Pharmacogenetics, Pharmacogenomics and Ayurgenomics for Personalized Medicine: A Paradigm Shift

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The value of health care can be increased tremendously through individualized medicine. With the promise of individualized medicine, healthcare professionals will be able to better predict disease risk, prevent development of disease and manage treatments more efficiently thereby allowing people to be healthier and active longer. The developments in the area of pharmacogenetics/pharmacogenomics can help the physicians achieve the target of personalized medicine. Personalized medicine will come to mean not just the right drug for the right individual, but the right drug for the specific disease affecting a specific individual. The use of personalized medicine will make clinical trials more efficient by lowering the costs that would arise due to adverse drug effects and prescription of drugs that have been proven ineffective in certain genotypes. The genotypic experiments have laid valuable insights into genetic underpinnings of diseases. However it is being realized that identification of sub-groups within normal controls corresponding to contrasting disease susceptibility could lead to more effective discovery of predictive markers for diseases. However there are no modern methods available to look at the inter-individual differences within ethnically matched healthy populations. *Ayurveda*, an exquisitely elaborate system of predictive medicine which has been practiced for over 3500 years in India, can help in bridging this gap. In contrast to the contemporary system of medicine, the therapeutic regimen in *Ayurveda* is implicated on *tridoshas* and *prakriti*. According to this system, every individual is born with his or her own basic constitution, which to a great extent regulates inter-individual variability in susceptibility to diseases and response to external environment, diet and drugs. Thus the researchers in India have demonstrated that integration of this stratified approach of *Ayurveda* into genomics i.e. *Ayurgenomics* could complement personalized medicine.

Key words: Pharmacogenetics, pharmacogenomics, *Ayurveda*, ayurgenomics, personalized medicine

The drug development process today is driven by the idea of "one size fits all"[1]. However the significance of personalized medicine (PM)/individualized medicine (IM) has been long understood by the clinicians. Hippocrates, the father of western medicine, advocated PM. He considered factors like age, physique and patient's constitution while prescribing drugs[2] since all patients did not respond to drug therapies in a uniform and predictable manner[3].

An individual's response to any drug may be attributed to several factors including external and physiologial environment, overall health profile and the genetic constitution[4]. It is important to identify the factors that predispose an individual to diseases and predict their progression followed by developing a customized drug regimen for every individual to minimize side-effects. This is one of the major challenges. With the advances in molecular biology and genetics, pathogenesis of many diseases has been traced to variation in DNA[5,6]. With the availability of the sequence of human genome, it would now be possible that each individual would have a personalized health regime based on his/her genetic make-up. This information will help the physicians to prescribe an appropriate medication for targeting the disease in the right manner in the right dose in individual patients to achieve maximum therapeutic benefit with minimal, tolerable adverse effects. IM can increase the value of health care by allowing the physicians to give the right treatment from the very beginning[6].

Western health science has studied the relationship between genetic constitution and disease pathology

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and its treatment. This work has led to the emergence of pharmacogenetics and pharmacogenomics that describes the genetic reasons for variance in drug response in populations[7]. It is being realized by increasing number of researchers that identification of subgroups within disease suffering population may lead to more effective discovery of predictive markers for diseases. Modern medicine lacks in the methods to identify these inter-individual differences[5]. PM/IM has been practiced in *Ayurveda* for thousands of years. Every individual possesses a unique constitution (*prakriti*). This *prakriti* forms the basis of health and disease in *Ayurveda*. It uses the three-fold classification system of *tridosha* theory to treat an individual[7]. In the 21st century, efforts are being made to bridge the two medical practices with the human genome and to merge them gradually. In the present article an attempt has been made to highlight the importance of integrating the empirical approach of contemporary medicine and *Ayurveda*. The developments in the field of *Ayurgenomics*, an integrated field utilizing genomics and principles of *Ayurveda*, for drug development and to achieve the concept of PM has are also discussed. The following sections describe the significance of pharmacogenetics/ pharmacogenomics, *Ayurveda* and *Ayurgenomics* at length.

Pharmacogenetics:

The notion that genetic variants might modulate variability in drug actions, was first proposed by the English physiologist Garrod[3]. He suggested that enzymatic defects not only lead to aggregation of endogenous substrates in "in-born errors of metabolism", but also to aggregation of exogenously administered substrates, such as food, toxin and drugs, with clinical concerns. The word 'pharmacogenetics' was first used by Vogel of Heidelberg, Germany in 1959[3]. The science that analyzes individuals' responses to therapeutic agents and their genetic inheritance is called pharmacogenetics[8]. Pharmacogenetics can thus be defined as the science of determining the genetic differences on metabolic pathways which can affect individual responses to drugs, both therapeutically and adversely[8]. The term has been coined together from the words pharmacology (the study of action of drugs in the human body) and genetics (the study of inheritance of traits).

The observations of role of genetic variation in response to drugs date back to the 1950s, encompassing suxamethonium chloride, a muscle relaxant and a drug metabolized by N-acetyl transferase. In the late 1960s, Vesell showed remarkable similarity of disposal for several drugs in identical twins who share 100% of their genes in contrast to fraternal twins who only share 50%[9]. This data along with bell-shaped distribution of drug disposal after standard dosage in unrelated members of a population supported the inference of polygenic control of drug metabolism for many drugs. Since relatively few drug responses or adverse drug reactions are regulated by a single gene, the development of pharmacogenetics over the years has been at a slower pace. In addition, difficulties in family studies and lack of DNA study with drug response contributed to the delay in an expansion of this science. However advances in human biochemical genetics in the first half of the 20th century set the stage for pharmacogenetics[8].

Individual variations in response to a drug are due to the differences in the pharmacodynamics, including receptor and transporter polymorphisms[10]. The variations that are often based on genetic makeup, can cause differences in metabolic pathways of drug action and elimination[10]. These variations can influence the rate of absorption, distribution, metabolism, and elimination of the medication leading to varied plasma concentrations or excretion profiles followed by lack of efficacy or inducing toxicity[11]. Understanding the role of genetic polymorphisms in drug responses will thus ensure better therapeutic efficiency and will reduce the incidences of adverse reactions as the drug will be tailored to suit the genetic constitution of patients. Significant implications in determining the dosage regimens and the competence of therapeutic prescriptions can be achieved through advances in the field of pharmacogenetics. Development of targeted therapeutic interventions could thus be expedited through pharmacogenetics since the pharmacophore will be premediated exclusively for the responder group. Thus the main aim of the pharmacogenetic study may be to adapt the therapeutic strategies to suit an individual's genetic profile, minimizing their adverse reactions and maximizing their efficiency[12].

In pharmacogenetics, phenotypes are scrutinized by low or exaggerated pharmacological effects, frequency of side effects, and difference in the rate of metabolism. Procedures for monitoring metabolic

capacity involve administering a probe drug and determining the ratio between the parent drug and its metabolite in body fluids or other tissues[13]. The analytical technologies involved in this process are time consuming and also involve repeated collection of samples. Metabolic phenotyping can be influenced by sample stability and external factors such as age, nutrition, health, and concurrent medications[14]. These limitations can be evaded by genotyping due to establishment of a genetic association. Genotyping helps in identification of structural variations in individual DNA for particular traits independent of its functional effects. This approach is being used increasingly in biomedical research and molecular diagnostics. Being relatively easy to perform, genotyping generally requires a small sample of peripheral blood or buccal swab from patients. Therefore, unlike metabolic phenotyping, it is less invasive and is not influenced by drug-drug or food-drug interactions. The genotyping methods that are commonly used include polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP), allele-specific PCR, mass spectrometry, fluorescent dye-based high-throughput genotyping and gene chip technology[15].

With emergence of the Human Genome project and the development of the genome sciences in the 1990s, the term 'pharmacogenomics' came into existence. The terms pharmacogenetics and pharmacogenomics are often used interchangeably[16], and a unanimous and precise definition of either remains elusive. Whilst pharmacogenetics is generally referred to study or investigation of genetic variations leading to varied responses to pharmaceutical products, pharmacogenomics is a broader application of genomic technologies for development of new drug and/or further categorization of existing drugs[17].

Pharamacogenomics:

Pharmacogenomics is a branch of science that deals with the systematic identification of all the human genes, their products, inter-individual and intra-individual variation in expression and function. Pharmacogenomics differs from pharmacogenetics in the level of its application. Whilst the former is for a population, the latter is more individualistic as the difference between the two is the initial approach of the science[18]. Pharmacogenetics starts with an unexpected drug response and evaluates its genetic cause, while pharmacogenomics begins with looking for genetic variations within a population that may explain certain observed responses to a therapeutic drug. There are many tests related to drug response that have already been incorporated into current clinical testing[19,20]. Moreover, it is likely that the variety of such tests will expand in the future as more data would connect variation in alleles, response to drugs and clinical outcomes. The demand for clinical testing of genetic markers is expected to increase as genetic variation becomes more connected to patient management[21]. Such increased demand may require the testing of multiple markers in numerous patient samples in a rapid and parallel manner.

Testing of genetic variants or mutations utilizing high throughput assays includes, (1) simultaneous testing of hundreds samples from different patient (parallelizing), and/or (2) simultaneously analyzing multiple genetic loci for an individual (multiplexing), and/or (3) obtaining very rapid results. In a clinical laboratory, the choice of technological method for a genetic test is strongly influenced by the testing goals[22].

The developments in the field of molecular biology and bioinformatics have permitted for extensive analysis of human nucleic acid sequence and protein expression. Genome-wide association studies (GWAS), for instance, have taken advantage with methods for analyzing thousands of single nucleotide polymorphisms (SNPs) across large populations pooled with data from clinical outcome and comprehensive statistical methods. Individual SNPs or combinations of variants associated with drug response have been identified through these studies[22].

SNP status can be determined using microarray techniques, either to identify disease risk factors or for pharmacogenomic studies. This approach employs differential hybridization of nucleic acid oligonucleotides to determine the presence of sequence variants[22].

Approaches to probe 10–200 pharmacogenomic markers can also be used as opposed to the whole genome SNP arrays. Dedicated microarray technologies can be used to probe targeted genetic markers at a lower cost. Additionally, traditional allele-specific PCR, also known as amplification refractory mutations system, is commonly used

in many laboratories. Though low throughput, these methods have the advantage of being very inexpensive, easy to perform and interpret, meeting the requirements of many clinical laboratories[23].

Pharmacogenomics has the potential to transform the way medicine is practiced, by substituting the broad methods of screening and treatment with a more personalized approach that takes into account both clinical factors and the patient's genetics[24]. The physicians can thus utilize pharmacogenomics alongside traditional clinical practices to predict which drugs are more or less likely to work, appropriate dosage to achieve therapeutic response, and the drugs to be avoided on basis of associated adverse events.

Benefits of pharmacogenetics/pharmacogenomics[18]:
Now that the human genome has been read in practically full detail, there is widespread optimism that in the near future, it will be possible to tailor the treatment to the individual patient on the basis of the patient's genotype. Development of target-oriented drugs will maximise their therapeutic efficacy and minimize the damage to neighboring healthy cells. The clinicians could prescribe specific drugs based on the genetic profile of the patients, thereby decreasing the likelihood of adverse reactions. The likelihood of a drug overdose can be decreased, as the dosage would be based on the genetic constitution of the patient than on his/her body weight and age, as in the conventional approach. The advent of validated pharmacogenetic markers could be included in clinical trials to increase the demonstration of therapeutic benefits without exposing "nonreceptive" subjects. Undertaking pregenetic screening of those patients taking part in a clinical trial should also make the clinical trials smaller, faster, and therefore less expensive.

Grey areas:
It is likely that an individual's response to a drug would be influenced by a number of genes. It means that targeting different drugs/receptors may be very complex. Few variations in an individual's genes do not cause any problem in the functioning of the gene. These variations may influence drug metabolism and hence it is important to identify these variations. However this process may be very cumbersome, difficult and time consuming. Genotyping may also involve an ethical issue. The assumption that an individual's race can indicate their genetic profile for drug response is itself problematic as it may mean that people from different ethnic groups who are affected by the same condition are given different access to treatment. It may broaden the healthcare gap between the rich and poor.

Whilst the use of a multitude of different techniques for detecting particular genetic variants has been described in published literature, many of these applications have only been explored in the research laboratories. The use of tests in the clinical laboratory requires quality control, extensive validation and continued quality assessment to comply with regulatory mandates and to provide robust, precise and reproducible results.

Incorporating pharmacogenomic testing in clinical laboratories poses many complexities particularly in terms of economics in a developing country. The introduction of a new assay for pharmacogenomics-based testing may require the purchase of capital-intensive equipment, expensive reagents, and compels additional training of laboratory staff.

A transition from a descriptive science to a predictive science is being experienced in biology. Whilst genomic medicine holds the prospect of transforming clinical medicine and public health, the current understanding of genetics and genomics among healthcare professionals is a major predicament for integration of genomic technologies into mainstream practice. Physicians and other healthcare providers who make the decisions related to PM are currently being trained conventionally with a focus on reactive treatment. Training of physicians who enter the era of PM is paramount and the traditional academic setting has to be customized in the light of the new paradigm[25].

Reduced market and increased drug cost will add to healthcare crisis. Pharmaceutical companies are interested in selling drugs to as many people as possible. Pharmacogenetics/pharmacogenomics would narrow down market for a particular drug.

According to modern science, humans are 99.9% identical and the phenotypic differences arising due to SNP contribute to the remaining 0.1%. The genotypic experiments have laid valuable insights into genetic underpinnings of diseases. However it is

being realized that identification of sub-groups within normal controls corresponding to contrasting disease susceptibility could lead to more effective discovery of predictive markers for diseases. There are no modern methods available to look at inter-individual differences within ethnically matched healthy populations. It is at this juncture that the insights from Ayurveda, the traditional Indian system of medicine, seem promising[26].

While the idea of IM in western medicine is a very recently entertained concept, Ayurveda, the ancient Indian science of medicine has long considered and practiced individualized treatment schedules. According to Ayurveda: "Every individual is different from another and hence should be considered as a different entity. As many variations are there in the universe, all are seen in human beings" quotes *Charaka Samhita*[27].

Ayurveda:

Ayurveda is not folklore or a herbal tradition, it is a natural system of health care that originated in India more than 5000 years ago. It accentuates the treatment of disease in highly individualized manner as it believes that every individual being unique has a different constitution. Based on the theory of *tridosha,* it classifies all individuals into different '*prakriti*' types with each type having varying degree of predisposition to different ailments. *Prakriti* being fixed at the time of birth, remains invariant throughout the lifespan. This is independent of geographical, racial or ethnic considerations and may provide adequate means of classifying phenotypes to be considered collectively for genotyping. Similarly it categorizes the drugs based on *rasapanchaka* (ayurvedic pharmacology), which states that the action of drug is ascribed to certain attributes present in the drug namely *Rasa* (taste), *Guna* (property), *Virya* (potency), *Vipaka* (post digestive taste), and *Prabhava* (effect), while in modern pharmacology the action of the drug is attributed to the chemical structure of a molecule[28]. The *rasapanchaka* modality provides treatment by taking into consideration the *prakriti* of the person as well as the pharmacodynamics and pharmacokinetic properties of a drug unlike a modern treatment that elicits varied response from person to person.

Probing different attributes of an individual such as anatomy, physiology and mental aptitude can help in the assessment of *prakriti*. At the anatomical level, for example, these constitutions differ with respect to build and frame of the body, color of the skin, eye and hair. The differences observed at physiological levels include food habits and digestive capability, affinity to gain weight, disease resistance and healing capacity. Additionally differences in preferences for taste, capability to memorize, and response to stress is also described. Ayurvedic practitioners resolve the "mixture impression" thus obtained to identify proportions of *Vata*, *Pitta*, and *Kapha* in an individual's *prakriti*. According to *Ayurveda*, perturbation of the *tridoshas* in an individual from his or her homeostatic state leads to a disease. These proportions of *tridoshas* are determined genetically (*Shukra Shonita*) and are influenced by the environment (maternal diet, lifestyle) during development.

Ethnicity (*Jatiprasakta*), familial characteristics (*Kulanupatini*), and geoclimatic regions (*Deshanupatini*) are known to influence the phenotypic variability[29]. Consequently the factors that contribute to inter-individual variability at the genetic or epigenetic levels are rooted in the concept of *prakriti*. The *tridoshas* work in conjunction in an individual and maintain homeostasis. Ayurvedic treatment aims to bring it back to its native state by appropriate dietary and therapeutic regime. A particular *dosha* is known to be altered by various factors namely food, medicines, lifestyle factors and therefore an individual specific treatment is provided. An individual, a disease condition, drug, diet as well as environment are described in terms of *doshic* components in Ayurveda and it aims to provide appropriate customizations to balance these states. The Ayurvedic system of medicine thus has a personalized approach in treating a patient with centuries of practice, appropriately termed as experiential science[30].

The basis of individual variations in Ayurveda indicates that the individuals of different *prakriti* may have different rates of drug metabolism associated with drug metabolizing enzyme (DME) polymorphism as well. An initiative was taken to correlate different *prakritis* and their biochemical and transcriptomic profiles[31]. In their study, Patwardhan *et al.*[32] used human leukocyte antigen (HLA) DRB1 types to compare individuals with their Ayurvedic *tridosha* classification. The data established a rationale and

preliminary experimental support for the concept of an association between HLA alleles and the Ayurvedic *tridosha* theory of individual *prakriti* types. This study laid the foundation for research in the field of investigating the correlation between Ayurvedic phenotypes and individual human genotypes, now termed as *Ayurgenomics*. Chen *et al.*[33] have used similar comparative HLA gene polymorphism approach and classification based on Traditional Chinese Medicine (TCM) theory. Both the studies have reported the implications of traditional classifications of human physiology and used analysis of DNA polymorphism to test the hypothesis that phenotypes identified in their respective traditional classification had a substantial biologic basis. Studies on correlation between CYP2C19 enzymes involved in metabolism of a number of drugs genotypes and *prakriti* have also been reported[34,35]. Thus the principle of *Ayurgenomics* seems to bear similarities with that of pharmacogenetics/pharmacogenomics and exhibits the potential to serve as a platform in achieving the concept of personalized drug therapy. Some attempts to integrate Ayurveda into pharmacogenetics have been made[36].

Ayurgenomics:

Ayurgenomics, an integration of the principles of Ayurveda with genomics, plays a vital role in explaining how current drugs can be used more effectively by targeting them on patients of particular *prakriti. Prakriti*-based medicine can help in changing the current scenario of global health wisdom through effective integration of 'omics'. Ayurveda offers its modalities by way of *ahara* (diet), *vihara* (lifestyle) and *aushadhi* (medication), which constitute the three pillars of *prakriti*-based medicine. Disease prevention and promotion of health towards longevity with a better quality of life, the base of PM, could be achieved through these attributes of Ayurveda.

The current limitation of clinical heterogeneity in molecular genetic analysis of complex traits can be overcome by *prakriti*. It can serve as a tool to sub-group both healthy and diseased individuals. However the primary challenge of *Ayurgenomics* could lie in establishing the correlation between DNA and *prakriti*. The Indian Genome Variation (IGV) consortium 2005, initiated the single largest study to discover the genetic landscape of IGV related to disease and response to drugs[27,37]. The database generated from the study could be vital in reducing bottle necks in individualized approach towards common, chronic and complex diseases both in India and globally. Central Council for Research in Ayurveda and Siddha (CCRAS), Department of Ayush, Ministry of Health and Family Welfare, and Government of India have already instigated research for standardization and drug discovery, treatment for acute and tropical diseases and supportive therapy to chronic diseases like psoriasis, cancer, schizophrenia, HIV among others[27].

Whilst Traditional Medicine (TM) is practiced by people globally to help meet their primary healthcare needs, it often falls into disrepute due to lack of adequate empirical or theoretical base. Advancements in the analytical and biological sciences, along with innovations in genomics and proteomics can play an important role in validation of these ancient therapies. Since the correlation between genomics/proteomics and TM has been reported recently, Ayurveda can be used in developing PM to obtain optimal response to treatment. Ayurveda and omics together can lay a foundation to achieve efficient and cost-effective strategies for prevention, diagnosis, outcome prediction and treatment of diseases. Identification of genetic variations underlying metabolic variability in *prakriti* may provide newer approach to pharmacogenomics. An interdisciplinary approach integrating genomics and TM is therefore worth exploring. A methodical integration of Ayurveda, modern science and modern medicine could be employed to attain IM that focuses on the use of the individual's molecular and 'omic' information. The golden triangle concept articulated by Mashelkar in 2003, can thus be investigated further to achieve PM and offer remedies to the challenging issues of health.

ACKNOWLEDGEMENTS

The Corpus grant from Jamsetji Tata Trust to The Foundation for Medical Research supported the author during compilation of this review. I would like to thank the staff at The Foundation for Medical Research for their inputs.

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Accepted 06 March 2015
Revised 26 October 2014
Received 21 November 2013
Indian J Pharm Sci 2015;77(2):135-141