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Review Article

Exploring AyuGenomics approach for understanding COVID-19 predisposition and progression

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ABSTRACT

Recent reports on COVID-19 suggest that, the susceptibility to COVID-19 infection and its progression have a genetic predisposition. Majorly associated genetic variants are found in human leukocyte antigen (HLA), angiotensin convertase enzyme (ACE; rs1799752: ACE2; rs73635825), and transmembrane protease serine 2 (*TMPRSS-2*; rs12329760) genes. Identifying highly prone population having these variants is imperative for determining COVID-19 therapeutic strategies. Ayurveda (Indian traditional system of medicine) concept of *Prakriti* holds potential to predict genomic and phenotypic variations. Reported work on *Prakriti* correlates *HLA-DR* alleles with three broad phenotypes (*Tridosha*) described in Ayurveda (AyuGenomics). This is suggestive of differences in immune responses in individuals with specific constitutions. Therefore, the reported studies provide clues for clinically relevant hypotheses to be tested in systematic studies. The proposed approach of Ayurveda-based phenotype screening may offer a way ahead to design customized strategies for management of COVID-19 based on differences in *Prakriti*, immune response, and drug response. However, this needs clinical evaluation of the relation between *Prakriti* and genetic or phenotypic variants in COVID-19 prone and resistant populations.

1. COVID-19 and integrative approach

The novel coronavirus disease (COVID-19) has emerged as a global pandemic challenge. The global mortality and morbidity with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an unprecedented public health emergency [1,2]. Continuously evolving statistics suggests an estimated overall COVID-19 mortality of 0.25–3.0% amongst the infected population [3]. The worldwide data has shown that co-morbidities such as: obesity, hypertension, diabetes, coronary heart diseases, and cerebrovascular disease act as risk factors for COVID-19 with increased risk of mortality [4]. The mortality is more than 14% amongst the elderly (over 80 years), 10% is associated with cardiovascular diseases, and 7% with diabetes [5]. The SARS-CoV-2 is novel + ssRNA virus which enters the human body through binding and priming of viral spike (S) protein with the human Angiotensin Converting Enzyme 2 (ACE 2) receptor and a protease Transmembrane Serine Protease 2 (TMPRSS 2) respectively [6]. The virus has an average incubation period of 5–6 days; however, in some cases it can be up to 14 days [7].

The SARS-CoV-2 infection manifests itself through a wide range of disease presentation ranging from asymptomatic cases, mild cases or to severe forms of infection leading to death. The individualized phenotypic characteristics play an important role in understanding the inter-individual variability in disease susceptibility and prognosis. The study of these phenotypic variations associated with differences in genetic patterns seems promising for achieving objectives including, identifying high risk and disease-resistant population as well as providing individualized pharmacotherapeutic management [8].

The traditional medicinal systems such as, Ayurveda, Traditional Chinese Medicine, Tibetan Medicine, and Korean Medicine have well-defined systems of constitutional types. They have personalized approaches for predicting disease predisposition and progression based on their fundamental theories [9]. AyuGenomics is one such approach that is based on integration of Ayurveda and

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modern genomics [10]. It presents an example of Integrative Medicine where conventional physiology meets ancient concept of phenotypic classifications.

2. AyuGenomics

Ayurveda defines health as a state of physical, psychological, social, and spiritual well-being. It is based on important doctrines such as theory of *Panchamahabhoota* (the five basic elements – Space, Air, Fire, Water, and Earth). Properties of *Aatma* (~Soul) called *trigunas* (psychological qualities - *Satwa, Rajas, Tamas*) interact with *Panchamahabhootas* leading to representation of typical phenotypes called *doshas* (three key biological humors – *Vata (V), Pitta (P),* and *Kapha (K)*). In Ayurvedic philosophy, these three *doshas*, are believed to determine the unique combination of physical, physiological, and psychological features of an individual. The *Prakriti* of a person is a consequence of the relative proportions of these three *doshas* [11–13]. According to Ayurveda, *Prakriti* is the inherent constitution of an individual established at the time of conception [14]. Each of this *dosha* is believed to regulate specific physiological process. For example, *V* is responsible for movements,*P* governs energy while *K* regulates lubrication, cohesion, and structure. It has been stated that the *doshas* are fundamental to all living systems and organisms at all levels of biological organization ranging from a single cell to the whole body [15]. Each individual has a different proportion of *tridosha* (~three phenotypes) and there can be dominance of one or more *dosha* in a person. This basic framework decides *Prakriti* of an individual. The *Prakriti* of a person is a function of dominant *doshas* within them. There are seven types of *Prakriti* namely: *Vata (V), Pitta (P), Kapha (K), Vata-Pitta (VP), Vata-Kapha (VK), Pitta-Kapha (PK),* and *Samprakriti*. The *Samprakriti* individuals have equal proportions of *V, P, K,* but, the chances of finding an individual with *Samprakriti* are very rare [16]. *Prakriti* decides an individual's physiological pattern, mental status as well as disease proneness. In accordance with each *Prakriti* Ayurveda has defined specific *ahara* (diet), *vihara* (lifestyle) and *aushadhi* (medication) for healthy living [17]. Studies showing regulation of physiological processes according to *Prakriti* types were reported previously [14]. Also some reports revealed susceptibility to chronic diseases such as cancer and diabetes mellitus differs with *Prakriti* [18,19] *Prakriti* of an individual remains unaffected throughout the life span as it is determined at the time of conception [20]. Further *prakriti* is independent of ethnicity, race, geography, and language [21,22]. Therefore, *Prakriti* or constitutional phenotype has relation with genotype. A correlation between genetics and *Prakriti* (AyuGenomics) was reported by correlating variation in *HLA-DRB1* gene and *Prakriti* types in a proof of concept study [23,24]. The AyuGenomics approach is used to decode pathogenesis and etiology of various diseases, study of metabolic differences, predicting disease susceptibility for rheumatoid arthritis, diabetes, understanding drug metabolism patterns, and to determine variations in physiological adaptions to the environment [12,25–27]. Thus, this unique approach may be advantageous for predicting disease susceptibility and prognosis of COVID-19.

3. COVID-19 and AyuGenomics

Genomics is the study of the full genetic complement of an organism (the genome) [28]. Pharmacogenomics is the study of how human genetic information impacts drug response and it aims to improve efficacy and reduce side effects [29]. Phenomics connects Omics data with phenotypes, but the current status of phenomics or pharmacophenomics both areas are less explored and still needs more work for clinically translational outcome. Ayurveda understands the individualized phenotype to a very deep level, considering all the possible confounding environmental factors for genotype to phenotype map [30]. To understand exact clinical phenotypes, Ayurveda has a clinically validated system of phenotypic prediction with regard to individualized disease state [26,31]. Thus, AyuGenomics connects genomics with Ayurvedic phenotypic approach for predicting disease susceptibility, prognosis, as well as therapeutic effectiveness.

Developing predictive markers for high-risk individuals, identifying the determinants leading to poor prognosis, and understanding variations in treatment response are needs of the COVID-19 management strategies. Age, gender, and ethnicity are suggested to be associated with the prognosis and severity of COVID-19 [32–34]. These variations may lead to complications in identifying the COVID-19 prone populations and calls for AyuGenomics like approach which is independent of race and ethnicity. Reyes et al. reported that, high altitude inhabitants are protected from adverse effects of COVID-19 due to their physiological adaptions [35]. A study following the AyuGenomics concept has previously shown association between *EGLN-1* polymorphism, *Prakriti* phenotypes, high altitude adaption, and susceptibility towards high altitude pulmonary edema (HAPE). As per this, *K Prakriti* individuals may be at higher risk for HAPE while *P Prakriti* individuals may be more protected [26]. Human variations related to immune response and their relation with *Prakriti* and disease susceptibility are well-documented in Ayurveda. According to this, order of eliciting immune response in different *Prakriti* individuals is $K > P > V$ [36]. A study showing, differential expression of CD markers according to *Prakriti* is a proof of concept for variable immune response among constitution types [37]. According to this study, a significant difference ($P < 0.05$) was observed in the expression of innate and adaptive immunity-specific CD markers such as *CD14* (monocytes), *CD25* (activated B cells) and *CD56* (Natural killer cells) among different *Prakriti* groups. *CD25* and *CD56* expression was significantly higher in K *Prakriti* samples than other *Prakriti* groups. Similarly, slightly higher levels of *CD14* were observed in P *Prakriti* samples. Xie et al. reported, a direct correlation between levels of soluble CD25 (sCD25) and severity of COVID-19. The study discovered, that the elevation of sCD25 leads to expansion of $CD25^{+}$ $PD\text{-}1^{+}CD8^{+}$ T cells enhancing pro-inflammatory immune response; rather than anti-viral immune response aggravating COVID-19 severity, which suggest a divergence between anti-viral and pro-inflammatory T-cell responses [38]. Another study reported robust NK cell response and some characteristic findings in advanced stage patients; the study suggests that the arming of cytotoxic molecules like perforin with effector NK cell phenotype CD56 bright is associated with COVID-19 severity [39]. Therefore, it will be very interesting to study the *Prakriti* specific immune profile of COVID-19 patients. Ayurveda literature extensively describes phenotypic determinants of *Prakriti* types. They form a non-invasive, robust, simple yet precise method to stratify individuals, and identifying specific gene markers may facilitate the sub-grouping of COVID-19 patients [37]. Table 1 summarizes the possible hypotheses which can be studied for understanding COVID-19 susceptibility, symptoms, prognosis, and therapy based on existing AyuGenomics reports.

3.1. Genetic variations associated with COVID-19

Patients infected with SARS-CoV-2 present a heterogeneous course of symptoms and disease severity. Amongst the various confounding factors, host genetics may play a major role in disease progression [44] SARS-CoV-2 enters the host cell by binding of spike protein's (S protein) S1 unit with human ACE-2 receptor present on target cells. Along with this, viral entry requires S

Table 1
Propositions based on available AyuGenomics studies for predicting COVID-19 pathophysiology and progression.

Prakriti	AyuGenomics Understanding	Hypothesis to be tested in COVID-19 population
V	Higher expression of inflammatory genes *IL-1-β,* TNF-α, and *CD 40* [12]	Higher risk of SARS-CoV-2 related adverse outcomes in *Vata* prakriti individuals
P	Higher expression of genes associated with innate immunity [40,41]	Lower risk of SARS-CoV-2 infection in *Pitta* prakriti individuals
	Predominant CYP2C19 extensive metabolizer genotype*(*1/*1, *1/*2, *1/*3)* [25]	Higher dose of drugs that are CYP2C19 substrates may be needed
	Higher levels of SGPT and SGOT [42,43]	Proclivity for hepatotoxicity
K	Higher expression of immune cells and genes associated with adaptive immunity [37,40]	Lower risk of SARS-CoV-2 related adverse outcomes
	Highest CYP2C19 poor metabolizer genotype*(*2/*2, *2/*3, *3/*3)* [25]	May need lower dose of drugs that are CYP2C19 substrates.
	Higher serum levels of triglyceride, cholesterol, lipoprotein, creatinine, urea [42,43]	Possible comorbid factors leading to clinical complications in *Kapha* individuals
V, P, K	Differential *HLA* genotype [23,24]	*Prakriti* dependent variation in SARS-CoV-2 antigenic presentation and immune cell activation

protein priming by cellular protease TMPRSS2. This protease cleaves S protein at S1/S2 and S2′ site enhancing the viral and cellular membrane fusion [6]. Other than lungs, the receptor is expressed in heart, brain, liver, pancreas, intestine, eyes, prostate, testis, and placenta which explains multiple organ failure in COVID-19 [45,46]. The viral infection results into imbalance between ACE/ACE-2 and renin angiotensin aldosterone system (RAAS) activation. This process facilitates COVID-19 progression and it is the cause of severe disease in comorbid patients [47,48]. Genetic polymorphisms in *ACE* and *TMPRSS2* are likely to be associated with COVID-19 susceptibility and progression [49]. This might be a major factor responsible for ethnic and geographical variation between disease prevalence and severity [50]. The manifestation and development of SARS-CoV-2 depends on the interaction between the virus and the individual's immune system [51] In this process, major histocompatibility complex (MHC) encoded by human leukocyte antigen (*HLA*) are involved in presentation of viral peptide to immune cells [52]. Genetic variants of *HLA* were found to be modulating the immune response in SARS infections [53,54]. Table 2 summarizes the reported effects of genetic polymorphisms in SARS-CoV-2 infection.

Genome wide single nucleotide polymorphism (SNP) analysis in 262 subjects belonging to three *Prakritis* showed that 52 SNPs' were significantly different between *V, P, K* individuals (65).Variations in *HLA* genotype according to *Prakriti* have been reported. It was observed that, *HLA DRB1*02* and *HLA DRB1*13* alleles were absent in *V* and *K Prakriti* respectively. Whereas, higher allele frequency of *HLA DRB1*10* was found in the *K* than *V* and *Prakriti.* [23].

Therefore, studying association of all these variants (Table 2) with *Prakritis* may provide some important insights. Such a study might help to filter groups of high-risk individuals and prediction of their disease prognosis without cumbersome molecular diagnosis procedure for every individual.

3.2. Prakriti based phenotypic variations among individuals

The SARS-CoV-2 infection is characterized by an alteration of immune regulatory network. Immunological profiling of COVID-19 patients indicated, decreased innate antiviral defense coupled with elevated cytokine production drives disease progression [62,63]. This is defined by low levels of Type I and Type III interferon and higher levels of IL-6 [62,63]. It has been observed that, multiple facets of the immune functions are differentially modulated according to *Prakriti* types. *P Prakriti* is reported to have a higher expression of genes involved in innate immunity, whereas *K Prakriti* has a higher expression of genes involved in adaptive immunity [40]. Also, inflammatory markers such as *TNF α* and *IL-6* are found to be highly expressed in *VK* and *K.* [19].

Asymptomatic patients pose a major challenge for COVID-19 management because they tend to infect others. They are capable of transmitting the SARS-CoV-2 infection person to person and their communicable period lasts up to 21 days. Younger age, normal computarized tomography (CT) images, absence of lymphopenia, and leukopenia are some of the characteristics of these patients [64] According to the Diamond Princess study, the proportion of asymptomatic patients is 17.9% [65]. It was seen that the isolation and RNA testing of asymptomatic individuals, particularly among the high risk population (e.g. health workers) helped to eliminate SARS-CoV-2 from an Italian village [66]. One of the probable reasons behind asymptomatic individuals is variable disease resistant ability corresponding to *Prakriti* types. It has been reported that, *Kapha Prakriti* individuals have the next highest disease resistance following *Samprakriti* i.e. balanced *Prakriti* types individuals [67]. Assessment of *Prakriti* types with different susceptibility to COVID-19 infection among asymptomatic COVID-19 cases can be a useful tool to determine its associations with disease subtypes. Currently detection of such asymptomatic individuals remains a challenge

Table 2
Single nucleotide polymorphisms associated with COVID-19.

Gene	Variant	Results	Reference
ACE 1	rs1799752 I/D	Significant negative correlation between *ACE1* II genotype and COVID-19 cases and deaths	[55]
		Significant direct correlation between ACE 1 DD genotype and COVID- 19 severity	[56,57]
ACE 2	rs73635825 p. Ser19Pro p.His378Arg	May affect SARS-CoV-2 recognition and infection	[58]
TMPRSS2	rs12329760 p.Val192Met	Not involved in interaction between TMPRSS2 and SARS-CoV-2 spike protein (S1 domain). Allele frequency was found to be less in severe patients than mild and general individuals	[59,60]
HLA	*HLA-A* 11:01, HLA- B*51:01, HLA- C*14:02*	Significantly associated with serious outcome of COVID-19 patients	[59]
	*HLA-B*46:01*	Smallest number of predicted binding peptides for SARS-CoV-2, suggesting that individuals with this allele may be susceptible to COVID-19	[61]
	*HLA-B*15:03*	Higher binding capacity for SARS-CoV-2 peptides suggesting protective immunity for COVID-19	

and an integrative medicinal approach like AyuGenomics can help overcome this challenge. Establishing such associations can be an effective strategy for predicting disease predisposition, identifying high risk patients, and planning treatment approaches.

Lymphopenia has been used as one of the effective predictors of prognosis. Elevation of pro-calcitonin, serum ferritin, LDH, SGPT, bilirubin, and SGOT concentrations along with low serum concentration of albumin are the other factors being considered [68–70]. These altered biochemical profiles are also co-related with presence of co-morbidities such as diabetes, obesity, asthma, etc. [43,71] Sethi et al. have reported significant variation in biochemical profiles between three *Prakriti* types (otherwise within normalLaboratory range) [40]. In another study, alkaline phosphatase, SGPT and SGOT levels were found to be higher in *P Prakriti*. *K Prakriti* showed higher serum levels of triglyceride, cholesterol, lipoprotein, creatinine, urea. *V Prakriti* showed higher levels of serum proteins (albumin, globulin) [42].

Recently, populations across the globe are being vaccinated against COVID-19. Variations in immune response to vaccines have been observed between populations [72]. As explained earlier, innate and adaptive immune response differ as per *Prakriti* types [37,40] Hence, it will be interesting to study the variations in vaccine response according to *Prakriti* types. Such approaches may be useful for effective vaccine strategy.

Extensive efforts are ongoing for drug repurposing to identify effective and safe treatment for COVID-19. The authors (KJ) have reported correlations between drug metabolizing enzyme CYP2C19 and *Prakriti*. The data indicates extensive metabolizer genotype was predominant in *P Prakriti* while poor metabolizer genotype was highest in *K Prakriti*. [25] Such studies for different pharmacokinetic parameters are required as they may be useful in deciding dose and monitoring adverse effects of various COVID-19 therapeutics.

Thus, the reported studies provide clues for planning clinically relevant hypothesis to be tested in systematic studies. The studies on *Prakriti* types associated with molecular, biochemical, and clinical features of COVID-19 patients is the need of the hour.

4. Discussion and conclusion

Global burden of COVID-19 is gradually increasing and the disease is likely to remain an inevitable part of human life in the upcoming years. Although different measures are being taken for controlling the current pandemic, it continues to spread in varied patterns throughout the world. Identifying newer and simpler approaches for filtering high risk population might prove as one of the key strategies to control the spread of COVID-19. The onset and progression of SARS-CoV-2 infection differs between individuals. This might be the result of genetic and phenotypic variations. Considering such variations to predict the susceptibility and prognosis of COVID-19 might be beneficial. The genetic make-up and phenotypic characteristics are variable according to Ayurveda constitution types. For instance, *Pitta Prakriti* individuals are *Sukumar* (~tender), they may show fast progression in organ failure. Similarly the factors like *Dooshyam* (examination of all Dhathus and *doshas*), *Desham* (examination of all surroundings), *Balam* (examination of strength), *Kalam* (examination of season), Analam (examination Agni), *Prakruti* (examination body constitution), *Vayas* (examination age), Satwam (examination mental power), Satmyam (examination compatability), and *Aaharam* (examination food habits) can play a major role in progression of COVID-19. Several studies have reported an association between *Prakriti* and obesity, hypertension, diabetes mellitus, coronary heart disease, etc. [19,37,73–75]. Such approaches can be some of the important ways to classify and manage disease-susceptible populations. The reported studies so far provide clues for clinically relevant hypotheses to be tested in systematic studies (Table 1).

The studies on *Prakriti*-based stratification of genetic variations, differential immune responses, and clinical features of COVID-19 can be useful tools for predicting prognosis and planning an effective therapeutic strategy. Therefore, Ayurveda based phenotyping may offer an effective and robust, clinical prediction approach for prevention, control, and personalized management of the COVID-19 crises. This requires large-scale clinical studies to assess the relationship between *Prakriti*, genomics and phenotypic markers for disease progression, immune response, and therapeutic response. Data from such studies will shed more light on disease prone populations that can be predicted using simple Ayurveda-based *Prakriti* assessment. Pharmacogenomics exploration with Ayurveda *prakriti* that is currently used for COVID-19 therapeutics will also be useful to increase the precision of therapeutic personalization.

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Conflict of interest

The corresponding author Prof. Kalpana Joshi is an editorial board member and Dr Preeti Chavan-Gautam is an associate editor of Journal of Ayurveda and Integrative Medicine. However, both of them were not involved in any reviewing and publication process related to this manuscript in order to facilitate double anonymized review.

Author contributions

Vedika Bhat: Data curation, Writing- Original draft preparation, Methodology, Literature review, conceptualization.

Swapnil Borse: Data curation, Writing- Original draft preparation, Methodology, Literature review, conceptualization, Supervision.

Preeti Chavan-Guatam: Data curation, Writing- Reviewing and Editing, Methodology.

Kalpana Joshi: Conceptualization, Supervision, Methodology, Reviewing.

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