Guest Editorial

AYURVEDA AND PHARMACOGENOMICS

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The world is moving towards personalized medicine. In allopathic medicine, this means that prevention, diagnosis, and treatment are all tailored to the characteristics of each individual patient. The sequencing of the human genome has allowed for the detection and identification of DNA sequences and protein expression in tissues, saliva, blood and urine. The ability to undertake genome-wide association studies (GWAS) has led to the identification of many common genetic risk variants for multiple human diseases. Scientists are even beginning to perform in depth studies on healthy patients, and are employing strategies called "integrative personal omics profile (iPOP)" [1]. This type of analysis merges genomic, proteomic, metabolomic, and antibody studies in a single individual over time. However, it is widely recognized that it is difficult to interpret much of the genome, and that many diseases such as diabetes and cancer involve multiple genes and multiple cellular pathways as well as environmental factors. That being said, western medicine is also beginning to acknowledge that a person's phenotype is indeed related not only to disease risk, but also to treatment response.

In Ayurveda, personalized medicine has been practiced for thousands of years. The central concept of health and disease revolves around the uniqueness of the individual and uses the three-fold classification system of *tridosha* theory. This individual constitution (or *Prakriti*) is based on differences in physiological and psychological characteristics and is not dependent on race or ethnicity. The classification of constitution into three contrasting phenotypic categories or doshas that include *Vata, Pitta,* and *Kapha* is fundamental to the practice of Ayurveda. The *Prakriti* of an individual is determined at the time of conception and does not change over the person's lifetime. Thus, *Prakriti* can be equated with our own individual genome, and this idea of unique individuality makes Ayurveda one of the earliest documented medical traditions that incorporated the concept of personalized and preventive medicine. Ayurveda also documented that the susceptibility to different diseases as well as the features of the disease is dependent on the individual's *Prakriti*. Therefore, Ayurveda stresses an understanding of both the physical and psychological nature of the individual, as well as an appropriate diet and lifestyle strategy in order to maintain health and prevent and/or ameliorate disease. Previously, western science and Ayurveda have appeared to be at opposite ends of the medical spectrum, with western science focusing on treating disease, and Ayurveda focused on maintaining health and balance as well disease management. However, in the 21st century, these two medical practices are being bridged by the human genome and are slowly converging. But there are significant differences in how allopathic medicine and Ayurveda approach the role of the individual's genome or *Prakriti* in health and disease.

Western science has concentrated on the relationship between genetic factors and disease pathology and treatment. Much attention has focused on genetic polymorphisms, small genetic mutations that occur within a population with a frequency greater than 1%. Many of these genetic polymorphisms and genetic variants have been associated with multiple diseases such as cardiovascular disease, cancer, and diabetes. A new field of pharmacogenomics is emerging out of this work. Pharmacogenomics is the study of the genetic basis for variance in drug response in populations. The goal of pharmacogenomics is to use genetic information to improve the likelihood that individuals will respond in a positive manner to their medication and to reduce the chances of adverse reactions. The underlying hypothesis

to these studies is that the variability in drug response is due to variations in the individual genome. Pharmacogenomics can be further divided into two categories, Pharmacodynamics and Pharmacokinetics. Pharmacodynamics involves the way in which a drug interacts with a biological system, i.e. through specific receptors. Pharmacokinetics is the process by which a drug is absorbed, distributed, metabolized, and excreted. There have been a number of success stories in the areas of both pharmacodynamics and pharmacokinetics.

Within pharmacodynamics, a great deal of progress has been made, particularly in the treatment of cancers. For example, a subset of patients with lung cancer who have epidermal growth factor receptor mutations show improved clinical responsiveness to tyrosine kinase inhibitors[2]. Tyrosine kinase inhibitors are also used in the treatment of some leukemias. Similarly, HER2 (human epidermal growth factor receptor 2)-directed therapies in HER2-positive breast cancers have been shown to decrease the risk of distant metastasis and improve overall survival rate [3]. Within pharmacokinetics, the genetic control of the metabolism of two drugs stand out as excellent examples of the power of pharmacogentics. The first example is codeine, an opioid analgesic used to treat pain. Codeine is metabolized to morphine by CYP2D6, a member of the cytochrome P450 mixed-function oxidase system. CYP2D6 has genetic variants that result in some individuals being poor metabolizers and some individuals being fast metabolizers. The drug is not as effective in poor metabolizers and can be life threatening in fast metabolizers. Genetic testing is now available for CYP2D6, although it is not routinely used by physicians prescribing codeine[4]. The anti-coagulant Warfarin is another good example of the success of pharmacogenomics. Warfarin levels must be maintained within a narrow therapeutic range and common genetic variations in the genes CYP2C9 and VKORC1 have been associated with variability in blood Warfarin levels following standard dosing[4, 5]. The FDA has recently modified the Warfarin label, providing recommended daily dosages based on the CYP2C9 and VKORC1 genotype. These examples, although success stories, raise the issue that there are limitations to progress using the current allopathic genetic strategy. One major constraint is that healthy and diseased states are typically characterized and followed using a small number of assays that measure a limited number of biomarkers.

Ayurveda, on the other hand, takes the opposite approach. Many phenotypic characteristics are considered simultaneously through the evaluation of *Prakriti*. The challenge is how to merge the concepts of *Dosha* with evidence-based western medicine. It is very encouraging to see that these studies have already begun, initiated in large part by researchers in India. Studies have examined genetic and biochemical correlates in extreme *Dosha* constitutions[6], and *Dosha* has also been correlated with the psychologic somatotype theory of ectomorph, endomorph, and mesomorph described by William H. Sheldon[7]. Studies have also found associations of *Dosha* with cardiovascular risk factors, insulin resistance, and inflammatory mediators[8], Rheumatoid Arthritis[9], diabetes[10] , and metabolic variability[6]. While these studies are an excellent beginning, what is now needed is to connect *Prakriti* with genotype using standardized, evidence-based research that will be accepted by scientists from all over the world.

As a neuroscientist trained in Ayurveda, I believe there is much that Ayurveda will contribute to personalized medicine. However, there are two roadblocks that must be overcome in order to perform research studies that will be validated and accepted by western medicine. The first is the development of a standard *Dosha* questionnaire that is agreed upon by the Ayurvedic community, and that all scientists can use for studies linking *Dosha* with genetic variants, cellular processes, and human physiology. Also, some consensus must be reached as to the way in which *Dosha* is linked to molecular biology. For example, some studies use an "extreme" *dosha* type for analysis whereby only pure *Vata, Pitta,* and *Kapha Prakritis* are used. Other studies are more flexible, and combine *Vata/Pitta* and *Pitta/Vata* into one doshic subtype. It will be very difficult to extrapolate information across many studies if researchers around the world are all using different criterion and classifications of *Dosha*. Therefore, a standard *Dosha* analysis must be developed and implemented.

The second important issue is consistency in the herbs and formulations that are used in scientific studies. In the U.S., the FDA does not regulate these herbs, and there

are large variations in the quality of these herbs. Therefore, it is difficult to make comparisons from study to study when herbs from different suppliers with differing standards of quality are used. This problem is not restricted to Ayurvedic herbs, this is a major problem with natural products research in general. However, the Ayurveda community has an opportunity to take the lead on this issue. Ideally, a certifying body could be created, composed of members from both India and the west who would create a set of standards and guidelines for the preparation of herbs for scientific studies. Suppliers of herbs would have to meet these standards in order to be certified, and researchers would be confident in knowing that the herbs they obtain from certified suppliers have met standard criteria for both quality and purity.

Ayurveda has advocated for personalized medicine for thousands of years. The central concepts of health and disease revolve around the uniqueness of the individual. It is intriguing that in the twenty-first century, western allopathic medicine is gradually embracing the idea that the unique genome of the individual plays an integral role in the disease process and the response to drug therapy. It will be fascinating to see how modern scientific studies will merge the ancient concepts of Ayurveda with western allopathic medicine, leading to new insights into human health and disease.

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