PHARMACOGENOMICS – A NEW PERSPECTIVE IN CLINICAL HEALTHCARE

S. Karthika [a], PK. Ragunath [a]

ABSTRACT

The post-genome era has heralded the beginning of incorporating genome-wide approaches in processes beginning from drug discovery to clinical prescription with the ultimate aim of viewing modern medicine as personalized molecular medicine. A pioneering step in this direction is the development of Pharmacogenomics – the study of the interplay of genotype and drug efficacy that seeks to identify the variant genes affecting the response to drugs in individual patients. These variations can be used to predict whether a patient will have a good response to a drug, a bad response to a drug, or no response at all. Pharmacogenomic studies encompass the sum of all genes, i.e., the genome with respect to its its impact on pharmacokinetics and pharmacodynamics. Initially termed as Pharmacogenetics, it is now synonymous with Pharmacogenomics.

A classical example cited in literature is the existence of a polymorphism in the metabolism of the antituberculous drug – Isoniazid (INH) that affects the catalytic activity of the acetylating enzyme, thus leading to slow acetylation of INH. Certain populations of the world are associated with this polymorphism making them slow acetylators. Similar polymorphisms have also now been studied in many other genes of pharmacogenomic significance.

The use of non-automated and automated methods for profiling genotypes has tremendously helped to reveal the association of single nucleotide polymorphisms, with their corresponding phenotype.

Apart from the pharmaceutical impact, another significant role of pharmacogenomics has been found in preventive medicine. It also suggests restructuring the current design of clinical trials by considering the relevant genetic variations that may considerably affect the trial outcome. Critical clinical decisions will also be benefitted by the understanding of the genotype-phenotype associations. Thus it has a promising role to play in diverse areas of clinical healthcare including diagnostics, therapeutics, disease prevention and target-based drug discovery.

Pharmacogenomics - the rational genomics-based therapeutic approach requires several important issues to be addressed such as the quantum of information that can be and needs to be divulged to the patient, clinician acceptance and critical ethical and legal questions.

This review gives a brief insight into this developing field that has a vast potential in clinical research and healthcare. A pharmacogenomic approach is a vision for the future where personalized medicine will be focused on the patient who has a disease and not just looking at the disease per se.

Key words: *Single nucleotide polymorphism, pharmacogenomics, pharmacokinetics*

INTRODUCTION

The completion of the Human Genome Project (1,2) in 2003, signified a turning point in the field of biosciences and development of high-throughput technologies. It paved the way for numerous innovations and many scientific advancements of the Post Genome Era in biological sciences. During the course of the project, the presence of sequence variations led to the inclusion in the last part of their last five-year plan to identify and map these variations. With their occurrence roughly every 1000 base pairs, single nucleotide polymorphisms (SNPs) are among the most common genetic variations (3).

The National Centre for Biotechnology Information (NCBI), a division of the National Library of Medicine (NLM) at the National Institutes of Health (NIH) in U.S. has been actively involved in the genome sequencing efforts and is now a popular resource for molecular biology information (1). It played a key role in launching an initiative towards identifying and mapping the SNPs which culminated in the NCBI establishing the Single Nucleotide Polymorphism database (4) (http://www.ncbi.nlm. nih.gov/SNP) in collaboration with the National Human Genome Research Institute (NHGRI). This has now become an international effort and many research institutions in various countries are involved in this task. Currently, many SNP databases exist that can be accessed on the internet. Eg. A similar Japanese population based SNP database has also been created (http://snp.ims.u-tokyo.ac.jp/) (5).

Role of Polymorphisms in Pharmacogenomics

Genetic polymorphisms contribute greatly to the inter-individual variations observed in complex human phenotypes, such as disease susceptibility and our responses to drugs or environmental chemicals (6). Hence, understanding these variations will assist in unraveling the relationship of individual/population genotype(s) with the response to therapeutics. The study of association between genetics and drug response is called pharmacogenomics. The potential role of genomics and pharmacogenomics in clinical research and medical healthcare is in modifying the existing disease management strategies that will

CORRESPONDING AUTHOR :

Dr. S. KARTHIKA
Department of Bioinformatics
Sri Ramachandra University
Porur, Chennai - 600 116
email : bioinformatics@srmc.edu / drkarthika@gmail.com
[a] Dept. of Bioinformatics

additionally incorporate the knowledge of genetic polymorphisms in drug disposition and effects. This will make a significant contribution to the pursuit of developing better, safer drugs as a part of personalized drug therapies in an era of personalized medicine where the right drug will be given to the right patient (7,8). **Pharmacogenomics** is thus, a science that examines the inherited variations in genes that dictate drug response and explores the ways these variations can help predict the outcome of administering therapeutic medications as good, bad or no response to the drug(s).

This is closely related to **Pharmacogenetics** which has been mainly concerned with the study of the genetics of drug metabolism and genetic factors affecting drug targets such as receptors. Presently, these terms are used synonymously.

Trends: Past and Present

Many phenotypic differences in drug absorption, distribution, metabolism and elimination (ADME) are partly a reflection of polymorphisms in genes encoding drug metabolizing enzymes, drug transporters, and/or drug targets (e.g., receptors, enzymes) (9). Initial pharmacogenetic studies focused on monogenic traits where these variations affected drug metabolism. Current studies look at high-throughput techniques that reveal the significance of many candidate proteins, influencing pharmacokinetics and pharmacodynamics of a drug – the former involving mechanisms that influence the concentration of a drug reaching its target(s) and the latter, the drug target itself (10).

For many drugs, the difference in patterns of patient response has been attributed to variations in pharmacokinetic rather than pharmacodynamics. But recently, it seems that pharmacodynamic variability is usually more pronounced than in pharmacokinetics. Some examples of the role of pharmacogenomics on pharmacokinetics are cytochrome P-450 isoenzymes, dihydropyrimidine dehydrogenase, and thiopurine methyltransferase; some examples of pharmacogenomics revealing variations in pharmacodynamics involve cholesteryl ester transfer protein, angiotensin-converting enzyme, and serotonin transporter (11). Genes of pharmacogenomic significance can be classified as 1) polymorphisms affecting metabolism of drugs, 2) affecting drug transport and disposition and 3) polymorphisms affecting drug targets. The first category includes cytochrome P450s which is involved metabolizing drugs such as Nicotine, Warfarin, Omeprazole, Cyclosporine etc.), N-acetyltransferase -2 (associated drug – INH) and Thiopurine S-methyltransferase (drug metabolized - 6 Mercaptopurin, 6-Thioguanine and Azathioprine). Polymorphisms affecting drug transporters such as MDR-1 (Multidrug Resistance Protein) affect digoxin transport. Individuals homozygous for a particular variant with a high MDR-1 gene expression had lower levels of plasma digoxin levels following oral administration of the drug. Polymorphisms affecting drug targets such as dopamineD3 receptor affects response to some antipsychotic drugs, those in angiotensin converting enzyme influence the response to ACE inhibitors and polymorphisms in cholesteryl ester transfer protein modify response to cholesterol lowering statin – Pravastatin.(12)

The majority of drug responses involve many proteins and their corresponding genes could have several polymorphisms making it unlikely that a single polymorphism in a single gene could result in a high degree of drug response variability in a consistent fashion. Thus, genomic approaches seem more appropriate to study the contribution of polymorphisms of several genes involved in a particular drug response. Such approaches to pharmacogenomics have shown promise in relating drug target polymorphisms to response or toxicity, and incorporating this strategy in drug discovery and development is a new approach that is being used by many pharmaceutical companies (13). Two such FDA approved pharmacogenomics-based drugs available currently in the market are Herceptin® (Genentech) and Velcade® (Milleneum). Herceptin® (Trastuzumab) is indicated for treatment of HER2 protein overexpressing, metastatic breast cancer. Velcade® (Bortezomib), a proteasome inhibitor is indicated for treatment of Multiple Myeloma.

A combination of pharmacogenomics and personalized medicine will eventually change the method of current drug prescription to one where drug selection and dosage process for any given patient will be advanced by genomic knowledge and information gained by these strategies (14).

Metabolic phenotyping studies can be done by administering a probe drug or substrate and measuring the metabolites with the clinical outcomes if any. The disadvantage of this approach is that it tends to be labor intensive and requires repeated sample collection from the individual or patient, being tested. On the other hand, genotyping allows determination of individual DNA sequence variants associated with particular traits. DNA sample is commonly obtained from whole blood cells and buccal cells. Genomic DNA is isolated from from other cellular material. After a specific region of interest is identified and amplified, using polymerase chain reaction (PCR). Subsequently, gel electrophoresis is often performed to verify that PCR was successful and that the amplified target sequence is the correct size. . Some of the commonly used genotyping methods include gel electrophoresis-based techniques, such as polymerase chain reaction (PCR) coupled with restriction fragment length polymorphism analysis (RFLP) does not rely on automated technology and is practical for laboratories genotyping a limited number of samples. Other gel electrophoresis-based techniques include multiplex PCR, and allele-specific amplification. Automated genotyping methods include Pyrosequencing, in which the principal allele discrimination method is a primer extension reaction coupled with a luciferase-based enzyme reaction. TaqMan uses fluorescence-labeled probes,

in addition to PCR primers, in the reaction mixture, enabling PCR amplification and allele discrimination in the same step. Mass spectrometry differentiates DNA molecules based on their mass. Denaturing high-performance liquid chromatography (DHPLC) using a reverse-phase ion-pair column, helps discriminate between variant and nonvariant. Some otther fluorescent dye-based high-throughput genotyping procedures include including oligonucleotide ligation assay and direct heterozygote sequencing. The latest advances in genotyping include Microarrays. (15,16)

The development of a new related field that serves to complement pharmacogenomics is that of pharmacoproteomics. The combined effort will endeavour to enhance the development of personalized medicines. The high-throughput techniques in pharmacoproteomics have a potential contribution in the area of molecular diagnostics that forms an essential component of personalized medicine. As the functional impact of genetic variations is seen in the functioning of the encoded protein, pharmacoproteomics will explain the functional phenotypic consequence of the patient-to-patient variation, to a greater extent than that offered by the genotype alone. Another role foreseen is in characterization of multifactorial diseases where it can help match a particular target-based therapy to a particular marker in a subgroup of patients (17).

An innovative and exciting prospect, this specialization of genomics has an immense potential in successful development of better, effective therapeutics as it will play a role in overcoming important setbacks in the traditional process of drug discovery. Genomics and its derivative fields along with their high throughput technologies promise to influence different stages of drug discovery process such as target selection, lead identification, lead optimization, thus yielding safer and effective drug candidates (18).

Role of Pharmacogenomics

- **In Disease Management & Therapeutics – Some recent examples:**

Many biological systems and their diseases have been the focus of pharmacogenomic studies with a potential impact in areas ranging from screening, diagnosis, monitoring therapy response, choice of drugs etc. Some highlighting examples in this regard include diseases such as Acute Lymphoblastic Lymphoma, Asthma, Gastric Cancer, Multiple Sclerosis and Osteoporosis.

Acute Lymphoblastic Leukemia

The childhood-onset disease Acute Lymphoblastic Leukemia is a notable case where pharmacogenomics models have been suggested which could aim at providing maximum efficacy with minimum adverse effects of existing therapeutic medications when prescribed using the patient genotype with favourable response and low toxicity, or to identify novel therapeutic targets in lymphoblasts that are resistant to conventional antileukemic drugs (19). These drug targets possessing polymorphisms that favour optimum drug response with low toxicity and lesser chances of relapse will be ideal for developing newer, safer and more effective chemotherapeutic agents for cancer therapy. ALL is also perceived to serve as a model for similar pharmacogenomic application in other human cancers. Early treatment response involving measurement of minimal residual disease reflects, both drug responsiveness of leukemic cells and host pharmacodynamics/pharmacogenomics, has been considered the most reliable prognostic indicator for gauging the intensity of treatment. (20).

Asthma

Beta2-agonists are the most effective bronchodilators available providing rapid relief of asthma symptoms and the degree of the drug response varies greatly between patients and genetic factors have a major role in it (21). Pharmacogenomic analysis of the commonly used anti-asthmatic agents such as ß-agonists, leukotriene modifiers, and corticosteroids showed that relative risk–benefit ratio of a particular therapeutic course for an individual patient could be identified by using "panels" of polymorphisms. Targeted therapy will thus help provide optimum benefit for asthma patients who respond preferentially to certain medications and avoid toxicity by prescribing drugs after assessing the likelihood of adverse drug reactions (22).

Gastric Cancer

Therapeutics based on the genotyping of each patient is also predicted as the future goal of personalized medicine (or tailor-made medicine) for chemotherapeutic management of advanced gastric cancer with drugs such as 5-fluorouracil, Paclitaxel, Docetaxel etc that are associated with side effects and drug resistance. These drugs play a role in management of advanced gastric cancer and complements surgical management of one of the common malignancies in the world (23).

Multiple Sclerosis & Osteoporosis

Another area of potential impact is foreseen in diseases that presently, have no definitive treatment eg. the neurodegenerative disease - Multiple Sclerosis (24). and diseases where therapy is typically required for several years before outcomes can be evaluated for an individual eg. the systemic skeletal disease – Osteoporosis (25). These are being investigated currently.

- **Understanding Disease Mechanisms of Biological Systems**

There has been a significant increase in understanding of biological systems and their disease mechanisms eg. the cardiovascular system. Pharmacogenomic approaches are emerging for many medications used in different cardiovascular conditions that would assist clinicians in decision-making being more precise to optimize the benefit-to-risk ratio. When combined with molecular imaging, molecular pathway mechanisms can be studied that will allow us to monitor health and disease and enable the enormous shift from genetic to genomic medicine (26).

- **Critical Clinical Decisions**

The use of the anticoagulant Warfarin, is difficult due to the variations in the dose required to have a therapeutic effect, and the adverse effect of serious bleeding. The drug interferes with the recycling of vitamin K in the liver which reduces the activation of several clotting factors. Many genes seem to be involved in the biotransformation and mode of action of this drug and the outcome of large ongoing studies of these along with assessment of environmental factors, will suggest a method to predict the required warfarin dose with minimized risk of haemorrhage (27).

Administering anti-fungal drugs in the immunocompromised state or for refractory/ persistent mycoses is another daunting scenario. Genes with potential pharmacogenomic significance include a) drug transporters involved in absorption and excretion, b) phase I enzymes (e.g., cytochrome P450-dependent mixed-function oxidases) and phase II enzymes (e.g., glucuronosyltransferases) contributing to metabolism, and c) molecules involved in drug distribution (e.g., albumin, A1-acid glycoprotein, and lipoproteins). Tools of population genetics can be used to define inter-individual variation in drug ADME and yield pharmacogenomic models for the observed genetic variations in antifungal pharmacokinetics (28).

Monitoring and management of adverse drug reactions of chemotherapy in cancer patients is another application of Pharmacogenomics. The impact of polymorphism in cytidine deaminase that metabolizes the anticancer drug - Gemcitabine was studied in Japanese cancer patients. A particular genotype harboring a nonsynonymous SNP, (Ala70Thr) was associated with decreased clearance of gemcitabine, and increased incidences of neutropenia when patients were coadministered platinum-containing drugs or fluorouracil.(29)

Enhanced Diagnostic Tests

Several technologies used in personalized medicine include SNP genotyping, haplotyping, gene expression studies by biochip/microarrays and proteomics. Molecular diagnostics will play a key role in personalized medicine where therapy and diagnosis will be integrated (30). In January 2005, the US Food and Drug Administration (FDA) granted market approval for the first pharmacogenetic test using a DNA microarray, the AmpliChip CYP450 GeneChip(R) (AmpliChip), which genotypes cytochrome P450 CYP2D6 and CYP2C19 (31). It classifies individuals into two CYP2C19 phenotypes (extensive metabolizers [EMs] and poor metabolizers [PMs]) by testing three alleles and into four CYP2D6 phenotypes (ultrarapid metabolizers [UMs], EMs, intermediate metabolizers [IMs], and PMs (32). Cytochrome P450 is one of the best studied drug-metabolism associated protein complex in the light of pharmacogenomics.

The application of this knowledge is relevant to the population type being considered for therapy. Poor metabolizers (PMs), lacking the enzyme, account for up to 7% of Caucasians for CYP2D6 and up to 25% of East Asians for CYP2C19. Patients having three or more active CYP2D6 alleles; the Ultra Rapid Metabolizers account for up to 29% in North Africa and the Middle East. As CYP2D6 metabolizes many of the psychiatric drugs, psychiatry has become the pioneer for the practical clinical use of pharmacogenetic testing that has relevance in the usage of drugs such as tricyclic antidepressants and antipsychotics (33). Evaluation of pharmacokinetics of citalopram in relation to genetic polymorphism of CYP2C19 was done in Chinese volunteers whose genotypes and phenotypes were known before administering the drug and studying its varied effects. Citalopram, a potent and selective serotonin reuptake inhibitor is used as an antidepressant. It is mainly metabolized to *N*-desmethylcitalopram and further demethylated to didesmethylcitalopram, the latter being catalyzed by CYP2C19, CYP2D6 and CYP3A4. This study supported the involvement of CYP2D19 in catalyzing this reaction and showed the varied genotype of this gene leads to differences in drug pharmacokinetics when comparing poor metabolizers (PM) and extensive metabolizers (EM). Some of the findings included moderately higher $t_{1/2}$ values of citalopram in PMs than the EMs. The CL_{oral} (oral clearance) of citalopram in poor metabolizers (17.1 $\pm$ 2.0 l/h) was significantly lower than that of extensive metabolizers (24.1 $\pm$ 1.6 l/h). PMs showed significantly longer t_{max} values of desmethylcitalopram than in extensive metabolizers (34). CYP testing is also applicable in toxicology and ADME profiling to guide drug development. Combined with pharmacotherapy, it can aid in effective decision-making regarding choice of drugs and dosage (35).

Another landmark test to identify metastatic colorectal cancer patients with indications for use of topoisomerase I interactive drug – irinotecan was approved by FDA in 2005. The genetic test (Invader *UGT1A1* Molecular Assay), conducted on genomic DNA from peripheral blood, identifies homozygosity for the *UGT1A1*28* allele. Such patients clear irinotecan and its metabolites more slowly than the rest of the population, and so have greater exposure to active drug after a standard dose. The FDA-approved test label states that "a reduced initial dose should be considered for patients known to be homozygous for the *UGT1A1*28* allele"(36,37).

Role in Clinical Trials

The post-genome era has led to advances such as high-resolution SNP maps and technical approaches like microarray have enabled incorporating genome-wide association studies in clinical trials and can contribute by identifying disease-susceptibility genes useful as prognostic indicators, process of drug discovery, and selection of therapy. An SNP map containing genetic variants relevant to drug transport, metabolism, and receptor interaction can be significant in drug selection and point to conditions where careful drug dosage monitoring is required (38).

At the 42nd American Society of Clinical Oncology (ASCO) annual meeting in Atlanta, Eli Lilly and Company,

a leader in thoracic cancer, unveiled two breast cancer studies involving pharmacogenomics and its chemotherapies GEMZAR® (Gemcitabine HCl) and ALIMTA® (Pemetrexed). They are among the early trials involving pharmacogenomics in breast cancer treatment and have so far shown signs of being able to predict response related to both general and drug- specific chemotherapy and biomarker analysis.

Clinical Data Inc. has launched the Phase III clinical trial for the depression drug Vilazodone and concurrently looking forward to develop a diagnostic test based on genetic biomarkers that can predict drug efficacy and response.

Many pharmacogenomics based clinical trials are currently underway in different phases of study. Eg. Some at the US National Institute of Health are mentioned at URL: http://www.clinicaltrials.gov/.

Improved Prospects in Preventive Care

If risk for a given disease is predicted to be high, as judged by the SNP pattern of a patient, preventive therapy and lifestyle adjustments (diet, exercise, etc) may be implemented (38). This could help prevent the onslaught of diseases that can be managed by preventive measures before the onset of the actual disease.

Current Databases

PharmGKB - The Pharmacogenetics and Pharmacogenomics Knowledge Base, is a publicly available Internet research tool developed by Stanford University with funding from the National Institutes of Health (NIH) and is part of the NIH Pharmacogenetics Research Network (PGRN), a nationwide collaborative research consortium. Its aim is to aid researchers in understanding how genetic variation among individuals contributes to differences in reactions to drugs. The database is a central repository for genetic, genomic, molecular and cellular phenotype data and clinical information about people who have participated in pharmacogenomics research studies. The data includes, but is not limited to, clinical and basic pharmacokinetic and pharmacogenomic research in the cardiovascular, pulmonary, cancer, pathways, metabolic and transporter domains (39) available at URL: http://www.pharmgkb.org/

Human Membrane Transporter Database - for Drug Transport Studies and Pharmacogenomics is another related database which currently contains data on more than 250 human membrane transporters and related proteins, their structure, function, sequence variants, and substrates, especially drugs. As this database is intended to support pharmacogenomic studies, it also provides information on sequence variants, altered functions caused by polymorphisms/mutations, and the (patho) physiological role and associated disease (40) available at URL: http://lab.digibench.net/transporter/.

Limitations and Obstacles

Though found to influence many clinical situations, there are others where it may not be very useful. An example for this is the assessment of variations in metabolism of and clinical response to many commonly prescribed non-steroidal anti-inflammatory drugs (NSAIDs), though cytochrome activity plays an essential role in the drug metabolism (CYP2C8/9) (41). The market withdrawals of rofecoxib (Vioxx) and valdecoxib (Bextra) led to great interest in assessing the side effect profiles of cyclooxygenase (COX) inhibitors. CYP2C9 genotype is considered a risk factor as many COX inhibitors are CYP2C9 substrates in vitro. But the study showed that apart from the effect of CYP2C9 genotype, a major determinant of clearance of this category of drugs, it was also felt necessary to consider CYP2C8 genotype for some of them and, possibly, CYP3A4 activity for some others (42). Hence prescribing these over-the-counter drugs with the relevant genotypic information may not be easily accepted by the clinicians and patients alike as some of them are prescribed for simple symptomatic relief.

There are inherent obstacles that have to be surmounted for the widespread use of pharmacogenetics and include difficulties such as economic feasibility and awareness among medical practitioners regarding the application and interpretation of results (31, 43).

Apart from educating the healthcare personnel and assessment of questions in ethical and legal concepts, public awareness about consent and implications of genetic testing in drug therapy and disease management is also a pressing need (44). This would aid interpretation of risk assessment tests where a predisposition to a pathological condition may not mean actual suffering from the disease. Adequate preventive measures can be instituted where tests indicate a higher probability of disease in later years, ultimately preventing many illnesses. But the burden of the information and fear may be unintended outcomes that also have to be weighed carefully.

CONCLUSION

The traditional approach of one-drug-fits-all does not cater to the need of smaller populations/subpopulations that show a similar phenotypic profile with the others but have an underlying distinct genetic signature that consequently leads to variation in drug response.

Pharmacogenomics combining the potential of genomics with pharmacology has tremendous practical potential to significantly enhance the ability of clinicians to use medications in a safe and effective manner (13). The future is not far away when these will be a part of the personalized drug prescription and estimates foresee this by the year 2015, according to the lay journal *Time*(45) and 2020, by *JAMA*(46).

An overall decrease in the number of adverse drug reactions, the number of failed drug trials, the time taken for approval of a drug, the duration of medication administered, the number of medications taken by patients before eventually finding the effective therapy, the pathological effects of a disease (through early detection), and a simultaneous increase in the range of possible drug targets will promote a net decrease in the cost and improve the quality of health care.

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