Review Article
AMERICAN JOURNAL OF PHARMACY AND HEALTH RESEARCH
www.ajphr.com
2015, Volume 3, Issue 1
ISSN: 2321–3647(online)

ARE WE READY FOR PERSONALISED MEDICINES? AN INSTINCT ON PHARMACOGENOMICS

Prosenjit Chakraborty[1], Abhimanyu Thakur*[2], Partha Pratim Mahata[1], Chandrakant Kumar Prasad[2], Aishwarya Roy[2]

1. BCDA College of Pharmacy & Technology, 78, Jessore Road, Hridaypur, Barasat, Kolkata.
2. Dept. of Pharmaceutical Science, Birla Institute of Technology, Mesra, Ranchi, Jharkhand.

ABSTRACT

Pharmacogenomics is moving beyond single-gene effects to study the effects of inheritance in pharmacokinetic and pharmacodynamic pathways involving multiple gene products. Pharmacogenomics aims to develop rational means to optimize drug therapy with respect to the patient's genotype to ensure maximum efficacy that had a minimal serious event. In this kind of occurrences there is an advantage of personalized medications in which drugs and drug combinations are optimized for each individual's unique genetic makeup. However, the translation of Pharmacogenomics to the bedside will require the education of physicians and other healthcare professionals in clinical genomic science generally and in its application to therapeutics in particular. Patients will also have to become informed regarding application of genomics to drug selection and dosage. In the present article, an attempt has been made to review the scenario of Pharmacogenomics and to assess the extent of knowledge and its acceptability in the field of healthcare.

Keywords: Pharmacogenomics, Players, Genetic Abnormalities, pharmacists, Health education.

*Corresponding Author Email abhithakurmanyu@gmail.com
Received 30 December 2014, Accepted 06 January 2015

Please cite this article as: Thakur A *et al*., Are We Ready for Personalised Medicines? an Instinct on Pharmacogenomics. American Journal of Pharmacy & Health Research 2015.

INTRODUCTION

The end of the twentieth century, and the beginning of the twenty-first, witnessed the convergence of two separate but intertwined developments in medicine and biomedical science. The "genomic revolution" has resulted both in a striking increase in our knowledge of genomics and in the development of techniques for rapidly obtaining large quantities of genomic data[1, 2]. At the same time, a "therapeutic revolution" has resulted in the development of drugs that can be used to successfully to treat or control diseases that range from hypertension and depression to childhood leukemia[3, 4]. However, the development of these potent and effective therapeutic agents also increased the importance of inter-individual variation in drug response differences that varied from potentially life-threatening adverse drug reactions at one end of the spectrum, on the other end there is a greater chance of undesired therapeutic effect. The application of classical genetic techniques concluded that inheritance was an important factor responsible for individual variation in drug response. That realization half a century ago (before the Human Genome Project) led to the birth of the discipline of Pharmacogenetics[5–7]. There are many factors apart from the inheritance for e.g., the patient's age, sex and also any other drugs which are administered to the patient in their diseased state which also contribute to variation in drug response. However, the convergence of rapid developments in genomics and molecular pharmacology has provided an unusual opportunity to move towards the goal of individualized drug therapy. The ultimate promise of Pharmacogenetics is the possibility that knowledge of a patient's DNA sequence might be used to enhance drug therapy for maximum therapeutic effect, patients only given target drugs which are likely to respond and to avoid adverse drug reactions. The subsequent discussion will briefly review the process by which the disciplines of Pharmacogenetics and Pharmacogenomics have developed, and then turn to challenges associated with the "translation" of these disciplines from the research laboratory till the corner of the bed, with the temporary purpose of developing the individualized drug therapy[8, 9]. The concept that inheritance can have an important role in individual variation in drug response originally grew out of clinical observations of the large differences among patients in their response to "large" doses of a drug. Attempts to understand that variation led to twin studies that demonstrated that plasma concentrations or other pharmacokinetic parameters are highly heritable for listed drugs as same as the invention of large variations in the level of the drugs or the metabolism of the drug that were inherited as Mendelian traits. Many of those early examples, and even today most of the incidences involving pharmacokinetics factors that affect

the drug concentration. When the patient is administered a drug, it should be well absorbed and distributed to the site of action, then occurs binding at the target site which undergo metabolism and excretion[10]. First and foremost among the challenges we face as we attempt to transfer Pharmacogenomics to the bedside is the science itself. Until we get a very strong report supporting the result of Pharmacogenomic testing improvised for patient care, that testing no longer required the therapeutic encounter. We also need to be sensitive to the fact that the development of Pharmacogenomics is happening at a time when the biomedical research enterprise as a whole is undergoing significant change. Another significant issue is the fact that several major "players" will determine how rapidly this branch of biomedical science advances and how quickly scientific advances will move to the bedside. The players are research organizations which include hospitals, biotechnology industry, and drug regulatory authorities, healthcare professionals who takes care of the patients need and the ultimate population- the patients.

Pros of Pharmacogenomics[11, 12, 13]

Some of the pros of Pharmacogenomics have been found such as powerful medicines, safer drug, appropriate dose, advanced screening for diseases, better vaccine, improved drug discovery and approval process, reduced overall cost of healthcare.

More Powerful Medicines: Pharmaceutical companies' research for manufacturing drugs are dependent on genes associated proteins, enzymes and RNA molecules. This allows discovery of targeted drug therapy for different kind of diseases. The therapeutic effects will not only be maximized also the damage to the cells will be reduced.

Safer Drugs the First Time: Instead of the standard trial-and-error method of matching patients with the targeted drugs, doctors will prescribe the best suitable drug therapy from the very beginning after analyzing the patients' genetic profile. Not only this process will save time, but also will increase the safety and tolerance level, having faster recovery time with minimal adverse effects. Pharmacogenomics excel with the potential of reducing the death rates from estimated 100,000 resulting from adverse drug response in the United States and simultaneously 2 million hospitalizations are reduced.

Appropriate dosage: The dosage depending on the person's genetics and its metabolism in the body will give more prevalent results than the dosage based on the age and weight which likely maximize the therapeutic efficacy decreasing the occurrence of overdose.

Advanced Screening for Disease: Knowing one's genetic code will allow a person to make adequate lifestyle and environmental changes at an early age so as to avoid or lessen the severity of a genetic disease.

Better Vaccines: The new generation vaccines from DNA or RNA overrules the benefits the existing vaccines with no risk, infection occurrence is being stopped by activating the immune system. These vaccines will be easily stored, affordable and stable engineered to carry various strains of pathogen once at a time**.**

Improvements in the Drug Discovery and Approval Process: Pharmaceutical companies will be able to discover potential therapies more easily using genome targets. The targeted drug therapy, which failed earlier will give results when they are grouped with the niche population. The drug approval process facilitated as trials for a specified genetic population whose successful outcome will be higher. The clinical trials will be cost effective and will only be population targeted in a responding drug which also minimizes the risk.

Reduced Overall Cost of Health Care: The number of adverse drug reactions is reduced along with failed drug trials; time taken for the approval of the drug, time period of drug administered to the patient to find a therapeutically effective therapy, the disease effect in the body will increase the range of targeted drugs decreasing the health care cost.

Role of Pharmacogenomics

For breaking as many as 30 different classes of drugs cytochrome P450 enzymes are responsible. Inactive forms of CYP can cause drug overdose in the patients for not being able to eliminate the amount of the drug from the body. Modern day's researchers examine variations in CYP450 genes by monitoring patients and genetic tested. The chemical compounds are screened by pharmaceutical companies examining the availability of broken forms of the different variants of CYP 450 enzymes**.** Another enzyme called TPMT (Thiopurine methyl transferase) plays an important role in the chemotherapy treatment of common childhood leukemia by breaking down a class of therapeutic compounds called thiopurines. A certain percentage of Caucasians with the genetic variant prevents from the production of an active form of the protein. Resulting thiopurines toxic levels get elevated in the patient due to the inactive form of TMPT failed to break the drug. Nowadays, doctors screened patients suffering from deficiency by a genetic test, while the TMPT activity is being monitored for determining the appropriate level of thiopurine dosage [14,15,16].

Significant Pharmacogenomic Testing

Warfarin

Warfarin is a commonly prescribed anticoagulant which has a narrow therapeutic range. The response to warfarin therapy depend upon various patient related factors such as age, sex, race, diet, the genetic variation in the drug metabolizing enzyme (CYP2C9) and drug target gene (VKORC1). It suggests that Pharmacogenomic testing may allow more patients to safely benefit from warfarin therapy. CYP2C9 is the major metabolizing enzyme of S-warfarin, which is more potent than the other isomer of warfarin (R-warfarin). The specific population with CYP2C9*1 allele or wild type variant have normal warfarin metabolic activity. On the other hand those who possess two polymorphic variants CYP2C9*2 and CYP2C9*3 allele have less capacity to metabolize warfarin, thus associated with decreased warfarin activity, diminished warfarin clearance and reduced warfarin dosage requirements. The standard dosing regimen of warfarin, in a person carrying CYP2C9*2 or CYP2C9*3 allele leads to warfarin toxicity or increased risk for bleeding due to reduced warfarin metabolism. These variant carriers only required low initial dose of warfarin, as CYP2C9*2 reduce warfarin metabolism by 30%, and CYP2C9*3 reduce warfarin metabolism by 90%. The variant takes longer than normal time, up to 4 weeks to achieve the target INR[17, 18, 19].

Codeine

Genetic polymorphism have been well established in the CYP2D6 family, which is responsible for the metabolism of many drugs such as codeine, nortriptyline, metoprolol, selective serotonin reuptake inhibitors (SSRIs), simvastatin and tamoxifen. A large number of women receives codeine for obstructive pain while breastfeeding, which is metabolized through CYP2D6. A person with two non-functional alleles at CYP2D6 is considered to have poor metabolism, whereas a person with one or two functional allele is considered to have extensive metabolism and one who has duplicated or amplified active CYP2D6 gene is considered to have ultra-rapid metabolism. At conventional doses, subjects who are poor metabolizers of CYP2D6 genotype will get no therapeutic benefit from codeine because it will not convert into its active form. Ultra metabolizer subjects who can metabolize codeine have high levels of morphine, resulting in higher side-effect with shorter control of pain[20]. Case was reported on fatal opioid poisoning in a breast fed neonate whose codeine prescribed mother was a CYP2D6 ultra rapid metaboilizer[21].

Tamoxifen

An estrogen receptor antagonist, tamoxifen; widely used for breast cancer treatment. It is an apodrug needed metabolic activation via CYP2D6 which helps in the conversion of 4-hydroxy tamoxifen and endoxifen, having greater affinity towards estrogen receptors with the potency of suppressing estrogen dependent proliferation of cancer cells of breast. It has been suggested that

the genetic polymorphism of CYP2D6 influence the plasma concentration of the active metabolites of tamoxifen and thus the clinical outcome. Individual variation in tamoxifen metabolism gets affected by genetic polymorphism, CYP isoforms such as sulfo transferase and UDP glucuronosyl transferase contributes but in lesser amount[22].

Abacavir

Abacavir is a nucleoside reverse transcriptase inhibitor. It is a component in the HAART regimen for the treatment of HIV infection. The drug is well tolerated in most of the patients, but 2.3-9 % of people who receive abacavir therapy developed serious life threatening hypersensitivity reactions. The symptoms of abacavir induced hypersensitivity reactions- fever, skin rashes, fatigue, gastrointestinal symptoms and respiratory symptoms are developed within 6 weeks of initiation of therapy and resolved within 72 hours after the withdrawal of the drug. While correlating these reactions with genetics, patient who carrying HLA-B*57:01 allele are at higher risk for developing this abacavir induced hypersensitivity reactions. The FDA recommends genetic testing for HLA-B*57:01 allele before staring the drug therapy and the therapy is not recommended in patients testing positive for the HLA-B*57:01 allele[23].

Azathioprine

Azathioprine (AZA) and 6-Mercaptopurin (6-MP) are widely used for the treatment of inflammatory bowel disease. The catabolism of these drugs is mediated by the enzyme TPMT. The most common variants of TPMT are TPMT*2, TPMT*3A and TPMT*3C. About 89% of the population has normal or high TPMT enzyme activity, 11% have low activity, and 0.3% of the population possesses two copies of this variant allele so they have negligible TPMT activity. This variability in the enzyme activity will result into higher chance of bone marrow suppression in people who possess reduced TPMT activity due to the conversion of 6-MP to produce higher levels of 6-TG. It requires azathioprine dosage reduction up to 90%[24].

Significance of Single Pharmacogenomic Trial

Many authors over the years have held up the promise that Pharmacogenomic clinical trials can be smaller than their nonPharmacogenomic equivalents[25-27]. This is certainly true if the Pharmacogenomically targeted population has a smaller variance in any efficacy or safety outcome compared to a heterogeneous 'all comers' sample[28]. Clinical trial sizes scale with the variance of measurements i.e. with the square of typical measurement error[29]. A homogenous population segment of patients selected on a specific biomarker should have a smaller error variance and thus need a smaller trial to investigate. However, to non-aficionados of statistics made belief that Pharmacogenomic trials are special beyond the ordinary regulatory strategies

about trial sample size. Often pharmaceutical executives say mistakenly, or led unscrupously made believe a segmented medicine is always cheap and quick to develop. Considering the weight of evidence requirements is an illuminating way of understanding that the sizes of Pharmacogenomic trials are not exceptional when it comes to regulatory sufficient proof[30].

Pharmacogenetics of Thiopurine-S-methyltransferase

Clinical Pharmacogenetics

S-methylation of thiopurine drugs catalyses thiopurine-S-methyltransferase[32, 33]. Acute lymphobastic leukaemia of childhood, inflammatory bowel disease treated with the drugs as well as training in the organ transplant recipients. Thiopurines have a narrow therapeutical index; which explains differences between the doses to get the desired therapeutic effect, causing little toxicity are quite useful agent [34]. The major toxicity of thiopurines is myelosuppression (bone-marrow suppression), which can be life-threatening[34, 35].

Molecular Pharmacogenetics

The most common variant allele for TPMT in Caucasians is TPMT*3A, an allele primarily responsible for the trimodal frequency distribution shown in Fig. 2A, that has a frequency of approximately 5% in Caucasian populations[36, 37, 38]. This variant allele has two non synonymous coding single-nucleotide polymorphisms (cSNPs)—SNPs that result in alterations in the encoded amino acids[39]. TPMT*3A is rarely, if ever, observed in East Asian populations, in which TPMT*3C is the most common variant[40]. Individuals homozygous for TPMT*3A are at greatly increased risk for life-threatening myelosuppression when treated with standard doses of thiopurine drugs[35, 41]. However, they can be treated with these drugs at approximately one-tenth the standard dose, but even then only with careful monitoring[42].

Molecular mechanism

The allozyme encoded by TPMT*3A is degraded rapidly by a ubiquitin- proteasome mediated process[43, 44]; so, subjects homozygous for this allele have little or no detectable TPMT protein in their tissues[37, 39] and very little protein is observed after the transfection of cultured mammalian cells with expression constructs for this allozyme[37, 43]. There is also evidence that chaperone proteins such as heat-shock protein-70 (HSP70) and HSP90 might be involved in targeting the TPMT*3A variant allozyme for degradation [43]. Decreased protein level— often resulting from accelerated degradation—is a common Pharmacogenomic functional mechanism[45].

Education for Health Care Professional and Patient

Most of today's healthcare professionals were educated before the advent of the genomic revolution. If individualized drug therapies get translated to Pharmacogenomics, an effort made

to the "genomic" education for all healthcare professionals includes clinician, dentists, nurses, pharmacists. That educational effort will have to begin with the genomic "vocabulary" the "ABCs" of genomic science as applied to medicine. For example, physicians mostly educated at the time when it was not necessary to understand what a "TATA BOX" is. However, a VNTR involving the TATA box of the UGT1A1 gene is important in the pathophysiology of Gilbert's syndrome (benign unconjugated hyperbilirubinaemia) as a result of decreased glucuronide conjugation in subjects having seven rather than six repeat elements[46, 47, 48]. Furthermore, this same polymorphism contributes to inherited variation in the toxicity of drugs such as the anti-neoplastic agent IRINOTECAN (Pfizer)[49]. For clinicians it was important to know the meaning of "VNTR", it was also important for them to have a brief idea about the concepts of genomics and Pharmacogenomics. Therefore, the example provided by the UGT1A1 VNTR illustrates the need for continuing education programs in genomic medicine that are directed to all members of the healthcare team. Medical journals have already recognized this need, and, for example, both the New England Journal of Medicine[50] and the Mayo Clinic Proceedings[51] have published series of articles intended to inform the practicing physician with regard to the application of genomics to clinical medicine. Ultimately, patient should also need to be educated to have the understanding and acceptance of Pharmacogenomic testing. Furthermore, significant social and ethical issues must be addressed if the science underlying Pharmacogenomics is to have its full potential impact on the clinical practice of medicine and if patients and physicians are to embrace this new science enthusiastically. In some ways, Pharmacogenomics' ethical issues are much more simple specially the area of genomics, all the data does not get stigmatized, ,the physician can have alternative treatments in response to a test result, for e.g. rise or lowering dose of the drug, selecting a different drug. For instance, the physician might have to lower the dose of the drug after the genetic test result, TPMT genetic polymorphism. Administration of a standard dose of 6-mercaptopurine to a patient homozygous for the TPMT*3A variant allele would clearly endanger the patient [35, 36, 41]. However, in many ways, the ethical and social issues involved in Pharmacogenomics do not differ from those that exist elsewhere in genomic medicine. Patients confidentiality is of prior importance which enhances public confidence assuring that genomic information will only benefit the patient and will not allow discrimination [52, 53]. Ultimately, society has to find politically acceptable ways to ensure that patients can be certain that they will receive the benefits of genomic medicine without the risk of discrimination. Obviously, those solutions will differ from country to country because of differences in their systems of healthcare delivery and variation in political climates.

Role of a Pharmacist

All disciplines in the curriculum of pharmacy get affected to the understanding of a drugs' response through Pharmacogenomics. Pharmacy institutions and organizations also practitioners plays a major role in educating healthcare professionals for making the best use of advance Pharmacogenomic research, and in defining the role of pharmacists and scientists for the use and development of gene based therapies, and based on patient specific genetic information treatment choices are made. Pharmacogenomics have importance in scientific, academic and clinical field; where pharmacists play three important roles: researchers, educators, clinical pharmacist[31]. As researchers**,** pharmacists will have to play a critical role in developing novel drugs with highly specific targets, new study methodologies for studying drug therapy and criteria that are tailored to Pharmacogenomics based drug discovery. As educators, the transformation to clinical practice advancing from of Pharmacogenomics requires the training of current and future pharmacists for its role in interpreting, managing, applying and delivering the information about Pharmacogenomics. In addition to the science, however, pharmacists require an advanced training in the ethical, legal, social aspect implication regarding its application in healthcare. As clinicians, due to the expansion in the pharmaceutical practice, the major players are pharmacists and clinicians individualizing therapies on the basis of genetic variations. Although the science of Pharmacogenomics will provide an increased level of accuracy in selecting specific drug therapy for individual patients, it will not replace the art of clinical judgment in practice because of the confluence of social, behavioral, economic and environmental factors[54].

Outlook and Current Opinion

Today, pharmacists assist physicians by checking items listed on a prescription for possible interaction between drugs; tomorrow's pharmacist could conceivably interpret genetic profile and genetic test. Core competence now serves as the dominant framework for the education of health professionals, replacing a centuries-old model of knowledge-based learning and testing. This new imperative requires that health professionals master not only the knowledge base of their discipline, but also that they understand why, when, and how that knowledge should be applied to improve health outcomes for their patients[55]. It is essential that pharmacist and organizations responsible for training and teaching health professionals understanding the guidelines and be compliance with it and also integrating the genetic content implemented in their education. Pharmacists and health professional current competencies includes knowledge, skills on three fundamental features[56, 57]

i. Genetics of disease, allowing understand how the identification of disease associated genetic variations facilitates development of preventions and therapies;

ii. Pharmaceutical research and drug developments, allowing to understand how therapy protocols are ranked into a patient's genetic profile, and way the company influence the development of new drugs;

iii. Ethical and socioeconomic factors are primary step to identify the essential factors which contribute in a successful integration of Pharmacogenomics in terms of international health and public policy.

iv. Finally, Pharmacogenomics will make the practice of pharmacy and medicine less an art and more a science, hereby improving the efficacy and reducing the toxicity that result from therapy.

Table 1: Some common known genetic abnormalities and their effect in pharmacotherapy[31]

GENE	Polymorphism (nucleotide translation)	Molecular effect	Drug	Effect on therapy
Cytochrome P450 family	Various Polymorphism	Decreased enzyme activity	Various	Inter-individual variability in Pharmacokinetics
TPMT2, 3A, 3C	Various Polymorphism	Rapid degradation	6-MP Thioguanine	Hematopoietic Toxicity
UGT1A 28	TA repeats in 5' promoter	Low expression	Irinotecan	Neutropenia toxicity
MDR1	(C3435T)	Low expression	various	Drug resistance
TYMS	3 tandem repeats	High expression	5-FU, Metatrexate	Drug resistance
DHFR	T91C	Increased enzyme activity	Metatrexate	Drug resistance
MTHFR	(C677T)	Lower enzyme activity	Metatrexate	Toxicity
c-KIT	(T1982C) (T81421A)	Constitutive signal activation	Imatinib	desensitizes activity in GIST
c-KIT	D816V	Unknown	Imatinib Semaxinib	Good response in t[8;21]-positive AML
EGFR	L858R	Unknown	Gefitinib Erlotinib	Good response in NSCLC
BCR/ABL fusion gene	t(9;22) BCR/ABL	Constitutive signal activation	Imatinib Dasatinib Nilotinib	Good response in CML
ABL	T315I M351T		Imatinib	Drug resistance
PML/RARα	T(15;17)	Block of	All Trans	Good response in

fusion gene	PML/RARα	maturation of Myeloid cells	Retinoic acid [ATRA]	AML-M3 subtypes
ADRB1 ADRB2	R389G	G-protein alteration	b-bloccants	desensitizes activity
MHC class B 1	Several SNPs including codon K751Q	HLA-B~5701 aplotype	Abacavir	Hypersensitivity
VKORC1	Many, VKORC1 haplotypes including codon G3673A	associated with a higher/low warfarin dose	Warfarin	Variable anticoagulant effect

Abbreviations: TPMT = thiopurinemethyl transferase; UGT1A1 = UDP-glucuronosyl transferase 1A1; MDR1 = multidrug resistance 1; TYMS = thymidylate synthase; DHFR= Dihydrofolatereductase; MTHFR = 5,10-methylene tetra hydrofolate reductase; EGFR= Epidermal Grow Factor Receptor; 5-FU = 5-fluorouracil; 6-MP = 6-mercaptopurine; AML= Acute Myeloid Leukemia; NSCLC= Non-Small Cell Lung Cancer; CML= Chronic Myeloid Leukemia; ADRB: adrenergic b-receptors; VKORC1: Vitamin K epoxide reductase Complex 1; the present list need to be uncomprehensive. Genes for genotyping test are available for clinical diagnostics or others considerations.

CONCLUSION

Pharmacogenetics and Pharmacogenomics hold out the promise of helping to achieve the goal of individualized drug therapy. Unlikely, the incidences of repeated countervailing pressures have decreased the translation from Pharmacogenomics to clinics. Now Pharmacogenomic testing in clinical settings needs large and complex studies; economic invariability in pharmaceutical industry need to accept the outcome of the individual, the inherent variability in response of the drug; measured pace parallel of the inclusion of the new science in the process of evaluating a drug followed by regulatory authorities.

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