Review Article

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Genomic Counterparts to Human Constitution (*Prakriti*)

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Abstract

Background: *Prakriti* (constitution) of a man has genetic and acquired aspect; the genetic aspect depends upon sperm and ovum, while acquired constitution develops in relation to environmental factors such as climate, season, time factor, age, race, familial inheritance. New approaches and development in modern science improve and accelerate the concept of *Prakriti*. This short discourse gives us a clue to fundamentals of *Prakriti* as met with in Ayurveda and evidence based scientific supporting data validating and approving it. **Aim and Objectives:** To revalidate the Ayurvedic genetic concept of *Prakriti* in light of evidence based studies. **Materials and Methods:** Information extracted from various classics such as *Brihattrayi* (*Charaka, Sushruta, Ashtanga Hridaya* and *Ashtanga Sangraha Samhita*) and published information on recent research developments of *Prakriti* including original articles in Pubmed, Scopemed, Pubmed Central Databades, Dhara online database and other allied databases were taken into study for the review. Reported data was analyzed and represented for current review. **Conclusion:** Contemporary evidences confirm and establish *Prakriti* as genetic theory of modern science. The current work appears to be the first of its kind and can be considered as reference standards for future studies.

Keywords: Ayurveda; Personalized medicine; *Prakriti;* Genetics.

Introduction

Prakriti (constitution) is conductive state of *Dosha*, formed at the time of formation and development of *Garbha* (uterus) due to self-excitatory causes and which runs from birth to death.[1] At the time of union of sperm and ovum, predominance of *Dosha* (humour) decides the constitution of every individual.[2] According to the permutation and combination of different *doshas* in different stages, *Prakriti* of an individual varies viz. *Vataja, Pittaja, Kaphaja, Vata-Pittaja, Pitta-Kaphaja, Vata-Kaphaja* and *Vata-Pitta-Kaphaja*.[3] Predominance of one, two or all three *Dosha*, in various proportions, affects fetus. Exhibition of such predominance is *Dosha Prakriti* of that individual.[4] *Prakriti* of a man has genetic and acquired aspect; the genetic aspect depends upon sperm and ovum.[5] While acquired constitution develops in relation to environmental factors such as climate, season, time factor, age, race, familial inheritance.[6]

In contemporary view, defects of sex gametes (sperm and ovum), action associated with soul, status of uterus, time (of conception, age of uterus, season at time of conception, of gaining strength etc.), food and regime of mother are factors affecting fetus. All these factors vitiate *Dosha* which results in impairment of shape, color and sensory-motor organ of fetus.[7]

Prakriti has been one most notable basic construct of Ayurvedic health care philosophy. It fundamentally explains the biological specificity operating at cellular and genomic level and is held largely responsible

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for distinctions among individuals in various arenas of functions and appearance.[8] Knowledge of *Prakriti* subtype may go a long way in health maintenance by making one aware of suitable and unsuitable substances applicable on a one-to-one basis.[9] *Prakriti* has remained a subject of extensive exploration in the recent past. As a result, it is now better understood in terms of its genomic and biochemical correlations and subsequent clinical applications.[10,11,12,13]

These days, when refined techniques have made it possible to reach micro-world, need has arisen to perceive and discuss the fundamentals of *Prakriti* with contemporary science. Present review is aimed to revalidate the Ayurvedic concept of *Prakriti* in light of evidence based studies.

Methodology

Information extracted from various classics i.e. *Brihattrayi* (*Charaka, Sushruta, Ashtanga Hridaya* and *Ashtanga Sangraha*) and published information on recent research developments on *Prakriti* including original articles in Pubmed, Scopemed, Pubmed Central Databades, Dhara online database and other allied databases were taken into study for the review. Reported data was analyzed and represented for the current review.

Genetic Concept of Prakriti: The Ayurvedic Acumen

Researches in the field of genetics has explored that all living things are complex of large number of independent heritable units.[14] These genes are transferred to the offspring from parents as when one germ cell from father combines with one from mother; the individual has his full complement of genes.[15] Even today, it can be comfortably concluded that the mother and father through medium of their germ cells, chromosomes and genes exert influence on individual nature of human being. This modern approach is similar to Ayurveda, where *Shukra* (sperm), *Shonita* (ovum), *Prakriti* (the nature of parental germs) act as influencing factors in constitution and temperament of individual. Furthermore, *Charaka* has also given an indication that the sex determination of the child also depends upon *Shukra-Shonita* predominance of germoplasm. *Sushruta* also holds *Sukra* or *Artava* predominance responsible for the sex determination of the fetus.[16] This concept of Ayurveda resembles in essence the modern theory of genes or X -Y chromosomes. Alike Ayurveda, where *Prakriti* is said to be of various types, modern researchers have now established that genetic makeup of individuals in a population vary. Current researches related to *Prakriti* are proving the genetic association with it.

Pharmacogenomics and Ayurgenomics: A Way Towards Personalized Medicine

A systemic integrative approach forming the Golden Triangle of Ayurveda, modern science and modern Medicine can pave the path to personalized medicine and offer remedies to the challenging health issues.[17] *Prakriti* distinguishes and characterize a person apart from others and consists of anatomical, physiological and psychological makeup of a person. *Prakriti* is nothing but a human genome project applied by our Acharya to determine its influence on every aspect of life.

Pharamacognomics concept deals with genetic interactions with drugs, and having a great impact on drug design and development, and is inherently related to *prakriti*.[18] Pharmacogenomics, deals with the influence of genetic variation on drug response in patients by correlating gene expression or single-nucleotide polymorphisms with a drug's efficacy or toxicity. It is involved in the study of genes that code for drug metabolizing enzymes, drug receptors, drug transporters and ion channels or efflux systems. This personalized medicine approach aims to develop rational means to optimize drug therapy, with respect to each individual's molecular diagnosis unique genetic makeup, to ensure maximum efficacy with minimal

adverse effects.[19,20]

Study of *Prakriti* and its association with diseases has been defined since Vedic period. According to Ayurveda, pharmacogenomics is nothing but *Prakriti* based medicine.[21] In addition, *Purusham Purusham Vikshya Siddhant* (personalized medicine approach) is well employed by Ayurvedic physicians in diagnosis and treatment.[22]

Ayurgenomics is the integration of the principles of Ayurveda with genomics. The primary challenge of Ayurgenomics is to establish the correlation between DNA and *Prakriti*. Ayurgenomics seems to bear similarities with pharmacogenetics and has potential to be a platform to achieve personalized drug therapy. The understanding of Single Nucleotide Polymorphism (SNP) science leads to the concept of personalized medicine which gets parallel with the concept of Prakriti based medicine i.e. Ayurgenomics. Better understanding of the human genome has helped in understanding scientific basis of individual variation.[23]

Globally, there is a positive trend towards holistic health, integrative sciences, systems biology approaches in drug discovery and therapeutics that has remained one of the unique features of Ayurveda.[24] A golden triangle[25] consisting of Ayurveda, modern medicine and science will converge to form a real discovery engine that can result in newer, safer, cheaper and effective therapies. It will be in the interest of pharmaceutical companies, researchers and ultimately the global community to respect the traditions and build on their knowledge and experiential wisdom.[26]

A landmark study finds links between *Prakriti*, the fundamental principle of personalized medicine of Ayurveda, and modern genomics for development of predictive and personalized medicine. Human genome sequencing and subsequent mapping of genetic variability has allowed us to identify genetic variations and patterns of variability across diverse global populations. India has also put systematic and concerted efforts to identify relatedness amongst the diverse Indian populations at genetic level. The first step in this regard was the CSIR led Indian Genome Variation Consortium project which provided the first genetic landscape of India. more than 1000 individuals were screened, out of which 120 individuals of predominant *Prakriti* were identified, and subsequently 96 unrelated ethnically matched healthy individuals with predominance of either *Vata* (39 individuals), *Pitta* (29) or *Kapha* (28) *prakriti*, belonging to an age group of 18–40 years. The genetic background of subjects was reconfirmed through analysis of genetic similarity with this group and populations of the Indian genome variation project. The subjects shared genetic affinity with the Indo-European populations of North India.[27]

An exploratory study suggests discrete causal pathways for Rheumatoid Arthritis etiology in *Prakriti* based subgroups, thereby, validating concepts of *Prakriti* and personalized medicine in Ayurveda. Ayurgenomics approach holds promise for biomarker discovery in complex diseases.[28]

Progresses in Personalized Medicine

Scientists in pursuit of personalized medicine believe that although pharmacogenomics has already begun reaping benefits, the field is still in its infancy, and change will come gradually. Companies are now marketing CYP450 genotyping tests to physicians and the public to help predict optimal dose and drug efficacy.[29] The recent development of micro RNA microarray technology yields new insights in breast cancer. Personalized approaches for the prevention and treatment of breast cancer will not be realized by any one approach, but rather through multiple approaches acting in concert. The oncology workforce in the next decade will evolve novel technologies to deliver personalized medicine at cheaper costs as most hospitals and physician practices develop electronic medical records.[30]

The gene expression profile using microarray and compared between pathologic response

and residual disease group were investigated. In patient with breast cancer, a set of key gene that the marker predicted, whether paclitaxel would be response or not was investigated. The Bioinformatics group is constructing an integrated cancer genome database for clinical information, results of typing SNP, and gene expression data by micro-array for cancer patients to prepare an intellectual foundation of efficient identification of important genes related to treatment sensitivity or adverse effects of anticancer drugs.[31]

A higher level of genetic divergence was found between groups of populations that cluster largely on the basis of ethnicity and language. Indian populations not only overlap with the diversity of HapMap populations, but also contain population groups that are genetically distinct. These data and results are useful for addressing stratification and study design issues in complex traits especially for heterogeneous populations.[32]

Development of the IGV Browser that provides allele and genotype frequency data generated in the IGVC project. In IGV Browser one can analyze and compare genomic variations in Indian population with those reported in HapMap along with annotation information from various primary data sources.[33]

A correlation was established between the SNP of MDR1 2677 and drug response in patients receiving GEM chemotherapy. SNP of the genes for ATP-binding cassette transporters is related to the side effects of anticancer drugs and that of drug metabolism-related enzyme genes is involved in the activation of gemcitabine (GEM).[34]

Genetic Polymorphism and Prakriti

Genetic polymorphism (GP) is due to the difference in DNA sequence among individuals, groups, or populations. It may be the result of chance processes, or may have been induced by external agents (such as viruses or radiation). If a difference in DNA sequence among individuals has been shown to be associated with disease, it will usually be called a genetic mutation.[35] This concept may be related genetic concept of *Prakriti*. Ayurveda has narrated that, a part of seed (*Beejabhaga*) is responsible for formation of organ.[36] If the part of seed (sperm or ovum) is vitiated, it will result in the vitiation of the respective organ.

GP within a specific genotype may occur with different frequencies depending on racial or population factors, which evolved from selective geographic, regional, and ethnic factors. Inter-individual differences in response to drug therapy due to differences in acetylation of drugs are well-studied example of genetic polymorphism. These demographic and ethnic differences affecting genotype may be related to Ayurvedic concept of factors responsible for *Prakriti* which include *Jati Prasakta, Kula Prasakta* and *Deshanupatini* types of *Prakriti*.[37]

Adverse Reactions and Genetic Differences

Adverse Drug Reactions (ADRs) rank as the 4th leading cause for death, ahead of pneumonia, diabetes and traffic accident; and only about half of patients treated with conventional drugs adequately respond to pharmacotherapy.[38] A review of the pharmacogenetic literature showed that sizable portions of ADRs (30%) involved in drug therapy implicated genetic polymorphisms of drug metabolism by CYP2D6.[39]

The concept of personalized medicine is now all about DNA. Single nucleotide polymorphism (SNP) and epigenetic factors influence drug response and form basis of personalized medicine, whereas *Tridosha* theory forms basis of *Prakriti* based medicine. *Prakriti* based medicine and other traditional medicine systems have potential to offer remedies to challenging health issues such as adverse drug reactions, drug withdrawals and economic disparities among few.[40]

Association of Diseases and Prakriti: Clinical Evidences

Concept of *Prakriti* has remained a subject of extensive exploration in recent past and is now better understood in terms of its genomic and biochemical correlations and subsequent clinical applications.[41-44] Individuals from three most contrasting constitutional types exhibit striking differences with respect to biochemical and hematological parameters and at genome wide expression levels. Functional categories of genes showing differential expression among *Prakriti* types were significantly enriched in core biological processes like transport, regulation of cyclin dependent protein kinase activity, immune response and regulation of blood coagulation.[44]

Prakriti explains the biological specificity operating at cellular and genomic level and is held largely responsible for distinctions among individuals in various arenas of functions and appearance.[45] Significant association between CYP2C19 genotype and major classes of *Prakriti* types were observed in 75 individuals. Extensive metabolizer genotype was found to be predominant in *Pitta Prakriti*. Poor metabolizer genotype was highest in *Kapha Prakriti*. These observations are likely to have significant impact on phenotype-genotype correlation, drug discovery, pharmacogenomics and personalized medicine.[46] It also correlates with the *Agni* (~appetite) concept of different *Prakriti*. In individuals having *Vata* predominant constitution, due to the affliction of the site of *Agni* by *Vata*, their *Agni* is irregular. In individuals having *Pitta* predominant constitution, due to the affliction of site of *Agni* by *Pitta*, their *Agni* is sharp. Similarly, in *Kapha* predominant constitution, *Agni* is mild due to the affliction of the site of *Agni* by *Kapha*.[47]

There is a genetic basis for three major *Prakriti* and *Tridosha*, influencing DNA at the time of fertilization, so that an individual is developed with specific characteristics of a particular *Prakriti*. Association of *Vata* increases allele frequency in demographic receptor genes and serotoninergic receptor gene 5HTR 1B under study. All functions attributed to dopamine receptors are included in function of *Vata* in Ayurveda. Serotoninergic receptor gene 5HTR 2A shows a significant increase of allele frequency in *Kapha* associated *Prakriti*. *Kapha* plays an important role in maintaining immunological status. Human leukocyte antigen genes having role in host response to infections and profound effect on immunogenic susceptibility to various diseases, the frequency of which is high in *Kapha Prakriti* attest the scientific basis of *Tridosha* theory.[48] Genetic connotation of *Prakriti* showed a correlation between HLA alleles and *Prakriti* type, establishing a rationale and preliminary experimental support for concept of an association between HLA alleles and *Tridosha* theory of individual *Prakriti* types.[49] Recently a study reported complete absence of the HLADRB1*02 allele in the *Vata* type and of HLA DRB1*13 in the *Kapha* type. Higher allele frequency of HLADRB1*10 was noted in the *Kapha* type than in the *Pitta* and *Vata* types.[50] Ayurveda has also quoted that the *Kapha Prakriti* persons have more *Bala* which can helps to combat disease.[51]

Prakriti evaluations of normal 137 healthy individuals of either sex between the age group 18 to 30 years were done using a standardized validated questionnaire (TNMC *Prakriti* 2004). They observed ADP-induced maximal platelet aggregation (MPA) was highest among *Vata-Pitta Prakriti* individuals and these individuals responded better to lower dose of aspirin compared to other *Prakriti* types. Their results suggest that identifying *Prakriti* may help in individualizing therapy or predicting proneness to a disease.[52] Specific *Prakriti* is prone to disease with the influence of the same *Dosha*.[53]

In another study, intelligent quotient (IQ) of *Vata prakriti* individual was found less as compared to *Pitta prakriti* and IQ of *Pitta prakriti* less as compare to *Kapha prakriti*. Therefore, *Prakriti* assessment is one of the decisive guidelines in direction of career selection.[54] Similarly in Ayurveda, Intelligence is said to be more in and less in

Vata Prakriti persons.[55]

Apart from lipid profile, serum uric acid recently considered to be an independent predictor of cardiovascular mortality.[56] It was also found to be significantly higher in *Kapha* males, compared to other groups. Besides, *Kapha* males also had high levels of LDL, reduced prothrombin time and low expression of genes related to fibrinolysis (KRT1 and F2), features which are reported to increase risk for atherosclerotic conditions.[57] Susceptibility of *Kapha* individuals to cardiovascular and atherosclerosis also narrated in Ayurveda texts (*Dhamani Pratichaya*). It was also found that the levels of cholesterol, triglycerides, LDL-C and VLDL increased with age and were higher in *Kapha-Pittaja Prakriti*. So, life style changes and regular exercise must be done with increasing age and in *Kaphapittaja Prakriti*.[58] Hematological differences also correlated with gene expression levels. Higher expression of genes which affects hemoglobin levels HBA1, HBB, NOV[59] in *Pitta* compared to *Vata* and *Kapha* correlate with the differences in hemoglobin levels between the *Prakriti*.

Higher incidence of Diabetes was found in subjects of *Kaphaja* and *Vata-Kaphaja Deha Prakriti, Rajasika Manasika Prakriti*, mesomorphic body type and somatotonic temperament.[60,61] In another study, MTHFR C677T and A1298C genotypes were determined by PCR followed by restriction digestion for 54 type 2 diabetes mellitus (T2DM) patients and 56 matched normal controls. The study found an association between T2DM and MTHFR C677T but this association shows CT genotype is a protective genotype for T2DM. These genotypes did not show association with *Prakriti*.[62] 75 patients with established Parkinson's disease (PD) and closely related controls with no known neurologic disease were assessed for their *Prakriti*. Finding was highly significant, indicating that the incidence of PD is highest in those with *Vata Prakriti*.[63]

Future Perspectives

The concept of *Prakriti* is a repository in a vast Ayurvedic treatises that are yet unknown to people due to lack of scientific evidence of data. Ayurvedic concepts of paternal germ cell and their basic constituents (*Bija, Bijabhaga* and *Bijabhagavayava*), and their definite hereditary role in determination of individual are now well validated and approved by contemporary researches. On the basis of aforesaid clinical evidences it can be inferred that each specific disease poses as risk factor or show predominance to specific type of *Prakriti* individuals. Investigations in the field of genes and temperament have now shown that ancestry of individual gives the clue to respective temperament. It is now possible to demonstrate that attributes owe much to heredity, although it is impossible to specify what particular genes are involved. The whole matter is very complex and waits for far more investigations than have been done.[64]

In field of Pharmacogenomics, hopefully, once the genetic blue print gets revealed, researchers could create DNA tests to gauge individual's risk for conditions like diabetes and cancer, allowing for targeted screening or preemptive intervention. Although not all drugs can be personalized, there is most likely to be clinical significance in tailored medicine for prodrugs, drugs with narrow therapeutic drugs and drugs that target a key molecule or a critical pathway. Drug safety is the first arena in which patients can benefit from pharmacogenetics and pharmacogenomics.

Researchers have high expectations that the use of diagnostic DNA microarrays or gene chips will simplify and expand testing and have clinical applications in diagnosis, disease prevention, drug selection and dose calculation. Ayurgenomic seems to bear similarities with Pharmacogenomics. Further studies on these concepts and interdisciplinary approach of integrating genomics with traditional knowledge are highly anticipated, which may prove torch bearer in achieving the goal of personalized healthcare.

Conclusion

Ayurvedic concept of *Prakriti* is nothing but the definite genetic constitution. *Prakriti* of a person is individual just like a genome sequence. *Prakriti* theory is unique in terms of multi-faceted approach, however it is not been fully utilized to its potential. Contemporary studies confirm and establish the *Prakriti* as genetic theory of modern science. However, the Ayurvedic hypothesize give us a clear cut indication and a material for research to the scientists of today, which if proved may provide a revolutionary instrument to the mankind in the field of development of human organism and its personality.

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