced hyperglycemia and the effectiveness of sulfonylurea treatment\(^10\).

**Depression:**

The major obstacles faced by pharmacogenomics applied to depression and other disease and the practical application of research efforts has two different elements. First challenge: the quality and replicability of the research findings. Are they robust enough to guide clinical practice? Second challenge: the very real gap between robust, universally accepted research findings and changes based on clinical practice. Most antidepressants using now a days are monoamine reuptake inhibitors and act at the presynaptic transporters. Before depressed patients may use genetic techniques to improve their treatment, two key stages must take place\(^11\).

Antipsychotics attempt to inhibit mesolimbic dopaminergic neurotransmission by blocking D2 and 5-HT2A receptors, whereas antidepressants try to boost monoaminergic neurotransmission by preventing monoamine reuptake. In phase I, drugs are usually transformed by oxidation, demethylation, reduction or hydrolysis to make soluble compounds, which facilitates the elimination from the body\(^12\).

**Kidney Disease:**

The biomarkers to tailor medication dosing for decades with the measurements like creatinine clearance by nephrologist champions to estimate kidney function. The significant comorbidities and challenges by wide interpatient variability in medical responses by nephrologist patient care. The champions of pharmacogenomics to attain precision medicine in numerous illness areas touched by renal disease\(^13\).

Drug response variability include age, sex, ancestry, drug interactions and underlying liver or kidney disease are commonly recognised. The main objective of the precision medicine initiative is to "give the right drug, at the right dose, for the right patient," with the goal of maximising treatment response while minimising adverse drug reactions (ADR) in specific patients. Studies on pharmacogenomics employ two broad approaches. Single or several genes are first chosen based on pharmacokinetics and pharmacodynamics pathways in relation to the function of drug metabolism or transport, pharmacological targets, or illness vulnerability. Second unbiased approaches can be used, including genome wide association studies exome and whole exome sequencing\(^14\).

**Hypertension:**

Hypertension is one of the strongest modifiable cardiovascular risk factor, affecting a people world-wide. The blood pressure elevation is not only an affecting genetic factors but also contribute to inter-individual...
response to antihypertensive treatment. The antihypertensive drugs including beta blockers, ACE inhibitors, ARB, diuretics and CCB were reviewed by the article. A pharmacogenomic strategy based on the choice of the most effective and we’ll tolerated drug regimen 15.

Cardiovascular is leading cause of death globally, approximately 17 million deaths annually. Many genetic studies have aimed to clarify the causal genes of hypertension over past two decades. Several genetic polymorphism including single nucleotide polymorphism (SNPs), microsatellite and insertions/ deletions associated with hypertension were showed in the study. The genetic polymorphisms on blood pressure responses to antihypertensive therapy, some study failed to detect significant effects or replicate the previous finding 26.

**Major Depressive Disorder:**

Major Depressive Ailment is the most common psychiatric disorder and has the greatest effect on disability in the United States among all biological diseases 17. Depressive disorders are among the most common psychiatric conditions. 350 million people, according to the World Health Organization, are impacted.

The extent to which hereditary variables influence the likelihood of acquiring depressive diseases has been demonstrated in studies on families and twins 18.

**Psoriasis:**

This immune-mediated, chronic inflammatory disease affects 3% of adults and 0.1% of children and adolescents in the United States. Early systemic therapy that targets proinflammatory cytokines connected to the aetiology of psoriasis is thought to not only reduce systemic inflammation but also to improve long-term results by slowing the onset of comorbidities 19. Genetics has a role in the development of psoriasis.

**Pain:**

Around 100 million Americans are affected by pain, which also has an annual economic impact of $60 billion on the US. Pain is described as “an unpleasant sensory and emotional experience that is associated with existing or potential tissue damage or explained in terms of such damage,” by the International Association for the Study of Pain. Acute or chronic pain can be nociceptive, neuropathic, inflammatory, somatic, or visceral in origin 21. An old and ineffective method of pain management is a one size fits all strategy. Patient-specific genomic testing presents a complete and tailored therapeutic approach deserving of more study and evaluation, especially in light of growing genomic data and pharmacogenomic understanding 22.

**Alzheimer’s and Parkinson’s disease:**

Neurodegenerative diseases are common in developed countries where health concerns that place a significant psychological strain on families in developed countries, with important psychological burden for families and high cost for the society. This disease condition shares some common pathogenic mechanisms such as age-related decline, multiple genetic defects distributed across the genome, deposits of abnormal proteins in the brain, and diverse environmental risk factors. Pharmacogenomics accounts for 60-90% variability in drug pharmacokinetics and pharmacodynamics for the neurogenerative disease condition 23.

**Epilepsy:**

The way that different epileptic patients react to their medications varies greatly. Genetic factors heavily influence this variability. A new era in epilepsy treatment, centred on each individual and their unique epilepsy, is being established as a result of recent advancements in the genetics and neurology of the epilepsies 24. The international league against epilepsy defines an epileptic seizure as the brief presence of signs and symptoms. Because of unusually synchronised, intense, or excessive neural activity in the brain. Conceptually, epilepsy is defined as an enduring propensity of the brain to produce epileptic seizures, which have an impact on neurobiology, cognition, psychology, and society 25.

**Technologies**

The evolution of pharmacogenomics simultaneously increased genotyping technologies.

SNV panel testing is commonly used technology in PGx testing, either through commercially available micro-array platforms or with custom arrays 6.

A) **Commercial Arrays:** Two of the smaller commercial arrays are the VeraCode ADME core panel and the VeriDose core panel.

B) **Custom Arrays:** Several of the commercial arrays contain a high number of variants which makes fast turnaround time and interpretation challenges.

C) **Array Developments:** Both commercial and custom arrays are developed specifically for PGx which has multiple arrays with genome-wide coverage.

**Next Generation Sequencing Technologies (NGs):** These technologies are not yet routinely applied in clinical PGx. But often used in PGx research and disease genetics. NGS applications can be roughly categorized into three plans.

A) **Whole exome sequencing (WES),** it focusses on sequencing the coding regions of the genome which cover approximately 1–2% of the entire genome.

B) **Whole genome sequencing (WGS) which is aimed at** sequencing the entire genome, both coding and non-coding regions.

C) **Targeting sequence,** it targets of a region or panel of genes of interest.

**Long-Read Sequencing:** Long-read sequencing has been shown to be capable of solving complex loci genome wide. Currently for diagnosing the complex disease long-read
sequencing has been used. For example, complex genetic disease Parkinson’s disease ATXN10 is repeated.

Limitations of Pharmacogenomics

Pharmacogenomics has the potential to impact clinically relevant outcomes in drug dosing, efficacy, and toxicity, thus resulting in recommendations for testing. However, for PPIs and codeine, pharmacogenomics has not provided conclusive evidence to require such testing. A potential reason is that determining clinical relevance for some drugs will involve both genetic and nongenetic factors. Equally important is determining the extent of contribution of such factors. For example, adherence to therapy, antimicrobial resistance, and concomitant medication use are nongenetic factors that impact H pylori cure rates and all may play a significant role in treating disease. Due to the low prevalence of a specific variant allele in a studied population, numerous pharmacogenomic studies were conducted with small sample sizes. In PPI studies, there was an unequal distribution of homozygous EMs, heterozygous EMs, and PMs, with a smaller number of PMs.

A small sample size is a study design limitation that increases the probability of an error due to a lack of sufficient statistical power. Results from such studies may not be accurate. Pharmacogenetic study should also have sufficient statistical power, with an equal stratification of subjects across groups.

Impact of pharmacogenomics on PK & PD

There has been much interest in understanding the role of pharmacogenomics in ADRs, and this has centred mainly on the involvement of PK factors, in particular, drug metabolism. However, there is now increasing recognition that PD might also predispose to ADRs, although research into this area is not quite as far advanced as that on the pharmacogenomics of PK.

Pharmacokinetics

Pharmacokinetics describes drug process, including absorption, distribution, metabolism, and elimination. Drug absorption depends upon a variety of factors, including drug solubility (lipophilicity), formulation, molecular weight and route of administration. Factors influencing drug distribution include membrane permeability and plasma protein binding. The biotransformation or metabolism of drugs is generally classified into two types; phase I and phase II reactions. Drugs undergoing phase I or no synthetic reactions are oxidized or reduced to a more polar form. Oxidation is usually undertaken by the cytochrome P450 (CYP) enzymes. In phase II or synthetic reactions, a polar group is conjugated to the drug to increase drug polarity, therefore making the drug more soluble. Many drugs that cause ADRs are metabolized by CYP enzymes. The association between CYP enzymes and predisposition to ADRs has been reviewed comprehensively. Polymorphisms in the genes encoding for PK affect drug plasma levels and may result in increases (toxicity) or decreases (lack of drug action) in drug levels, either of which can lead to an adverse event.

Pharmacodynamics

Pharmacodynamics refers to the relationships between drug concentration at its site of action and the magnitude of its biological effect. Most drugs bind to cellular receptors, where they initiate a series of biochemical reactions that alter the cell’s physiology. The main determinants of a given drug’s PD properties are the specific molecular interactions between the drug and its target. The function of drug target proteins can also be influenced by genetic polymorphisms. An important example, discussed further below, is the variation in the efficacy of the beta 2 – agonist salbutamol due to a polymorphism of the gene that codes for beta 2 – adrenergic receptors.

CONCLUSION

Genetics and pharmacology are two sciences that interact in many different ways as pharmacogenomics. The study of such interactions was aroused by some simple observations that indicated that monogenic differences could cause persons to respond differently to a drug. Unfortunately, both the effects of drugs and the effects of genes can vary a great deal, and the interactions of these two turned out to be often so complex that they are frequently hard to understand. Nevertheless, pharmacogenomics is the science that studies these interactions. Its purpose is to unlock some of the difficulties, to use as many facts as possible to improve medicine, and thereby to help all human beings.

REFERENCES


