ABSTRACT

Deciphering human genome has ushered modern bio-medical science towards a future hope of revitalizing current symptomatic or prophylactic treatment methods into personalized and predictive medicine depending upon an individual’s genetic makeup. Genetic variations related to person’s response towards drugs, differential susceptibility to disease and reciprocity of phenotypic attributes related to environment, ethno-racial origin and diseases to genotypes have not been meticulously apprehended yet. Acharya Charaka explains, “योगमासाां तु यो विद्याद्देशकालोपपावितम्। पुरुषां पुरुषां िीक्ष्य स ज्ञेयॊ विषगुत्तमः॥” [1], that one is the best physician who knows how to administer the medicine in accordance with their region (habitation and procurement of medicinal plants) and time and Prakriti (Psychosomatic constitution) of each person individually. This is probably the first classical reference in the history of Indian medicine on Pharmacogenomics. Ayurveda classifying a person on the basis of “Prakriti” or unchangeable constitution type might be an advantageous inclination towards personalized medicine. Several genomic studies augmented the possibilities of yet undisclosed genetic basis of Ayurveda, which could further be integrated or complemented to current medical diagnosis and treatment. Further deep dive into the extremes of utilizable science and technology of this holistic practice remained quintessential for better enlightenment of future bio-medical science to fight all fiends of ailments.

Keywords: Pharmacogenomics, Ayurveda, Ayurgenomics, Personalized medicine

PHARMACOGENOMICS

INTRODUCTION:

Pharmacogenomics is the study of how genes affect a person’s response to drugs. It combines Pharmacology (the science of drugs) and Genomics (the study of genes and their functions) to develop effective, safe medications and doses that will be tailored to a person’s genetic makeup.[2] Many drugs that are currently available are “one size fit”, but they don’t work the same way for everyone. It can be difficult
to predict who will benefit from a medication, who will not respond at all and who will experience negative side effects (i.e. ADRs). With the knowledge gained from the Human Genome Project, researchers are learning how inherited differences in genes affect the body’s response to medications. These genetic differences will be used to predict whether a medication will be effective for a person and to help prevent ADRs.

Pharmacogenomics aims to develop rational means to optimize drug therapy, with respect to the patients’ genotypes, to ensure maximum efficiency with minimal adverse effects. The field of the pharmacogenomics is still in its infancy. Its use is currently quite limited, but new approaches are under study in clinical trials. In the future, it will allow the development of tailored drugs to treat a wide range of health problems, including Cardiovascular diseases, Alzheimer disease, Cancer, HIV/AIDS and Asthma.

We Are All Different:
The reason people vary in their response to drug treatments lies in the genetic differences, or variations between them. Following the Human Genome Project, research has focused on comparing human genomes to understand genetic variation and work out which genetic variants are important in health and the way we respond to drugs.

Two types of variation are common in human genome:

1. **Single Nucleotide Polymorphisms (SNPs):** Changes in single nucleotide bases (A, C, G & T)
2. **Structural Variation:** Changes affecting chunks of DNA which can consequently after the structure of the entire chromosome. Structural variation can happen in a number of ways: - Deletion, Insertion, Duplication, Inversion and Translocation. Structural variation appears to be quite common, affecting around 12% of the genome. It has been found to cause a variety of genetic conditions.

**Finding Disease Variants:**
Humans share around 99.9% of their genomes. The 0.1% that does differ between each of us affects our susceptibility to disease and response to drugs. Although this doesn’t sound a lot, it still means that there are millions of differences between the DNA of two individuals. The way scientist look at disease variants is to compare the genetic makeup of a large number of people who have a specific disease with those that do not. This allows scientist to look for genetic variants that are more common in people with a disease compared to people without the disease. However, looking for a disease that is caused by variants in a single gene is the simplest example. There are many complex diseases where variants in many different genes might be involved. So, for this type of comparison to be effective very large groups of people need to be studied, usually in the tens of thousands, to find the variants with subtle effects on disease risk.

Researchers also try to pick individuals with similar phenotypes, in both the disease and healthy groups, so that the disease genes are easier to identify and study.

**Drug-Metabolizing Enzymes:**
There are several known genes which are largely responsible for variances in drug metabolism and response. Here we focus
on the genes that are more widely accepted and utilized clinically for brevity.

I. Cytochrome P450s
II. VKORC1
III. TPMT

### Summary for Drug Metabolism of Major CYPs

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Fraction of Drug Metabolism (%)</th>
<th>Example Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>20-30</td>
<td>Debrisoquine, meoprolol, sparteine, propoanolol, encainide, codeine, dextromethorphan, clozapine, desipramine, haloperidol, amitriptyline, imipramine</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>10</td>
<td>Tolbutamide, ibuprofen, mefenamic acid, diclofenac, isosartan, tetrahydrocannabinol</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>5</td>
<td>S-mephenytoin, amitriptyline, diazepam, omeprazole, proguanil, hexobarbital, propranolol, imipramine</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>40-45</td>
<td>Erythromycin, ethinylestradiol, nifedipine, trizolam, cyclosporine, amitriptyline, imipramine</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>&lt;1</td>
<td>Erythromycin, ethinylestradiol, nifidipine, trizolam, cyclosporine, amitriptyline, aldosterone</td>
</tr>
</tbody>
</table>

II. VKORC1: It is responsible for the pharmacodynamics of Warfarin[^4]

III. TPMT: It catalyzes the S-methylation of thiopurines, thereby regulating the balance between cytotoxic thioguanine nucleotide and inactive metabolites in hematopoietics cells.[^5] TMPT is highly involved in 6-MP metabolism and TMPT activity and TMPT genotype is known to affect the risk of toxicity. Excessive levels of 6-MP can cause myelosuppression and myelotoxicity.[^6]

**APPLICATIONS:**
A few more commonly known applications of pharmacogenomics[^7]

- Improve drug safety and reduce ADRs
- Tailor treatments to meet patients unique genetic pre-disposition, identifying optimal dosing
- Improve drug discovery targeted to human disease

- Improve proof of principal for efficacy trials.

Pharmacogenomics may be applied to several areas of medicine, including pain management, cardiology, oncology and psychiatry.

- A place may also exist in forensic pathology, in which pharmacogenomics can be used to determine the cause of death in drug-related deaths where no findings emerge using autopsy.^[8]

**CHALLENGES:**
Although pharmacogenomics is likely to be important part of future medical care, there are many obstacles to overcome before it becomes routine. There are often a large number of interacting genetic and environmental factors that may influence the response to a drug. Even when associations between a genetic variant and a drug response have been clearly

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[^4]: Reference 4
[^5]: Reference 5
[^6]: Reference 6
[^7]: Reference 7
[^8]: Reference 8
demonstrated, suitable tests still have to be developed and proved to be effective in clinical trials. The tests that have succeeded in a clinical trial still have to be shown to be useful and cost effective in a healthcare setting. Issues surrounding the availability of the test include:\textsuperscript{[9]}

- **The lack of availability of scientific data:** Although there are considerable numbers of DME involved in the metabolic pathways of drugs, only a fraction have sufficient scientific data to validate their use within a clinical setting.

- **Demonstrating the cost-effectiveness of pharmacogenomics:** sufficient evidence does not at this time exist to validate the cost-effectiveness and cost-consequences of the test.

Regulatory agencies will have to consider how they assess and license pharmacogenetic products. Health services will have to adjust to new ways of deciding the best drug to give an individual. Several challenges exist that slow the update, implementation and standardization of pharmacogenomics. Some of the concerns raised by physicians include:\textsuperscript{[10]}

- Limitation on how to apply the test into clinical practices and treatment
- A general feeling of lack of availability of the test
- The understanding and interpretation of evidence-based research
- Ethical, legal and social issues

**PHARMACOGENOMICS AND AYURVEDA**

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.\textsuperscript{[11]}

While the idea of IM in western medicine is a very recently entertained concept, Ayurveda 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.\textsuperscript{[11]}

**AYURVEDA**

Ayurveda is not folklore or 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 (specific effect), while in modern pharmacology the action of the drug is attributed to the chemical structure of a molecule. 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, e.g. 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 includes food habits and digestive capabilities, 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 tridosha in an individual from his or her homeostatic state to a disease. These proportions of tridosha are determined genetically (shukra shonita) and are influenced by environment (maternal diet, lifestyle) during development. Ethnicity (Jatiprasakta), familial characteristics (Kulanupatini) and geoclimatic regions (Deshanupatini) are known to influence the phenotypic variability. Consequently the factors that contribute to inter-individual variability at the genetic 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 estate by appropriate dietary and therapeutic regime. A particular dosha is known to be altered by various factors namely food, medicines and 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.

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) polymorphisms as well. An initiative was taken to correlate different prakritis and their biochemical and transcriptomic profiles. in their study, Patwardhan et al. used Human Leucocyte Antigen (HLA) DRB1 types to compare individuals with their Ayurvedic classification. The data established a rational and preliminary experimental support for the concept of an association between HLA alleles and the Ayurvedic tridosha 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. The study have reported the implication 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. Thus the principle of Ayurgenomics seems to bear similarities with that of pharmacogenomics and exhibits the potential to serve as a platform in achieving the concept of personalized drug therapy. Some attempts to integrate Ayurveda into pharmacogenomics have been made.

**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 (OGV) consortium 2005. Initiated the single largest study to discover the genetic landscape of IGV related to disease and response to drugs. The database generated from the study could be vital in reducing bottle necks in individualized approach towards common, chronic and complex disease both in India and globally. CCRAS, Department of Ayush, Ministry of Health and Family Welfare and Govt. 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. 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 can play an important role in validation of these ancient therapies. Since the correlation between genomics 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 variation underlying metabolic variability in prakriti may provide newer approach to pharmacogenomics. An interdisciplinary
approach integrating genomics and TM is therefore worth exploring. A methodological integration of Ayurveda, modern science and modern medicine could be employed to attain IM that focuses on the individual’s molecular and ‘omic’ information. The golden triangle concept articulated by Mashelkar in 2003, can thus be investigated further to achieve Personalized Medicine (PM) and offer remedies to the challenging issues of health.

REFERENCES:


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Jaimala Anmasaheb Jadhav, Aparna Ghotankar