

Traditional medicine and genomics

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ABSTRACT

'Omics' developments in the form of genomics, proteomics and metabolomics have increased the impetus of traditional medicine research. Studies exploring the genomic, proteomic and metabolomic basis of human constitutional types based on Ayurveda and other systems of oriental medicine are becoming popular. Such studies remain important to developing better understanding of human variations and individual differences. Countries like India, Korea, China and Japan are investing in research on evidence-based traditional medicines and scientific validation of fundamental principles. This review provides an account of studies addressing relationships between traditional medicine and genomics.

Key words: Ayurveda, personalized medicine, genomics, holistic approach, traditional medicine, traditional chinese medicine, sasang constitution medicine.

INTRODUCTION

One of the prominent challenges of the post-human-genome sequence era is to generate a detailed understanding of inheritable differences in the human genome. Structural and functional genetic differences in humans can take the form of single nucleotide polymorphisms (SNP),^[1] copy number variations (CNVs),^[2] and epigenetic or gene expression modifications.^[3-5] These inherited inter-individual variations in DNA sequence contribute to phenotypic variation, influencing an individual's anthropometric characteristics, risk of disease and response to the environment.^[6] Characterizing genetic variation may bring improved understanding of differential susceptibility to disease, differential drug response, and the complex interaction of genetic and environmental factors, which go to produce each phenotype.^[7]

Studying outcomes due to inter-individual differences requires classifying human populations into genotypic or phenotypic cohorts. Using demographic background to cluster human populations according to phenotype-representing-genotype has proved challenging.^[8]

Consequently, the design of large scale genotyping projects such as the international HapMap initiative, and their (future) applications illustrate the complexities and ambiguities associated with use of group labels in genomic research.^[9] Attempts to correlate phenotype characteristics associated with ethnicity, geographical division, or disease to genotypes have only had limited success. Using ethnicity or race as a basis for phenotypic variation is controversial; no current approach to identifying phenotypes associated with haplotypes is considered adequate.

Ayurveda, the traditional system of Indian medicine, Traditional Chinese medicine and Korean medicine all have well-defined systems of constitutional types used in prescribing medication bearing distinct similarities to contemporary pharmacogenomics. An interdisciplinary approach integrating genomics and traditional medicine is therefore worth exploring as a search for phenotypes that may collectively be considered for genotyping. This review summarizes research applying a genomic approach to investigate constitutional differences in various traditional systems of medicine from Asia. It provides consistent preliminary insights into the whole field.

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AYURVEDA AND GENOMICS

In its holistic foundation,^[10] Ayurveda uses a threefold classification known as *tridosha* theory consisting of *Vata*, *Pitta* and *Kapha dosha* for determining a person's mind-body classification. Tridosha theory introduces principles known as Vata - related to motion, Pitta - related to metabolism

and Kapha - related to lubrication and structure, to classify phenotypic groupings. Elements of Vata, Pitta and Kapha are present in all people, but with differing degrees of predominance.^[11,12] Each *dosha* is represented by different physical, physiological and psychological characteristics. *Vata* (V) has kinetic functions, and is manifested in mental functions such as enthusiasm, concentration etc. and physical functions such as respiration, circulation, voluntary actions etc. In modern physiology, nervous system activities are primarily assigned to it. Mental functions such as intelligence, clear conception and physical phenomena like digestion; assimilation, heat production, hormones, enzymes and metabolism are attributed to *Pitta* (P). *Kapha* (K) manifests in mental functions such as courage, and bodily functions such as tissue building, body strength, immunity, resistance and anabolic activity. V, P and K constitute regulatory systems respectively controlling input/output, turnover and storage making them universal properties of all living systems.^[2] *Doshas* are fundamental regulatory principles responsible for maintaining organism functioning and manifesting those characteristics typifying each individual.^[13] In the natural state of equilibrium, Tridosha is responsible for maintaining health; its vitiation results in disease. All derived Ayurvedic concepts concerned with physiology, pathology, diagnosis, prognosis, medicine and therapeutics, are based on the fundamental concepts of V, P, and K *dosha* phenotypes and their combinations at any given moment.

The Ayurvedic classification system classifies all individuals into different 'Prakriti' types based on relative proportions of each dosha. Prakriti constitutes the bodily constitution, temperament and fundamental form specific for every individual. It is held to remain unaltered during the lifetime, having been mostly determined at conception, with contributions from environmental factors including maternal diet and lifestyle. It is therefore thought to have strong genetic components. In Ayurveda, the Prakriti classification of an individual's constitution is based on differences in physical, physiological and psychological characteristics, and is independent of racial, ethnic or geographical considerations.^[14]

Prakriti assessment evaluates each Dosh's degree of dominance.^[15] It constitutes an important step in Ayurvedic advice, diagnosis and therapeutics. Many individuals can be categorized into one of the three extreme Prakriti types, Vata, Pitta and Kapha. Almost every individual has one dosha dominant with one or both the others subdominant. Subtle combinations of the three V, P, K. Prakriti types are as specific and individualized as the DNA sequence-based genetic makeup.

Prakriti specific treatment including medicine, diet

and lifestyle is a distinctive feature of Ayurveda.^[14] We hypothesize that (1) Prakriti has a genetic connotation that can provide a tool for classifying human populations based on broad phenotype clusters, and (2) The human phenome based on Ayurveda can provide a genetic basis for the three major constitutions or Prakriti.

Better characterization of the human genome has improved the scientific basis for understanding individual variation. The Ayurvedic Prakriti concept should be examined from a genomic perspective. Permutations and combinations of V, P, K attribute characters along with other host factors such as tissue status (Dhatusarata), twenty Gunas, digestive capacity and metabolic power (Agni), psychological nature (Manas Prakriti), habitat (Desha), and season (Kaala), lead to sufficient numbers of variants to define a unique constitution for every individual. Ayurveda thus describes the basis of individual variation.^[16] The importance of such individual variations in assessing states of health and disease was underlined as an important basic principle by Charaka some 4000 years ago: 'Every individual is different from every other and should therefore be considered a different entity; as many variations are there in the Universe, all are seen in Human beings.'^[17]

The concept of Prakriti plays a central role in understanding health and disease in Ayurveda, in a very similar way to the pharmacogenetics that is expected to become the basis of designer medicine.^[18] The fundamental principles of the Ayurvedic system of medicine can be used to create Designer Medicines. Identifying a genetic basis for 'Prakriti' constitutes a step towards this. Understanding relationships between Prakriti and genome is therefore important. Functionally, it will involve creating three organized databases capable of intelligently communicating with each other to give a customized prescription, human constitution (genotype), disease constitution (phenotype) and drug constitution. The 'Golden Triangle' of Ayurveda, modern medicine and modern science will converge to form a real discovery engine that can result in newer, safer, cheaper and effective therapies.^[19]

Every individual is different. Identifying factors that may determine a person's 'individuality', genotypes associated with phenotypes, and so classify human populations is therefore important. Current classification of human populations is broadly based on ethnicity; geographical location, language or self reported ancestry. However, such commonly used ethnic labels are inaccurate representations of genetic clusters, and do not reflect underlying genetic makeup.^[20] Identifying specific phenotypic features and correlating them with genotypes constitutes the major program of phenomics.^[21] However there is no consensus on how to define phenotypes, or which phenotypic features

are to be included in the database. Classifying human populations thus remains a major challenge to biomedical sciences.^[22]

Ayurveda has been investigated for this purpose, based on the hypothesis that Prakriti types (V, P and K) may offer phenotypic datasets suitable for analysis of underlying genetic variation. As a proof of concept, a first study evaluated 76 subjects both for their Prakriti and HLA DRB1 types, finding significant correlations in support of it.^[8,23] The study concluded that Ayurveda based phenomes may provide a model to study multigenic traits, possibly offering a new approach to correlating genotypes with phenotypes for human classification. To prove this hypothesis, more scientific exploration is required; differential gene expression analysis using micro arrays to identify up and down regulated genes in major Prakriti types. Such genes could be used for further analysis of DNA polymorphism, SNP analysis and gene expression in large populations of different ethnic groups.

The three major constitution types described in Ayurveda have unique putative metabolic activities, K being slow, P fast, while V is considered to have variable metabolism. We hypothesized that this might relate to drug metabolism and genetic polymorphism of drug metabolizing enzymes (DME). Inter-individual variability in drug response can be attributed to polymorphism in genes encoding different drug-metabolizing enzymes, drug transporters and enzymes involved in DNA biosynthesis and repair. Gene polymorphisms precipitate in different phenotypic subpopulations of drug metabolizer. Poor metabolizer (PM) have high plasma concentration of the drug for longer periods and so retain drugs in the body for longer times. Intermediate metabolizers retain drugs in the body for normal time periods. Extensive metabolizers (EM) retain drugs in the body for the least time, plasma concentrations being high for shorter periods.

Metabolic variability in different Prakriti types was studied using the drug metabolizing enzymes *CYP2C19/CYP2C9* gene polymorphism model. The distribution of *CYP2C19* and *CYP2C9* genotypes was investigated in 132 healthy individuals of different *Prakriti* classes.^[24] The results obtained suggest possible association of *CYP2C19* gene polymorphism with Prakriti phenotypes. EM genotypes were predominant in P Prakriti while PM genotypes were highest in K. It is interesting to note that *1/*3 genotype specific to the extensive metabolizer group was present only in P, while the *2/*3 genotype typical of the poor metabolizer group was observed in K as expected. Similarly, in case of gene polymorphism we observed that the occurrence of EM genotypes was significantly higher in P Prakriti. Our study thus demonstrated a probable genomic basis for metabolic differences attributable to Prakriti, possibly providing a new approach to Pharmacogenomics. Its results should be validated with a larger sample size.

Genome-wide expression and biochemical differences between Ayurveda-based Prakriti types have also been studied,^[25] revealing differentially expressed genes related to biological processes across different Prakriti types. Over-expression of genes related to immune response was seen in Pitta, whereas the Vata group showed differences in expression of genes related to cellular processes. Kapha males showed up-regulation of genes involved in cellular biosynthesis. A number of hub genes like *TLR-4*, *FAS*, and *HLA-DQB1* linked to complex diseases, and a few genes like *DPYD*, *ABCC1*, and *FTL*, associated with outcome of cancer treatment, were present in data-sets of genes differentially expressed among Prakriti types. Despite limitations like small sample size, objectivity in Prakriti assessment, use of extreme Prakritis and homogenous subject group, this study provides evidence that differences exist across different extreme constitutional types at gene expression level.

An attempt was made to integrate Ayurveda with functional genomics to identify pathways associated with activity of crude and active components of Ashwagandha, a herb used in cancer treatment.^[26] A similar study on the pharmacogenomics of medicinal plants has also been undertaken.^[27]

KOREAN CONSTITUTION MEDICINE AND GENOMICS

Sasang constitution medicine (SCM) is an integral part of traditional Korean constitution-based medicine. It recognizes four human constitutions: Tae-eum, So-Yang, So-eum, Tae-Yang, into which every human being is categorized, based on physical and physiological attributes. Although traditional Korean medicine is influenced by traditional Chinese medicine, SCM emphasizes sociological as well as biological attributes in determining constitutional types.^[28] Symptomatic observation like healthy state, disease-specific symptoms, major diseases and common symptoms are integral parts of SCM diagnosis. Individualized medicine is based on assumptions of variations in a. susceptibility to a particular pathological condition, and b. treatment response, similar to the way constitutional medicine is practiced in Ayurveda. Assumptions include an invariant constitution determined at birth, specific criteria for identifying Sasang constitution, and phenotypic variation predicting an underlying genetic basis for SCM.^[29]

Current studies are focusing on elucidating the genetic basis for these Sasang constitutions. Genome wide linkage analysis has identified genetic loci on chromosome 8q11.22–23 and 11q22.1–3, which include 14 labeled genes associated with Sasang constitution. Further examining the candidate gene loci would help to identify gene variations associated with particular Sasang constitutions.^[30]

To study association of genetic polymorphism in *MDR1*

with Sasang constitution, 270 individuals were genotyped for *MDR1* C1236T, *MDR1* G2677T/A and C3435T. Heterozygous mutants for *MDR1* C1236T (C/T) occurred with highest frequency for So-eum followed by So-yang. This indicated that individuals with C/T genotype were more likely to be So-eum type. Similarly in *MDR1* G2677T/A polymorphism wild type allele G was found to be associated with Tae-eum type. These results are suggestive of diagnostic value of constitutional types, but further studies are required to examine the effect of these associations on drug metabolism and thus drug response.^[31] According to SCM, there is inter-individual difference in susceptibility of an individual to a particular disease and response to a drug. An important finding of one study was that Sasang constitution is an independent risk factor for diabetes. Prevalence of diabetes was higher in Tae-eum (11.4%) followed by So-yang (5.0%) and So-eum (1.7%). Multiple regression showed that Tae-eum individuals were at greater risk of developing diabetes than So-eum individuals.^[32] Angiotensin converting enzyme gene (ACE), a candidate gene for cerebral infarction, was studied in different Sasang constitutions. Although there was no significant association between ACE gene polymorphism and cerebral infarction, Tae-eum has a higher susceptibility to cerebral infarction than other constitutions, So-eum seems to protect against cerebral infarction.^[33]

The unique characteristics of SCM determination of constitution, based on physical, psychological, symptomatic observation, as well as constitution-based medicine, are in agreement with individualized medicine. Increasingly, scientific evidence suggests a genetic basis for SCM. Further studies using modern technology-based genetic approaches could help establish SCM as an alternative to modern personalized medicine.

TRADITIONAL CHINESE MEDICINE AND GENOMICS

There are several similarities between Ayurveda and Traditional Chinese Medicine (TCM) including their holistic, individual classification systems. TCM is also based on a theory of constitution. Similar to other constitutional medicines, differentiation of constitution is based on differences in physical, physiological and clinical observations. TCM recognizes seven constitutions: Normality, Yin-deficiency, Qi-deficiency, Yang-deficiency, Phlegm-wetness, Wetness-heat, and Blood stasis. It assumes five 'elements' in the material world, earth, water, fire, metal, and wood, movement between which is governed by two opposed qualities of chi energy, Yin and Yang. A human being is considered a connection between space and earthly elements, while individual health is determined by the state of equilibrium between the two energies, maintained by Qi,

blood, moisture and essence, the four humors and internal organs. Yin-Yang imbalance is seen as the reason for development of disease states.^[34] Its theory of personalized medicine is a fundamental aspect of TCM, and medicines are prescribed in accordance with a patient's constitution. TCM recognizes that both susceptibility to disease, and drug response depend on individual constitution.

Genetic, scientific evidence for TCM's system of constitution has been elucidated, specifically for associations between different TCM constitutions and polymorphism in HLA class II genes DRB1, DPB1 and DQB1. Frequencies of alleles DPB1*0501 were significantly associated with Yin-deficiency, DRB1*09012 with Phlegm-wetness, and DQB1*03032 allele with the Qi-deficiency and Phlegm-wetness groups. Serological analysis of HLA alleles revealed an association between DR*04 and the blood-stasis group, and between DQ*09 and the Qi-deficiency and Phlegm-wetness constitutions. The study's findings indicate that TCM constitutions may have a genetic basis.^[35] Other studies have attempted to address the relationship between traditional medicine constitutions, and *HLA* polymorphism.^[36,37] TCM is found to be effective in treating various complex diseases like diabetes, cancer, Alzheimer's disease, metabolic syndrome, and chronic fatigue syndrome.^[38-41]

In parallel to constitution-genomic studies, are those of effects of Chinese herbal medicines on genetic regulation. Ginseng is considered to be one of the most effective drugs against angiogenesis and related diseases. The pharmacologically active components of ginseng, ginsenosides, have therapeutic value. Microarray data revealed the Rg1 category of ginsenosides to up-regulate a set of genes responsible for adhesion, and migration processes related to angiogenesis.^[42] Pharmacogenomic studies are required to investigate genomic pathways involved in physiological effects of ginseng, and other TCM herbal medicines. Similarly more studies should be undertaken to investigate possible associations between different genetic markers and constitution. Such studies would help make TCM better understood in terms of modern bioscience, promoting more effective integration with modern medicine.

TRADITIONAL JAPANESE MEDICINE AND GENOMICS

Traditional Japanese medicine has been used for 1500 years and includes Kampo-yaku (herbal medicine), acupuncture and acupressure (Shiatsu). Kampo is now widely practiced in Japan and is fully integrated into the modern healthcare system.^[43] Throughout the history of TCM and Kampo, the basic theories and the methods of diagnosis and treatment

have differed considerably from those of Western medicine. Western medicine uses disease-based diagnosis, while TCM and Kampo emphasize patient-based diagnosis. Kampo is based on TCM but is adapted to Japanese culture. It can be characterized as a simplified, positivistic and pragmatic version of Chinese herbal medicine.^[44] Kampo medicine is more informal than TCM and emphasizes practice rather than theory.^[45] The main theories of Kampo are the three substances (Qi, Blood, Water), the eight categories, the five parenchymatous viscera and the six stages of disease.

Kampo differs from TCM in its systems of diagnosis and treatment. Kampo uses a treatment 'formulation corresponding to Sho'; Sho is the patient's symptoms at a given moment. The concept of 'Sho' comes from the Zheng of TCM, but is simpler because of the simplified Kampo theory. Sho analyzes a patient's symptoms terms of Qi (well-being, energy, illness, vigour), Blood and Water; the eight categories (Yin–Yang, hypo- and hyper- function, hot and cold, superficialities and interior); the five parenchymatous viscera; and the six stages of the disease viz.: Taiyang, Shaoyang, Yangming, Taiyin, Shaoyin, & Jueyin.

Sho may be broadly defined as Kampo diagnosis in the epistemic framework of the Kampo view of illness. It provides the information, on which Kampo treatments are based.^[46,47] Recently there has been a trend to use a specific formula 'Kakkonto Sho', denoting symptomatic treatment with Kakkonto, to describe Sho more precisely.

In Kampo medicine, the process of diagnosis and treatment is called 'formulation corresponding to Sho'. When treating a patient, Kampo practitioners use the Sho diagnosis to identify the most suitable formula. The relationship between these steps is compared to that of a lock and key. In this way, every pathological condition is related to its most appropriate prescription.^[46,47] Japanese practitioners regard their work as assessing symptoms to identify the disease, so that they can then choose the correct Kampo drugs.^[48]

Kampo medicine emphasizes the relationship between the human body and its social and natural environment, and regard any disease state as one of imbalance, which its treatment should correct, by helping patients return to their equilibrium state. It places emphasis on results of clinical and laboratory studies.

It has been reported that exclusively western research models are used to study Kampo, and that the approach is compatible with conventional western disease nosology and conventional immunology.^[45] Hence, it has been proposed that evidence-based Kampo medicine should be easily accepted in the West.^[43] In contrast to Ayurveda, TCM and SCM there is a scarcity of literature on genomics and Japanese Kampo medicine.

Genomic and proteomic correlates of Kampo medicine have recently been reported.^[49,50] More studies and further evidence are needed for further integration of understanding of Kampo medicine with modern medicine.

FUTURE PERSPECTIVES

The traditional systems of medicine in Asia (Ayurveda, TCM, SCM, Kampo) are considered great living traditions.^[51] They are all closely related to each other. For example, all are based on theories of constitution. All identify unique qualities of each individual, and state the necessity of developing personalized medicine in order to obtain optimal response to treatment. This is similar to the science of Pharmacogenomics, which tries to identify individual differences between patients connected to drug metabolism, efficacy and toxicity at the genomic level. In addition to genotype variations, there may be differential expression of genes, copy number variations (CNVs) or epigenetic modifications leading to phenotypic variation. Current research in 'Omics' is focusing on the polygenic approach using high throughput technology rather than the single gene approach. Systems biology is an emerging field that aims at system-level understanding of biology through network analyses and molecular interactions. Its approach is more holistic than molecular medicine, which is purely reductionist. Systems biology therefore constitutes a means of bridging the gap between reductionist medicine and traditional medicine – at least partially. Using systems biology tools may therefore offer an attractive way to begin to approach the holism of traditional medicine.

Despite the growing enthusiasm of increasing numbers of western trained doctors for the practice of oriental systems of integrative medicine, there is still a shrill and often vociferous minority, which claims that because the traditional systems do not (sufficiently yet) have an adequate empirical or theoretical base, they must be invalid, inconsequential twaddle. Traditional systems have to use systematic scientific approach to dismiss these accusations.

As regards the human Prakriti, or physiological type, the series of experiments reviewed in this paper now demonstrate that it can be empirically validated at the genomics level. At the same time, it is important to acknowledge that the correlations so far observed do almost nothing to prove that individual physiologies have the properties claimed for them in the ancient traditions. Obtaining the necessary evidence will require a vastly greater amount of data on thousands of genes for large sample sizes. The current experiments establish that such data is well worth obtaining. It could initiate a plethora of scientific projects that will answer crucial questions about the foundations of human physiology, and lay out

strategies for developing scientifically validated approaches to preventive medicine, chronic disease care and treatments.

Under the scheme “Science Initiatives in Ayurveda”, the Office of Principal Scientific Advisors to Government of India, has initiated an ambitious project on Genomic variation analysis and gene expression profiling, using principles of Ayurveda. This initiative supports robust research with scientific precision, to further elucidate fundamental concepts of Ayurveda. Not only should it prove valuable in moving the field forward, it may well pioneer the trend for Ayugenomics and related traditional medicine research internationally and globally for coming decades.

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