

PARADIGMS

Ayurvedic Genomics: Establishing a Genetic Basis for Mind–Body Typologies

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ABSTRACT

Background: Ayurveda, India’s natural health care tradition, has a unique way of classifying human population based on individual constitution or *prakriti*. Ayurveda’s *tridosha* theory identifies principles of motion (*vata*), metabolism (*pitta*), and structure (*kapha*) as discrete phenotypic groupings. Patwardhan et al. (2005) hypothesized in a paper published in this journal that there is a genetic connotation to *prakriti* and as proof of this concept showed a correlation between HLA alleles and *prakriti* type, establishing 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 work is both part of and a catalyst for a wider revolution in the scientific investigation of Ayurveda in India, referred to as “Ayurvedic biology” and “AyuGenomics.” Subsequently, Chen et al. (2007) reported a similar study in this journal using a classification based on Traditional Chinese Medicine (TCM) theory.

Conclusions: The findings of a genetic basis for both Ayurvedic and TCM classifications indicate a commonality between Asia’s great medical traditions in their diagnostic typologies and a genetic basis for Asian traditional medicine’s theory of discrete and discernable groupings of psycho-physiologic differences. Accordingly, new horizons have opened for collaborative East–East research and for an individualized approach to disease management and activation of the full range of human potential, as articulated in Ayurveda and TCM.

INTRODUCTION

Over the past 6 years, the *Journal of Alternative and Complementary Medicine* (JACM) has hosted a series of papers on the validity of individual mind–body types found in the Ayurvedic medical system.

Ayurveda uses a threefold classification—known as *tridosha* theory—for determining a person’s mind–body classification. *tridosha* theory identifies principles of motion (*vata*), metabolism (*pitta*), and structure (*kapha*) as discrete phenotypic groupings, elements of which may be found in all people, but which predominate in sufficiently differing

degrees in individuals to form a threefold body typology. *Tridosha* theory and its diagnostic classifications allow for individually suited treatment and lifestyle recommendations.

In JACM in 2001, Hankey offered a framework, grounded in systems theory and chemical physics, for the validity of *tridosha* theory. The essence of this is that *doshas* constitute biologically universal mechanisms regulating those functions identified as fundamental by systems theory: input and output (*vata*), throughput or turnover (*pitta*), and storage (*kapha*). As such, the *doshas* are identified as fundamental to living systems and, as inheritable system attributes, are present in related forms in all organisms.¹ In a

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subsequent JACM paper, Hankey drew on scientific evidence for the primary significance of coenzyme A—a key component of fatty acid metabolism—which is universally present in all cells. He argued that the universality and function of coenzyme A support a systems analysis view showing congruence with the doshas.²

Subsequently, a statistical study in JACM by Joshi, reported as the first empirical test of the theoretical constructs of Ayurveda, used regression modeling with a sample of 117 healthy subjects to obtain a quantitative measure of the Ayurvedic *tridosha* level for *vata*, *pitta*, and *kapha*. Joshi's analysis applied an algorithmic heuristic approach to the qualitative diagnostic criteria used by Ayurvedic doctors. In comparing the algorithm with the *tridosha* assessments of Ayurvedic doctors, there was 75% convergence, significant at the $p < 0.05$ level.³

GIVEN A THEORETICAL AND STATISTICAL BASIS FOR AYURVEDIC TYPOLOGY, MUST THERE NOT ALSO BE A GENETIC BASIS?

This question is of keen interest to Indian scientists. A number of teams are now investigating the correlation between Ayurvedic phenotypes and individual human genotypes. A catalytic influence for a major Government of India funding initiative in support of this research, now known as AyuGenomics, was a JACM paper published by one of us (B. Patwardhan), with distinguished Indian colleagues.⁴

In this study, we used human leukocyte antigen (HLA) DRB1 types to compare individuals with their Ayurvedic *tridosha* classification. We selected the HLA DRB1 gene because it has multiple alleles or many alternative forms of genes. It is also known that susceptibility and resistance to many diseases, such as rheumatoid arthritis and type I diabetes, are primarily associated with genes encoding peptide-presenting HLA molecules. HLA genes exhibit a high degree of polymorphism in various ethnic groups, and the association between HLA alleles and disease is usually quantified by typing HLA alleles expressed by individuals with or without disease. This was an original application of a comparative HLA DRB1 gene analysis to the field of traditional medicine and its mind–body typologies. We chose HLA type as a key indicator based on our group's expertise in the immunopathology of rheumatoid arthritis, where a cohort of patients was available. As HLA DRB1 gene analysis had not been applied to the traditional medicine context before, there was strict adherence to international standards in applying the methodology. The 14 alleles selected were taken in accordance with the Nomenclature Committee of the World Health Association for factors of the HLA system.⁵

The data showed a correlation between HLA alleles and *prakriti* type, establishing a rationale and preliminary experimental support for the concept of an association between

HLA alleles and the Ayurvedic *tridosha* theory of individual *prakriti* types.

Subsequently, M.S. Valiathan, an eminent Indian cardiologist and scientist with authority in Ayurveda, propounded a vision and views on “Ayurvedic biology”: “Since innate disposition determines the manifestation of diseases and individual response to treatment, one of the first things a physician does is to determine the *prakriti* (body type or nature) of his patient. This is necessary to personalize treatment in accordance with the basic principle of Ayurvedic therapeutics. The description of the features clearly suggests that the innate dispositions or *dosha prakritis* represent phenotypes. Classifying humans based on phenotypes offers a challenge to biomedical science which has currently the technology to look for underlying genetic variations among the phenotypic datasets.”⁶

Valiathan's decade-long vision for research on Ayurvedic biology⁶ was built on views initially articulated at a symposium of the Indian National Science Academy (INSA) in New Delhi followed by the 70th Annual Meeting of the Indian Academy of Science (IAS) at Varanasi in 2004. INSA and IAS have recognized the significance of India's traditional knowledge and the need to understand it more fully through modern science. Their support for Valiathan's position led to funding from Government of India for the national research program “Science Initiatives in Ayurveda.”

One of the five multicenter projects is on “Genomic Variation Analysis and Gene Expression Profiling of Human *Dosha Prakriti* based on Principles of Ayurveda.” This project, inspired by the JACM publication of Patwardhan et al.,⁴ is a partnership of leading research institutes, including the Indian Institute of Science, Bangalore; the Center for Cellular and Molecular Biology, Hyderabad; the Foundation for Revitalization of Local Health Traditions, Bangalore; Manipal University; and University of Pune. In this ambitious program, studies related to gene expression profiling, single nucleotide polymorphism (SNP)–based genotyping, data validation by DNA sequencing, short tandem repeat (STR)–based genotyping, and gene polymorphism in P450, multidrug resistant (MDR), glutathione S-transferase (GST), N-acetyl transferase (NAT), and melanocortin receptors (MCRs) are being undertaken.

INDIA'S SCIENTIFIC REVOLUTION IN EXPLORING THE TENETS OF AYURVEDA

While India's revolution in research into Ayurveda is largely unrecognized in the West, it has been building steadily over the past decade or more. With the start of the 21st century, it has gained exponential momentum through combined intellectual exploration by Ayurvedic scholars and scientists, facilitated by Government funding initiatives.

Early stirrings of this momentum can be identified in such research programs as those of Professor Ranjit Roy Chaudhury,⁷ Chair of the International Clinical & Epidemiological Network (www.inclen.org), and his co-workers; and of

the late Dr. Shardini Dahanukar of TN Medical College, Mumbai, and her team.⁸ Support for these and related programs came primarily from the Indian Council of Medical Research, which pioneered research on Ayurveda under then-Director General Dr. G.V. Satyavati.

Addressing the pharmacogenetic perspective of Ayurveda, Dahanukar and Thatte^{8,9} have noted the different response styles to medication of people with different *doshic* constitutions or *prakriti*. They also noted a study on sibutramine in patients with obesity, which showed that most of the responders to the drug had a *pitta prakriti*, while most of the non-responders were of the *kapha prakriti*.¹⁰ At the Banaras Hindu University, Dr. K.N. Udupa, Dr. R.H. Singh, and colleagues promoted scientific integrated approaches to Ayurveda.¹¹

As an historical footnote, earlier pilot research—still awaiting adequate follow-up—presaged the genetic path being taken in Ayurveda today. Research on the effects of an Ayurvedic longevity formulation or *rasayana*, Maharishi Amrit Kalash Nectar (MAK-4), on liver cancer, found a dramatic increase in the levels of mRNA transcripts of two genes, glycosyltransferases, in the livers of rats.¹² Based on their preliminary findings, it was suggested that Ayurvedic herbal formulations be investigated for their potential to induce cellular mechanisms, including the alterations in the pattern of glycosylation that enable living organisms to resist or retard disease processes without any toxic effects. Fifteen years on, Ayurvedic Genomics is beginning to pick up this challenge.

Golden triangle initiative

A landmark article was published in 2003 by Dr. R.A. Mashelkar, then Director General of the Council of Scientific & Industrial Research (CSIR), and Secretary to Government of India.¹³ In his “On Building a Golden Triangle between Traditional Medicine, Modern Medicine and Modern Science,” Mashelkar’s now famous Golden Triangle concept was articulated. Calling for “mutual trust, respect and confidence between the practitioners of modern science and the holders of the ancient wisdom,” a new partnership was proposed between Ayurvedic knowledge, modern science, and biomedical research. The Golden Triangle initiative has led to substantial Indian government funding for Ayurvedic research, matched by support from private foundations and industry. During this decade, the Government of India established a new Department for Ayurveda, Yoga, Unani, Sidda, and Homoeopathy (AYUSH) that is making new advances in teaching and research.

While all of the new initiatives are selected on the basis of being of a high standard of scientific and intellectual rigor, some merit particular mention here. They illustrate the trend of breaking the boundaries of conventional natural products research to a full range of investigation: from genetics to public health.

Introduced via CSIR’s New Millennium Indian Technol-

ogy Leadership Initiative (NMITLI), a newly developed Ayurvedic knowledge resource allows drug researchers to start their investigations from standardized and safe botanical material. Industry has responded with enthusiasm. Partner Ayurvedic companies include Arya Vaidya Shala and Pharmacy, Zandu, Dhootpapeshwar, Dabur, Nicholas Piramal and Lupin, all well known and well regarded in India and internationally. The Ayurvedic Drug Manufacturers Association in India is also taking the lead to establish and maintain required standards in Ayurvedic medicines. Such efforts have led to an academic dialogue between regulators including the European Agency for Evaluation of Medicinal Products and the United States Food and Drug Administration.¹⁴

Reverse pharmacology

Another major scientific shift has been the recognition that in drawing on traditional knowledge, a natural products research strategy for drug development can follow a reverse pharmacology path. So, the usual drug development pathway—from laboratory to clinic—is actually reversed in the study of traditionally used herbal medicines. The strategy used in India has been from “Clinics to Laboratories,” where case studies, case series analyses, and observational studies, including cohort studies, all provide data on clinical use and outcomes of Ayurveda and serve as clues for mechanisms and therapeutic effects of well-established herbal drugs. This approach is described elsewhere with respect to herbal medicines for malaria.¹⁵ In this process, *safety* remains the most important starting point and efficacy becomes a matter of validation. The process also reduces the time and cost of development. In Mumbai, the Swami Prakashananda Ayurveda Research Center (SPARC), led by Dr. Ashok Vaidya, has recently been recognized by the Indian Council of Medical Research as a center of excellence in Reverse Pharmacology. A series of scientific papers elaborate further the scientific value and role of Ayurveda in drug discovery and development.^{16–18} and also as immunodrugs.¹⁹

Intellectual property protection and traditional medical knowledge

A number of high-profile cases of overseas patents being granted on Indian traditional knowledge raised the issue of protecting India’s storehouse of traditional medical knowledge against what has come to be known as “biopiracy.” Biopiracy refers to the unethical appropriation of culturally based biological, agricultural, or medical knowledge and/or formulations for private commercial gain, particularly by a company outside of the culture whose knowledge is being commercialized. India has challenged and overturned patents on turmeric for wound healing²⁰ as well as patents on variants of basmati rice and on the applications of products of the neem tree (*Azadiracta indica*), widely used in Ayurveda throughout India’s history as well as in areas settled by Indians, such as East Africa.²¹

India has embarked on a national program to establish for all Indian traditional medicines a database of what, in patent law, is known as “prior art.” Prior art is pre-existing knowledge that thereby contradicts claims of originality of subsequent patent applications for invention. The Traditional Knowledge Digital Library holds unique methodologies and technologies and has been able to provide scientific structures to traditional knowledge systems by developing a classification system now known as Traditional Knowledge Resource Classification. Recognizing the importance of such issues, the World Health Organization established a Commission on Intellectual Property Innovation and Public Health where a special study was commissioned to review the role of traditional medicine to offer affordable treatments.²²

Digital knowledge resources

Recent efforts in which our team in Pune, India played a lead role have identified the need to harmonize various traditional sources in the form of an easily accessible and retrievable information system. The result, an ambitious project named AyuSoft, involves systems standardization for an integrated, intelligent, and communicative decision support system based on Ayurveda (<http://ayusoft.cdac.in>). In IT terms, AyuSoft converts classical Ayurvedic texts into comprehensive, authentic, intelligent, and interactive knowledge repositories with complex analytical tools. This is a collaborative project of the Government of India’s Center for Development of Advanced Computing and the Ayurveda and the University of Pune.

THE GOVERNMENT OF INDIA AND THE REVOLUTION IN AYURVEDIC BIOLOGY

Government programs have played a lead role in the revolution in Ayurvedic biology. The Department of AYUSH is active in research and through them, an institution of National Importance in Ayurveda is being planned in private–public partnership.²³ India’s Department of Science and Technology and the Department of Biotechnology both support multidisciplinary research projects on enhancing the understanding of Ayurveda and Indian Traditional Medicine through modern biologic approaches. Reflecting the sea change taking place in biologic research emphasis, the Regional Research Laboratory at Jammu, long a leader in mainstream biologic and natural products research, has been renamed as the Indian Institute of Integrative Medicine (IIIM) and is pioneering multidisciplinary research on Indian traditional medicines.

Under the NMITLI program mentioned previously,²⁴ anti-arthritis and antidiabetic formulations based on Ayurveda are in Phase 3 clinical studies at some of India’s premier medical institutions. The range and high caliber of

participating institutions gives a sense of the significance behind this research endeavor. It is akin to the establishment of the NIH Collaborating Centers in CAM in the United States in the 1990s under the then NIH Office of Alternative Medicine. Leading collaborating centers in this India-wide R & D programme include the following: The All India Institute of Medical Sciences, New Delhi; The Nizam’s Institute of Medical Sciences, Hyderabad; G.S. Medical College and KEM Hospital, TN Medical College and Nair Hospital, Mumbai; Dr. Mohan’s Diabetes Specialties Center, Chennai; and The Center for Rheumatic Diseases, Pune; the Indian Institute of Integrative Medicine (IIIM); The National Botanical Research Institute; the Central Drug Research Institute, Lucknow; the Agharkar Research Institute; Bharati Vidyapeeth’s Interactive Research School for Health Sciences; and Bhavan’s Swami Prakashananda Ayurveda Research Center, Mumbai. Such efforts underscore the national importance given to the study of Indian traditional medicine by modern science.

Finally, returning to AyuGenomics, Manipal University, in Karnataka, with funding from the Technology Information Forecasting & Assessment Council has established a Center Of Relevant Research & Excellence (CORE) in the field of pharmacogenomics where studies on Ayurveda and genomics will have priority.

AYURVEDA AND TRADITIONAL CHINESE MEDICINE (TCM): A COLLABORATIVE RESEARCH STRATEGY FOR A COHESIVE VIEW OF TRADITIONAL MEDICINE THEORY AND GENOMICS

In an overview of Traditional Indian Medicine (TIM) and TCM that we published,²⁵ we noted: “Both TIM and TCM are great traditions with a strong philosophical basis and could play an important role in newer therapies and drug discovery and development processes. Considering the growing interest in alternative and complementary therapies and increased demand of herbal drugs, it would be of mutual benefit, if India and China share strengths and weed out the weaknesses. Such efforts would lead to science-driven promotion of these practices for newer therapies and medicines for emerging global markets.” Both Ayurveda and TCM aim to enhance the quality of life. Yet, superficially, they would appear to have differing diagnostic groupings and associated therapeutic recommendations. In TCM the systems of *yin* and *yang* and the five elements are fundamental, as are conceptualizations of certain bodily humors (*qi* status, Blood, Dampness, etc.), and internal organ systems (*zangfu*). Do underlying commonalities exist between Ayurvedic and TCM theories? If so, can modern science shed light on these, building bridges across cultural gaps of conceptualization and expression?

With this in mind, it was of interest to our research team to note a recent JACM paper by Chen et al. (2007),²⁶ accompanied by an invited editorial.²⁷ Although the Patwardhan et al. (2005)⁴ paper was not referenced, Chen et al. used the similar comparative HLA gene polymorphism approach and methodology pioneered by the Indian team and reported in their 2005 JACM paper. The two studies had commonalities in approach, methodology, and experimental tools. Both the Patwardhan et al. and Chen et al. papers studied the implications of traditional classifications of human physiology, and both used analysis of DNA polymorphism to test the hypothesis that phenotypes identified in their respective traditional classification had a substantial biologic basis. Moreover, both focused on the same gene (HLA), and used the same analytical tools to carry out the investigation. The fact that both systems found correlations with significant *p* values may at first appear surprising, considering current limitations in the scientific comparison of the two systems. On the surface, the quantities named in the two papers sound different and appear to be defined in unrelated ways. The fact that one paper established correlations between Ayurveda's *prakriti* classification and HLA allele frequencies, while the second paper was able to do the same for TCM phenotype classifications and frequencies of the same or related alleles might cause some confusion. However, those with deep knowledge of the two systems recognize that, historically, they have had profound contact in the past, and that current divergence is more a matter of superficial emphasis. Distinctions related to *yin* and *yang* are to be found in Ayurveda, which also makes use of a similar five-fold classification of qualities identified as "elements," to which the three *doshas* are related.

Both the Indian and Chinese systems recognize a concept of life force energy. In Ayurveda, this is known as *prana* and in TCM, *qi*. Both systems recognize the power of the life force energy to heal, terming it *pranic healing* in India, and in China, *qigong*. Both systems recognize that the life force energy takes on one of two different qualities, classified according to whether it is lighter (in both senses of the word), more masculine and space-like, or darker and heavier, more feminine and earth-like. The former is *yang-qi*, known in Ayurveda as *prana*, and the second *yin-qi*, known in Ayurveda as *shakti*. All life processes are said to result from the dynamic interplay between these two qualities.

A second classification of qualities of the life force energy is found as the different *acu-meridians* in TCM and as *nadis* in Ayurveda. Phrased in terms of a second, fivefold classification, these are subtle qualities. In TCM, they are similar to the subtle qualities of the materials named to represent them: wood, fire, metal, earth, and water. In Ayurveda, these subsidiary qualities are assigned to each of the five *subdoshas*. Forging future cooperation between these two systems could stimulate a new vision of human physiology for which the new approaches to *tridosha* have laid a strong foundation.

WISDOM GUIDING SCIENCE

In conclusion, it is worth noting that our own work, and that of the vast range of scientists now investigating Ayurvedic biology in India and abroad, has been guided by classical Ayurvedic texts and their parent corpus in the Vedic literature. These contain wisdom, the depth of which is only now beginning to be appreciated through the lens of modern science. A recent analysis article published in *Cell* on the importance of traditional medicine in developing affordable and safer therapeutic agents by using as an example advanced research on turmeric is exemplary of future trends.²⁸

The Vedic expression, or *sloka*, "*Yatha pinde, tatha brahmande*" expresses the view that "as is the microcosm, so is the macrocosm." What more precise account could there be that, underlying the vast systems of life that populate earth, and at the core of the structure and movement of universes, is a microscopic level in which this precise same order is mirrored?

AyuGenomics is not new; what is new is the emerging ability to recognize and begin to understand it, and what is exciting is not simply the emerging commonalities between modern and Ayurvedic science, but what the insights from Ayurvedic biology may offer for new understandings of human life and its greater potential.

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