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Review

Relevance between COVID-19 and host genetics of immune response

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ABSTRACT

The outbreak of coronavirus disease 2019 (COVID-19) was caused by the newly emerged corona virus (2019-nCoV *alias* SARS-CoV-2) that resembles the severe acute respiratory syndrome virus (SARS-CoV). SARS-CoV-2, which was first identified in Wuhan (China) has spread globally, resulting in a high mortality worldwide reaching ~4 million deaths to date. As of first week of July 2021, ~181 million cases of COVID-19 have been reported. SARS-CoV-2 infection is mediated by the binding of virus spike protein to Angiotensin Converting Enzyme 2 (ACE2). ACE2 is expressed on many human tissues; however, the major entry point is probably pneumocytes, which are responsible for synthesis of alveolar surfactant in lungs. Viral infection of pneumocytes impairs immune responses and leads to, apart from severe hypoxia resulting from gas exchange, diseases with serious complications. During viral infection, gene products (e.g. ACE2) that mediate viral entry, antigen presentation, and cellular immunity are of crucial importance. Human leukocyte antigens (HLA) I and II present antigens to the $CD8^+$ and $CD4^+$ T lymphocytes, which are crucial for immune defence against pathogens including viruses. *HLA* gene variants affect the recognition and presentation of viral antigenic peptides to T-cells, and cytokine secretion. Additionally, endoplasmic reticulum aminopeptidases (ERAP) trim antigenic precursor peptides to fit into the binding groove of MHC class I molecules. Polymorphisms in *ERAP* genes leading to aberrations in ERAP's can alter antigen presentation by HLA class I molecules resulting in aberrant T-cell responses, which may affect susceptibility to infection and/or activation of immune response. Polymorphisms from these genes are associated, in global genetic association studies, with various phenotype traits/disorders many of which are related to the pathogenesis and progression of COVID-19; polymorphisms from various genes are annotated in genotype-tissue expression data as regulating the expression of ACE2, HLA's and ERAP's. We review such polymorphisms and illustrate variations in their allele frequencies in global populations. These reported findings highlight the roles of genetic modulators (e.g. genotype changes in *ACE2*, *HLA*'s and *ERAP*'s leading to aberrations in the expressed gene products or genotype changes at other genes regulating the expression levels of these genes) in the pathogenesis of viral infection.

Abbreviations: ACE, Angiotensin Converting Enzyme; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HIV, Human immunodeficiency virus; HLA, Human leukocyte antigen; NSCLC, Non-small cell lung carcinoma; RAS, Renin-angiotensin system; SARS, Severe acute respiratory syndrome; SNP, Single nucleotide polymorphism.

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Contents

1. Introduction

Coronavirus disease 2019 (COVID-19) is an ongoing pandemic caused by the new corona virus (2019-nCoV also known as SARS-CoV-2) that resembles severe acute respiratory syndrome virus (SARS-CoV). This virus was first identified in Wuhan, China and has subsequently spread worldwide, resulting in significant mortality (Yuen et al., 2020). Worldwide, as of the first week of July 2021, more than 181 million cases of COVID-19 including 4 million deaths have been reported since 31 December 2019.

Countries, across the globe, have experienced massive number of cases and deaths. The countries differ in the extent of notified cases and death – see, for example, Fig. 1 (as extracted from https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases on 6th July 2021) for variations in the case notification rate during the period of week 24 to week 25 of 2021 across different countries. Countries differ in applied case definitions, testing strategies, extent of implemented social restrictions, extent of truly reporting the cases, lack of sufficient treatment regime and awareness/promptness to attend health facilities. However, differences in genetic susceptibility due to ethnicity and race across the different populations cannot be ruled out. Individuals from the different human races/ethnicities may differ in alleles/genotypes at key genetic polymorphisms, in the genes from the COVID-19 pathway, that lead to changes in the expression levels of key molecular components (such as ACE2 receptors) or in the activities of the gene products forming the COVID-19 pathway.

Numerous factors are known to contribute to the pathogenesis of infection starting from viral entry to onset of symptoms and to finally the activation of the immune response and viral clearance. Immune response to viral entry is mediated by the activation and initiation of human leukocyte antigen (HLA) class I and II molecules, which present viral antigens to $CD8^+$ and $CD4^+$ T lymphocytes, respectively. SARS-CoV-2 infection is initiated by binding of spike protein to Angiotensin Converting Enzyme 2 (ACE2) (Brojakowska et al., 2020), then processed through the endoplasmic reticulum to be presented to HLA class I molecules on the surfaces of infected cells. This is followed by activation of $CD8^+$ T-cells, and HLA class II molecules on the surfaces of presenting cells, which activates $CD4^+$ T-cells, resulting in the secretion of cytokines to stimulate the activation of B-cells and other immune cells.

In this review, we discuss the genetic variations in genes of crucial importance for the pathogenesis of COVID-19, such as *ACE2*, *HLA* and *ERAP* that are involved in mediating viral entry into host cells, antigen presentation, and cellular immunity. We examine these genes for polymorphisms that are known to be associated with traits relating to disorders, particularly hypertension, diabetes, and with anthropometric traits involving body composition and lipid profiles; we also examine expression quantitative trait loci (eQTL) variants that explain variations in the expression levels of above-mentioned genes. The study further elucidates the prevalent genotypes at such genetic modulators in different countries. Such highlighted variants are probably potential candidates for inclusion in screening tools to assess the risk and outcome of COVID-19 in different populations.

2. 2. Methods

We performed literature search using Medline (PubMed) for research publications citing terms that relate to immune response to SARS-CoV-2 infection. Genotype-phenotype associations reported by global genome-wide association studies (GWAS) were examined using the NHGRI-EBI GWAS Catalog (Buniello et al., 2019) available at https://www.ebi.ac.uk/gwas/. eQTL variants that regulate genes of interest in tissue-specific manner were extracted from publicly available genotype-tissue expression data using the web portal GTEx v8 (available at https://www.gtexportal.org). Selection criteria used to query GWAS Catalog was based on the P-value threshold denoting genome-wide significance ($P < 5.0E-08$); the threshold was relaxed when only few associations were seen at genome-wide significance. As regards querying the GTEx, selection criteria were based on significant P-values and Q-values. Data from 1000 Genomes Project Phase 3 (Auton et al., 2015) was used to examine allele frequencies at genetic variants in continental populations. Allele frequencies in Middle East populations were extracted from data on genetic variants published previously on Kuwaitis (Hebbar et al., 2020; John et al., 2018) (available from our in-house databases), on Qataris (Fakhro et al., 2016) (as available from http://clingen.igib.res.in/almena/) and on Iranians (Fattahi et al., 2019) (as available from http://www.iranome.ir/). The resources of GWAS Catalog, GTEx and allele frequencies were last accessed on 17th November 2020.

2.1. Angiotensin converting enzyme 2 (ACE2)

ACE2 is a component of the renin-angiotensin system (RAS), which is a homeostatic endocrine system that controls blood pressure and maintains fluid and electrolyte balance (Smyth et al., 2019). Cole-Jeffrey et al. (Cole-Jeffrey et al., 2015) stated that cardiopulmonary homeostasis is intimately controlled by the RAS

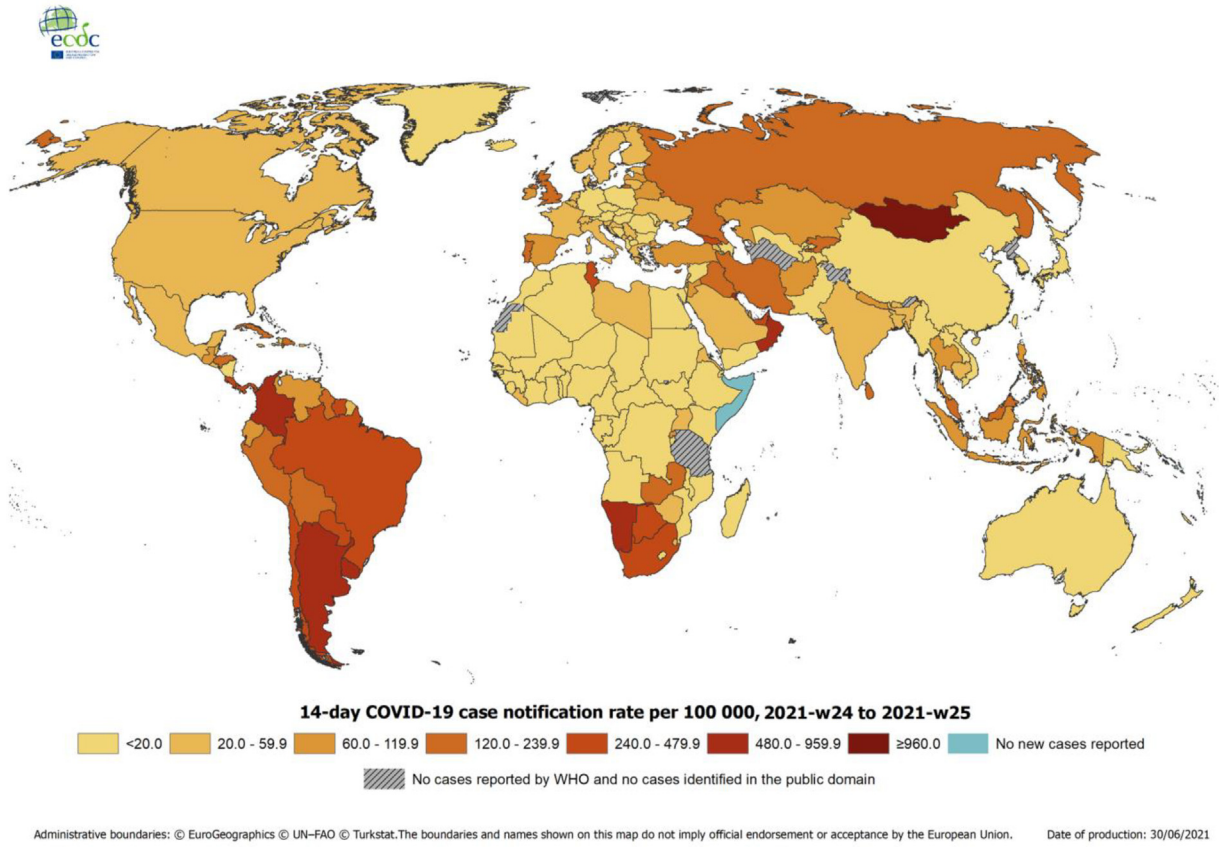

Fig. 1. Geographic distribution of COVID-19 cases worldwide during the period of week 24 to week 25 of 2021 (retrieved from https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases).

and the equilibrium between vaso-deleterious components (such as angiotensin-converting enzyme (ACE) and angiotensin II), and vaso-protective components (such as ACE2); it has a regulatory role in the functions of inflammatory cells by way of enhancing the reparative function of the dysfunctional endothelial progenitor cells (Jarajapu et al., 2013), and improving pulmonary arterial hypertension (Shenoy et al., 2013). Genetic modification of mesenchymal stem cells (MSC) to overexpress ACE2, by way of transducing MSCs with *ACE2* gene followed by infusing, improved the lung histopathology in mice with lipopolysaccharide-induced intratracheal lung injury (He et al., 2015). In a similar manner, human umbilical mesenchymal stem cells isolated for lentiviral-ACE2 transfection were effective in alleviating the lung damages in acute lung ischemia–reperfusion injury (ALIRI) rat models (Liu et al., 2014).

ACE2 facilitates entry of SARS-CoV-2 by way of acting as a receptor to which the spike protein of the virus binds. ACE2 is expressed at the surface of lung epithelial cells as well as certain other tissues and it has a regulatory role during overactivation of renin-angiotensin-aldosterone system. ACE2 receptors are extremely abundant on type 2 pneumocytes (Alifano et al., 2020), which are responsible for the synthesis of alveolar surfactants that facilitate gas exchange (Verdecchia et al., 2020). Binding of the SARS-CoV-2 spike protein to ACE2 impairs gas exchange, leading to hypoxia-related myocyte injury and the induction of immune-mediated cytokine storms (Huang et al., 2020; Song et al., 2020).

Li et al. (Li et al., 2003) reported that the coronavirus spike protein mediates viral infection by the efficient binding of its S1 domain with ACE2 and that the soluble form of ACE2 blocks the binding of the S1 domain with Vero E6 cells. Furthermore, SARS-CoV can efficiently replicate in ACE2-transfected cells. Thus, blocking the modification of ACE2 could inhibit viral entry. Also, variants of ACE2 due to polymorphisms in *ACE2* gene have varying affinities to viral proteins and hence could influence the outcome of COVID-19.

Polymorphisms in *ACE2* gene have been linked to increased risk of essential hypertension in multiple populations. A meta-analysis of case–control studies across different ethnicity provided solid evidence suggesting that *ACE2* gene polymorphism G8790A was probably a genetic risk factor for essential hypertension across different ethnic populations in female subjects and in Han-Chinese male subjects (Lu et al., 2012). A study on Caucasians with type 2 diabetes has shown that genetic variations in *ACE2* are associated with hypertension, reduced systolic function (in men) and increased left ventricular mass (in women) (Patel et al., 2012). Further, it has been proposed that *ACE2* polymorphisms are plausible candidates for pharmacogenomics; a variant from *ACE2* gene has been shown as an important predictive factor in the response to antihypertensive treatment with ACE inhibitors in Chinese female hypertensive patients (Chen et al., 2016a).

Janies et al. (Janies et al., 2008) reported that key mutations in the SARS-CoV S protein may be used to study the evolution of SARS-CoV genomes and "host shifts" across diverse hosts such as Chiroptera, carnivores and primates and to display on phylogenetic trees to illustrate the geographic spread of SARS-CoV.

Cure et al., (Cure and Cure, 2020) stated that the SARS-CoV-2 virus enters the cells through the attachment to the ACE2 enzyme at low cytosolic pH values, which leads to a reduction in angiotensin II resulting in further lowering of cytosolic pH; the resultant subsequent release of angiotensin 1–7 in the brain stem activates the sympathetic nervous system. This cascade of events increases pulmonary capillary leakage, resulting in the onset of acute respi-

ratory distress syndrome and in triggering cardiac arrhythmias by facilitating virus entry into the heart tissue. In addition, cytosolic pH is low in some comorbid conditions, such as diabetes, hypertension, obesity, old age, and smoking, which favours the entry and diffusion of the SARS-CoV-2 virus leading to increased morbidity and mortality in such cases. Meanwhile, Cai et al. (Cai, 2020) reported population disparities in gene expression levels of SARS-CoV receptors.

Yan et al. (Yan et al., 2020) reported that during SARS-CoV-2 infection, ACE2-expressing tissues become direct viral targets, leading to serious pathological changes, including severe acute respiratory syndrome, dysregulation of the RAS, progressive multiple organ failure, and even death. Alifano et al. (Alifano et al., 2020) strongly emphasized the importance of the role of ACE2 in COVID-19 and hypothesized that factors relating to ethnicity, polymorphisms, behaviours, associated illnesses, environmental factors, and medications may explain most of the aspects of the current outbreak. Chloroquine (CQ) administration can modify the affinity of ACE2 to the viral S protein by altering glycosylation; further research on the possible benefits/risks of CQ/hydroxy-CQ has been suggested as an appropriate step forward (Oscanoa et al., 2020).

Li et al. (Li et al., 2020) evaluated the role of ACE2 on SARS-CoV-2 infection and suggested that ACE2 is not only a viral receptor but is also involved in the regulation of cytokine secretion and replication of the viral genome. Notably, ACE2 expression was markedly elevated among cigarette smokers, suggesting that long-term smoking can be a risk factor for COVID-19. They also assembled protein–protein interaction networks and identified hub genes involved in viral infection and cytokine release.

2.2. Human leukocyte antigen (HLA) molecules

HLA molecules are critical factors involved in viral antigen presentation and induction of cellular immunity. It is well known that HLA molecules, particularly HLA class II molecules (DP, DR, and DQ), play important roles in the regulation and specificity of the immune response through the presentation of viral antigens to immune cells (Elahi and Horton, 2012). HLA class I and II molecules present antigens to $CD8^+$ and $CD4^+$ T cells, respectively (De Re et al., 2010; Lombard et al., 2006). Virus-infected cells are usually recognized and eliminated by $CD8^+$ T cells by binding to T-cell receptors and MHC class I molecules on the surfaces of target cells. MHC class I alleles bind to peptides with a particular set of anchor residues in the peptide-binding groove. Epitopes undergo proteolysis by proteasomes, which generates either mature epitopes that are ultimately presented by MHC-I, or precursor molecules that are extended by several amino acids at the amino (N) terminus. Such N-terminal-extended peptides are further processed by aminopeptidases to generate the final presented epitope (York et al., 2006).

HLA molecules present on the cell's surface bind to peptides of an infecting virus, triggering an immune response. Additionally, HLA-DQ variants affect the recognition and presentation of viral antigenic peptides, differentiation of T-cells, and the secretion of cytokines (Huang et al., 2017). Genetic variations in HLA-II genes have been linked to the risk and chronicity of infections with hepatitis C virus (HCV), hepatitis B virus (HBV), and human immunodeficiency virus (HIV) (Fitzmaurice et al., 2015; Xu et al., 2017; Yue et al., 2015). Genetic variants of *HLA-DQ* and *HLA-DP* have also been linked with the susceptibility to HCV and HBV infection (Yue et al., 2015; Li et al., 2017; Xu et al., 2017). A recent study by Shkurnikov et al., (Shkurnikov et al., 2021) could derive a risk score based on genotypes seen at genetic variants from HLA class I genes in COVID-19 patients from Russia and could associate the score with the severity of the COVID-19 in the Russian individuals; they further found that the score was applicable in an independent Spanish cohort of COVID-19 patients. Nguyen et al., (Nguyen et al., 2020) showed that individual HLA, haplotype, and full-genotype variability likely influence the capacity to respond to SARS-CoV-2 infection, and noted certain alleles in particular (e.g., HLA-B*46:01) that could be associated with more-severe infection. A remarkable study by Barquera et al (2020) identified many "generalist" HLA variants that are capable of binding strongly to the peptides of seven viruses (namely, coronaviruses including SARS-CoV-2, three influenza viruses and the HIV-1 virus of AIDS). The authors further noted that the global frequency distribution of HLA alleles coding for the strongest and weakest peptide binders, predicted in their analyses, indicates potential signatures of selective events occurring throughout human history. They find the frequency of the generalist HLA variants to differ significantly from one population to another (though they do not find specific differences in affinity for peptides of the new coronavirus) and provide insight into the reasons for differences in COVID-19 susceptibility between populations.

2.3. Endoplasmic reticulum AminoPeptidase (ERAP) molecules

As is the case with HLA molecules, endoplasmic reticulum aminopeptidase (ERAP) 1 and 2 are critical factors involved in viral antigen presentation and induction of cellular immunity.

Interferon-γ–induced ERAP1 expression varies among different tissues. ERAP1 was shown to influence the presentation of several peptides by trimming those composed of more than 8 or 9 amino acids to fit into the binding groove of MHC class I molecules. Thus, ERAP1 plays a major role in the creation of MHC-I epitopes either by trimming N-extended precursors to mature epitopes or by destroying mature epitopes that are composed of $\geq$9 residues to a size that is too small to bind to MHC class I molecules (Chen et al., 2016b; Hattori and Tsujimoto, 2013; York et al., 2006). Defects in ERAP1 can result in changes in antigen presentation by HLA-I and aberrant T-cell responses, which may affect susceptibility to infection and/or activation of the immune response.

Several allelic and genotypic variants from *ERAP1* gene have been linked to human diseases. Yao et al., (Yao et al., 2016) compared the frequencies of the *ERAP1* SNPs rs26653GC, rs26618TC, rs30187CT, and rs27044CG in Chinese Han and Polish Caucasian populations with non-small cell lung carcinoma (NSCLC) and found marked associations of all studied polymorphisms with NSCLC among Chinese, but not among Polish individuals (except for rs26618); this disparity was attributed to differences in genotype frequencies between the Chinese and Polish individuals. Another possible explanation lies in the disparities in the frequencies of HLA alleles between Caucasians and Asians (González-Galarza et al., 2015). Additionally, some antigenic peptides presented by MHC class I molecules are dependent on ERAP1 trimming, while others can fit into the groove of MHC molecules without trimming (Fruci et al., 2014). Furthermore, loss of ERAP1 or changes in ERAP1 could result in a marked disturbance in the antigen-processing pathway and a shift in the hierarchy of immune dominance during viral infection because ERAP1 trims precursor peptides in the endoplasmic reticulum to generate or destroy antigenic peptides. Consequently, changes in ERAP1 could result in a weaker or stronger immune response to viral peptides (York et al., 2006).

2.4. Prevalence of GWAS-annotated SNPs of the ACE2, HLA, and ERAP genes

The GWAS Catalog (Buniello et al., 2019) was searched for traits and disorders associated with variants from *ACE2*, *HLA* and *ERAP* genes (Supplementary Dataset 1). The *ACE2* gene is not associated with any traits in the GWAS Catalog, while variants of the *HLA* and *ERAP* genes are associated with disorders (particularly hyperten-

Table 1
GWAS-annotated variants of (1.A) and eQTL variants regulating (1.B) ACE2, HLA and ERAP genes with significant differences in allele frequencies among populations.

1.A. GWAS-annotated variants of the HLA and ERAP genes with significant differences in allele frequencies. Variants of ACE2 gene are not seen associated with traits in GWAS Catalog of global genome-wide association studies.

Variant	Gene	GWAS- annotated trait	Allele Frequency Pattern[@]
Rs3916500	*HLA-A*	Height	EAS:26%; AFR:0.1%
Rs10484554	*HLA-A*	Psoriasis	EAS:5%; QTR:28%
rs116576188	*HLA-B*	Ubiquitin carboxyl-terminal hydrolase 25 blood levels	AFR:8%; QTR:26%
rs1065386	*HLA-B*	Proliferative diabetic retinopathy	KWT:0.4%; EAS:59%
rs12191877	*HLA-B*	Psoriasis	EAS:5%; QTR:28%
rs12199223	*HLA-B*	Psoriasis	EAS:4%; QTR:23%
rs13191343	*HLA-B*	Psoriatic arthritis	AFR:9%; SAS:29%
rs4406273	*HLA-B*	Psoriasis	EAS:4%; QTR:23%
rs13191343	*HLA-B*	Psoriatic arthritis	AFR:9%; SAS:29%
rs9265503	*HLA-B*	Blood level of MHC class I polypeptide-related sequence B	QTR:10%; AFR:33%
rs2596492	*HLA-B*	TIE2 blood levels	KWT:0.4%; QTR:36%
rs9357121	*HLA-B*	Total and LDL cholesterol	AFR:0.8%; EAS:19%
rs2013717	*ERAP1*	ERAP1 blood levels	AFR:7%; EUR:23%
rs27033	*ERAP1*	Endoplasmic reticulum aminopeptidase 1 blood levels	EAS:13%; QTR:69%

1.B. eQTL variants for the ACE2, HLA, and ERAP genes with significant differences in allele frequencies

eQTL variant	Gene harboring the eQTL variant / gene regulated by the eQTL variant	GWAS- annotated trait	Allele Frequency Pattern
rs112171234	*ACE2* /*ACE2*	NA	AMR:3%; AFR:21%
rs6632704	*CLTRN* /*ACE2*	NA	QTR:41%; EAS:93%
rs4060	*CA5BP1-CA5B* /*ACE2*	NA	KWT:4%; AFR, SAS, AMR:69%
rs114712755	*HLA-B* /*HLA-B*	NA	SAS:4%; QTR:27%
rs117309887	*Intergenic (HLA-C, HLA-B)* /*HLA-B*	NA	AFR:8%; QTR:28%
rs12199223	*Intergenic (HLA-C, HLA-B)* /*HLA-B*	Psoriasis	EAS:4%; QTR:23%
rs2394987	*Intergenic (HLA-B, MICA)* /*HLA-B*	NA	SAS:7%; QTR:29%
rs9264255	*Intergenic (HCG27;HLA-C)* /*HLA-C*	NA	AFR:3%; EAS:21%
rs27039	*ERAP1* /*ERAP1*	NA	AFR:23%; AMR:61%
rs27433	*CAST* /*ERAP1*	NA	KWT:38%; QTR:85%
rs3797814	*CAST* /*ERAP1*	NA	AFR,EAS:9%; QTR:37%
rs7356594	*CAST* /*ERAP1*	NA	AFR,EAS:9%; QTR:37%

[@] , EAS: East Asians; AFR: Africans; AMR: Ad-mixed Americans; SAS: South Asians; EUR: Europeans; KWT: Kuwaitis; QTR: Qataris.

sion and diabetes) along with their risk factors, with anthropometric traits relating to obesity and with lipid traits. The phenotype traits associated with each of these genes in GWAS Catalog are as listed below.

HLA-A gene: Six *HLA-A* genetic variants are associated with multiple sclerosis, beta-2 microglobulin plasma levels, hemoglobin concentrations, height, and C-peptide levels in type 1 diabetes.

HLA-B gene: Forty-six *HLA-B* genetic variants are associated with psoriasis, Crohn's disease, hemoglobin concentrations, anthropometric traits, lipid traits, beta-2 microglobulin levels, albumin:globulin ratio, ankylosing spondylitis, alpha-2 macroglobulin receptor-associated protein levels, granzyme A levels, percentage of body fat, hypertension, angiopoietin 1 receptor levels, and proliferative diabetic retinopathy.

HLA-C gene: Eight *HLA-C* genetic variants are associated with body mass index, adjusted waist-hip ratio, smoking behaviour, beta-2 microglobulin levels, type 2 diabetes, mean corpuscular volume, mean corpuscular hemoglobin, C-reactive protein levels, and decreased glucose metabolism.

ERAP1 gene: Sixteen *ERAP1* genetic variants are associated with ankylosing spondylitis, chronic inflammatory diseases, psoriasis, endoplasmic reticulum aminopeptidase 1 levels, and psoriasis vulgaris.

ERAP2 gene: Nine *ERAP2* genetic variants are associated with Crohn's disease, diastolic blood pressure in hypertensive patients, chronic inflammatory disorders, inflammatory bowel disease, ankylosing spondylitis and psoriasis.

Further analysis revealed a number of variants from these genes with significant differences in allele frequencies among populations (Supplementary Fig. 1.pdf). Variants with particularly drastic differences in allele frequencies are as presented in Table 1.A.

It is to be noted that not all the traits mentioned above, as reported in GWAS Catalog, for variants from these genes are related to susceptibility to SARS-CoV-2 infection or seen in patients during the pathogenesis, progression and prognosis of the COVID-19. However, most of the reported traits are relating to disorders (inflammatory diseases, obesity, diabetes and hypertension) that are risk factors for COVID-19 severity and/or to those disorders (particularly diabetes and hypertension) for which new onset is seen in COVID-19 patients. The ones that are not directly related to obesity, diabetes and hypertension are macroglobulin levels, albumin, hemoglobin concentrations, corpuscular volume, gran-

zyme A levels, angioprotein 1 receptor, multiple sclerosis, ankylosing spondylitis and Crohn's disease. It has been proposed that albumin and globulin levels have diagnostic significance for COVID-19 (Feketea and Vlacha, 2020). Levels of changes in hemoglobin concentrations, corpuscular volume and other hematologic conditions are associated with the severity and clinical outcome of recovered COVID-19 patients (Mao et al., 2021). Decreased serum cytotoxic effector molecules including perforin and granzyme A, were detected in COVID-19 patients (Li et al., 2020a; 2020b). Hypoxia induces the expression of a number of angiogenic factors, including angioprotein-1 and angioprotein-2, to improve the blood supply in needed areas (Ng et al., 2011). Multiple sclerosis (MS) patients often have several other diseases, which are associated with a worse prognosis of COVID-19. The incidence of COVID-19 in MS patients was higher than that of the general population; however, they had a good outcome (Sepúlveda et al., 2021).

The traits associated with those variants from the *HLA* and *ERAP* genes with significantly drastic differences in allele frequencies among populations (as listed in Table 1.A) are height (as part of anthropometric traits relating to obesity), lipid levels (as part of traits relating to dyslipidemia), levels of ERAP1 (as part of viral antigen presentation and induction of cellular immunity), MHC class I polypeptide-related sequence B (as part of viral peptide-MHC class I binding affinity), diabetic retinopathy, psoriasis, psoriatic arthritis, USP25 levels and Tie2 levels. We elaborate on the relevance of these traits to COVID-19 as below:

Diabetic retinopathy: COVID-19 patients with diabetic retinopathy have a more than fivefold increased risk of intubation (Corcillo et al., 2021). A case report of acute, severe progression of diabetic retinopathy with vitreous haemorrhage in the setting of COVID-19 in a person with diabetes was recently reported (Akduman et al., 2021).

Psoriasis and psoriatic arthritis: A case report of an acute guttate flare of chronic psoriasis secondary to confirmed COVID-19 infection has been recently presented (Gananandan et al., 2020). The authors proposed dysregulation of innate immune response following stimulation of toll-like receptor 3 by viral RNA leading to production of pathogenic cytokines/chemokines IL-36-γ and CXCL8 as a possible mechanism for viral infection leading to psoriatic flare. A case report showing new-onset psoriasis in a 62-years old patient with COVID-19 has been recently reported (Mathieu et al., 2020). Further, a case report of psoriatic arthritis triggered by COVID-19 has been reported in a genetically predisposed patient (family history of psoriasis) in Italy (Novelli et al., 2021).

Ubiquitin carboxyl-terminal hydrolase 25 (USP25) levels: USP25 plays a protective role in virus or bacterial infection. USP25 deficient mice have been shown to be more susceptible to virus infection and LPS-induced septic shock (Lin et al., 2015).

Tie2 levels: It has been proposed that Tie2 activation protects against prothrombotic endothelial dysfunction in COVID-19 patients (Schmaier et al., 2021).

2.5. Assessment of expression quantitative trait loci (eQTLs) of the ACE2, HLA, and ERAP genes

eQTL variants that regulate the expression of *ACE2 gene* (Supplementary Dataset 2): By way of examining the publicly available genotype-tissue expression data, Cao et al., (Cao et al., 2020) reported 15 eQTL variants that regulate the expression of *ACE2*; such eQTL variants are located in the genes: *ACE2*, the gene Fanconi Anemia Complementation Group B *(FANCB)*, the intergenic region between the genes (Motile Sperm Domain Containing 2 and Ankyrin Repeat And SOCS Box Containing 9) (*MOSPD2,ASB9*), the intergenic region between the genes (Carbonic Anhydrase 5B Pseudogene 1 and Carbonic Anhydrase 5B) *(CA5BP1-CA5B)*, and Collectrin, Amino Acid Transport Regulator *(CLTRN)*. Of these 15 variants, 12 were associated with high expression level of the *ACE2* gene in adipose tissue, skeletal muscle tissue, testis, brain, artery and pituitary. They further concluded that East Asian populations have much higher allele frequencies in the eQTL variants associated with higher *ACE2* expression in tissues. We further found that allele frequencies of the variants that upregulate *ACE2* expression are almost two-fold greater in China (in general in East Asians) and Africa than in Middle Eastern countries. Two of the 15 eQTL variants (namely rs112171234 and rs75979613) that downregulate *ACE2* expression were seen in Qatar, but not in Kuwait or Iran; among continental populations, the rs112171234 variant was observed only in African and ad-mixed American populations. These differences in allele frequencies at the eQTL variants regulating the ACE2 expression can at least partially explain differences among populations in the susceptibility or response to SARS-CoV-2 under similar conditions.

eQTL variants that can regulate expression of *HLA* genes (Supplementary Dataset 2): Our examination of GTEx data, resulted in a list of (a) thirty variants, regulating HLA-A expression, from the genes: *HLA-A*, the intergenic region between the genes of (HLA-A and HLA complex group 9) (*HLA-A*, *HCG9*), the intergenic region between the genes HLA complex group 48 and HLA-A (*HCG48*, *HLA-A*), the intergenic region between the genes HLA-G and HLA-H (*HLA-G*, *HLA-H*) and the Tripartite Motif Containing 31 gene (*TRIM31*) regulate *HLA-A* expression; and (b) 28 variants, regulating *HLA-B* expression, from the genes of *HLA-B*, *HLA-C*, the intergenic region between the genes (HLA-C and HLA-B) (*HLA-C*,*HLA-B*), the intergenic region between the genes of HLA-B and MHC Class I Polypeptide-Related Sequence A gene (*HLA-B*, *MICA*), the intergenic region between the HLA Complex Group 27 gene and HLA-C gene (*HCG27*,*HLA-C*), the intergenic region between the MHC Class I Polypeptide-Related Sequence A gene and HLA Complex P5 gene (*MICA*,*HCP5*), and from the genes POU Class 5 Homeobox 1 (*POU5F1*), HLA Complex Group 26 (*HCG26*), Psoriasis Susceptibility 1 Candidate 1 (*PSORS1C1*), HLA Complex Group 27 (*HCG27*), and U6 SnRNA-Associated Sm-Like Protein LSm2 (*LSM2*),

eQTL variants that can regulate expression of *ERAP* gene (Supplementary Dataset 2): Our examination of GTEx data, resulted in a list of (a) twenty two variants, regulating the expression of *ERAP1*, from the genes of Calpastatin (*CAST*), *ERAP1*, the intergenic region between *ERAP1* and *ERAP2* genes (*ERAP1*,*ERAP2*), and the intergenic region between the *CAST* and *ERAP1* genes (*CAST*,*ERAP1*); and (b) one variant from the *ERAP2* gene regulating expression of itself.

Further analysis revealed a number of eQTL variants from the genes mentioned-above to have significant differences in allele frequencies across different populations (Supplementary Figure 2). Particularly significant variants are as presented in Table 1.B.

3. Conclusions

This review focussed on (i) the important roles that the *ACE2*, *HLA* and *ERAP* genes play in the regulation of viral antigen presentation and induction of cellular immunity to SARS-CoV-2; and (ii) how changes or defects in these molecules alter the immune response.

Further, we examined the differences in allele frequencies of key genetic variants from the *ACE2, HLA* and *ERAP* genes and discussed the following findings:

(i) By way of examining the GWAS Catalog, that presents results of published global genome-wide association studies, we identified association signals involving variants from *ACE2*, *HLA* and *ERAP* genes. The associated phenotypes were

often the traits, prognostic markers, and disorders that are related to susceptibility to SARS-CoV-2 infection or seen in patients during the pathogenesis, progression and prognosis of the COVID-19. We further illustrated that the allele frequencies at these variants differed significantly among populations; variants associated with psoriasis, diabetic retinopathy, measurements of LDL, total cholesterol, USP25, ERAP1, MHC Class I and Tie2 levels differed drastically in allele frequencies across the populations.

(ii) By way of examining the GTEx portal of genotype-tissue expression data, a number of eQTL variants that regulate the expression of the *ACE2*, *HLA* and *ERAP* genes were identified. The allele frequencies at these eQTL variants differed across the different populations. The eQTL variants regulating *ACE2* were seen from (*ACE2*, *FANCB, MOSPD2, ASB9, CA5BP1, CA5B, CLTRN),* those regulating *HLA-A* were from *(HLA-A, HLA-G, HLA-H, HCG9, HCG48, TRIM31),* those regulating *HLA-B* were from *(HLA-B, HLA-C, HCP5, HCG26, HCG27, MICA, POU5F1, PSORS1C1, LSM2*), those regulating *ERAP1* were from (*ERAP1, ERAP2, CAST*), and the variant regulating *ERAP2* was from *ERAP2*. It will be interesting to probe these genes, in future works, for involvement in COVID-19 pathway.

Differences in allele frequencies at these variants associated with COVID-19 related traits and at the eQTL variants regulating the expression of *ACE2*/*HLA*/*ERAP* genes can at least partially explain the differences among populations in the susceptibility or response to SARS-CoV-2 under similar conditions.

The findings discussed in this review highlight the roles of genetic modulators in the pathogenesis of viral infection. It is very important to understand the different effects of *ACE2*, *HLA*, and *ERAP* polymorphisms in SARS-CoV-2 infection in order to elucidate the prevalent genotypes in different countries and possible associations with the susceptibility to infection with SARS-CoV-2 and the outcome of COVID-19. The highlighted variants provide a reliable and accurate screening tool to assess the risk and outcome of COVID-19 among different populations. Eventually, these data can be incorporated as a preliminary screening tool of high-risk groups.

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Author contributions

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sjbs.2021.07.037.

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