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Research Article

Ethnic disparities in the distribution of gene expression modulating polymorphisms in key pro-inflammatory cytokines associated with COVID-19 severities

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ABSTRACT

The severity of the coronavirus disease 2019 (COVID-19) is linked to pro-inflammatory cytokine levels. There are still many unanswered questions regarding COVID-19 pathogenesis and prognosis. Significantly increased levels of pro-inflammatory cytokines characterize severe COVID-19 compared to those with a mild-to-moderate form of the disease. In this study, we used *in silico* tools to explore the variant allele frequency distributions of three important pro-inflammatory cytokine genes: interleukin-6 (*IL-6*), interleukin-8 (*IL-8*), and tumor necrosis factor-alpha (*TNFA*), as well as their linkage disequilibrium (LD) patterns in worldwide populations. These cytokines were chosen for their pro-inflammatory properties, importance in determining COVID-19 outcomes, and potential as disease treatment targets. Twenty-two of the variants correlate with altered cytokine expression levels, which may also influence the expression of several other mediators of immune responses. These variants also appear to be associated with several COVID-19 comorbidities, such as diabetes, asthma, obesity, and heart conditions. At least one variant (rs1800795 in *IL6*) is likely associated with an altered response to TNFA inhibitors, which are considered COVID-19 treatment options. The European super-population has high variant allele frequencies (VAF $\geq$ 0.2) at thirteen of these variant loci. High genetic heterogeneity at these loci is present in the admixed American populations, whereas the East Asian populations appear genetically more homogeneous. Interethnic differences are more pronounced at the *IL6* SNP loci, which may cause variances in the expression level of a long non-coding RNA gene, *IL6-AS1*. Stronger and more extensive LD ($R^2 \geq 0.8$) exists among the *IL6* and *IL8* variants in the European super-population and among the *TNFA* variants in the East and South Asian populations. In general, the European super-population has higher frequencies of haplotypes with multiple variant alleles. Such interethnic differences may shed more light on the disparities in COVID-19 severities and the responses to treatments across ethnic groups.

Introduction

COVID-19 is caused by a coronavirus, aptly named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Wu et al., 2020). As of the writing of this article, SARS-CoV-2 has infected more than 761 million people and claimed over 6.8 million lives in 225 countries, areas, or territories around the globe (https://covid19.who.int/,Accessed: March 23, 2023). Europe is thus far the most heavily affected area, followed by the Americas, Southeast Asia, and Africa. Interethnic differences in COVID-19 outcomes cannot be fully explained by differences in socio-economic status or pre-existing health conditions (Mulholland and Sinha, 2020). Ethnicity is, however, a complex construct comprising genetic

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makeup, sociocultural identity, behavioral patterns, environment, historical processes, and socio-political experiences (Lee, 2009; Pan et al., 2020). Thus, differences in COVID-19 severity across ethnic groups can be attributed to multiple factors, such as socio-economic and health inequalities and genetic predisposition (El-Khatib et al., 2020).

Many unanswered questions remain regarding COVID-19 pathogenesis and prognosis (Cevik et al., 2020). Clinical manifestations of SARS-CoV-2 infection in humans range from mild symptoms to severe respiratory failures (Hu et al., 2021). While a proper antiviral immune response can prevent COVID-19 from becoming severe, the absence of such protective immunity can lead to massive destruction of tissues in multiple organs, especially those with high expression of angiotensin-converting enzyme 2 (ACE2) (Shi et al., 2020), and even death (Li et al., 2020). Severe COVID-19 is characterized by significantly increased levels of pro-inflammatory cytokines and reduced T lymphocytes compared to those with a mild-to-moderate form of the disease (Mulchandani et al., 2021). Especially following SARS-CoV-2 infection, host cells undergo pyroptosis and release damage-associated molecular patterns, which cause neighboring cells to produce pro-inflammatory cytokines (Tay et al., 2020). These cytokines recruit monocytes, macrophages, and T cells to the site of infection, promote further inflammation, and thus create a pro-inflammatory feedback loop (Tay et al., 2020). This overproduction of circulating inflammatory mediators, including cytokines and chemokines such as interleukin (IL)-1, IL-2, IL-6, IL-7, IL-8, IL-10, tumor necrosis factor-alpha (TNF-α), granulocyte colony-stimulating factor (G-CSF), monocyte chemoattractant protein-1 (MCP1), macrophage inflammatory protein 1 alpha (MIP1α), CXC-chemokine ligand 10 (CXCL10), C-reactive protein (CRP), ferritin, D-dimers and so forth, generates the "cytokine storm" in patients with severe COVID-19 (Gasparello et al., 2021; Hojyo et al., 2020; Ragab et al., 2020). Although no unifying definition of “cytokine storm” currently exists, it is one of the main focuses of studies exploring COVID-19 pathogenesis as it is the primary suspect for causing multi-organ failures in patients with severe COVID-19 (Fajgenbaum and June, 2020).

Elevated levels of several cytokines have been associated with COVID-19 severity, but specific cytokines among these play more critical roles in the pathogenesis of this disease compared with others. For example, significantly higher levels of circulating IL-6, IL-8, IL-10, IL-2R, and TNF-α, have been consistently found in patients with severe COVID-19 compared to those suffering from a mild-to-moderate form of the disease (Mulchandani et al., 2021). Among these five molecules, serum levels of IL-6, IL-8, and TNF-α in COVID-19 patients during hospitalization are strong and independent predictors of survival (Del Valle et al., 2020). It has been proposed that serum levels of IL-6 and TNF-α can be used to suggest therapeutic options (Del Valle et al., 2020). Moreover, both IL-6 and IL-8 can be used as biomarkers for COVID-19 severity and prognosis(Li et al., 2021). Elevated levels of plasma IL-6 significantly correlate with higher mortality (Smieszek et al., 2021). Additionally, the duration of illness in patients with severe COVID-19 is positively associated with serum levels of IL-8 (Ma et al., 2021). IL-8 is a potent regulator of neutrophil and monocyte chemotaxis that plays a significant role in acute lung damage. In such patients, elevated levels of IL-8 are associated with an increased risk of mortality and reduced ventilator-free and organ failure-free days (Mulchandani et al., 2021). The formation of Neutrophil Extracellular Traps (NETs) followed by neutrophil activation by IL-8 is one of the underlying mechanisms of COVID-19 pathogenesis. NETs promote immunothrombosis and lead to lung cell death, organ failure, massive neutrophil infiltration, and the development of Acute Respiratory Distress Syndrome (ARDS) (Cesta et al., 2022). Elevated levels of TNF-α are strong predictors of poor outcomes and contribute to organ damage in COVID-19 patients (Del Valle et al., 2020). COVID-19 confirmed that patients requiring ICU have a higher plasma TNF-α level than non-ICU patients (Huang et al., 2020). Recent studies have shown that

increased levels of pro-inflammatory cytokines are associated with diabetes and its complications (Shoily et al., 2021), cardiovascular diseases (Stentz et al., 2004), hypertension (Liu et al., 2017), acute and chronic kidney diseases (Mihai et al., 2018; Ortega and Fornoni, 2010), and asthma, among others (Lambrecht et al., 2019). These conditions are also associated with COVID-19 severity and/or mortality (Bajgain et al., 2021; Ng et al., 2021).

Indeed, the correlation of elevated pro-inflammatory cytokine levels with COVID-19 severity makes these molecules feasible therapeutic targets. Several therapeutic monoclonal antibodies targeting inflammatory mediators, including IL-1β, IL-1ra, IL-2, IL-6, IL-8, IL-17, IL-33, G-CSF, GM-CSF, IP10, MCP1α, MIP1β, TNF-α, and complement component-5 are currently under clinical trial for managing COVID-19 associated cytokine storm (Hussein et al., 2020; Patel et al., 2021; Robinson et al., 2020). Promising results in this regard have so far been obtained using anti-IL-6 drugs such as tocilizumab, sarilumab, and siltuximab that both inhibit *trans*- and classical signaling (Castelnovo et al., 2021; Du et al., 2021). Whereas anti-IL-6 drugs are associated with some sorts of adverse reactions, the use of specific inhibitors of metalloproteinase 17 (ADAM17) and soluble glycoprotein 130 fused chimera (sgp130Fc) are more effective and safer strategies to specifically inhibit pathological IL-6 *trans*-signaling in patients with severe COVID-19 since IL-6 also offers some anti-inflammatory effects (Du et al., 2021). Two IL-8 inhibitors – HuMax-IL-8 and Reparixin, are also being investigated as potential COVID-19 therapeutic agents. The human monoclonal antibody HuMax-IL-8 targets IL-8 overexpression in multiple cancer types, whereas Reparixin is an allosteric inhibitor of IL-8 that significantly reduces neutrophil recruitment and NET formation (Cesta et al., 2022).

Elevated levels of pro-inflammatory cytokines are associated with increased susceptibility to several COVID-19 comorbidities. Besides, variants in the genes encoding inflammatory mediators can be associated with altered responses to therapies targeting pro-inflammatory cytokines(Enevold et al., 2014; Padyukov et al., 2003). Understanding inter-ethnic differences in pro-inflammatory cytokine levels helps identify the relatively more vulnerable groups, make appropriate public health policies, and make informed therapeutic decisions concerning COVID-19.

There have been a few studies reporting differences in inflammatory cytokine levels among individuals of different ethnicities (Coe et al., 2011; Ho et al., 2005; Mayr et al., 2007; Ness et al., 2004; Stowe et al., 2010; Yao et al., 2018). However, these studies have mostly focused on US residents. Levels of pro-inflammatory cytokines can depend on both non-genetic factors such as age, gender, smoking habits, etc. (Rothaug et al., 2016) as well as genetic factors such as certain genotypes at expression quantitative trait loci (eQTLs) (Guan et al., 2020). Differences in allelic and haplotype frequencies of such variants across ethnic groups may have clinical implications (Hassan et al., 2003).

In the present study, we explored the allele frequency distributions and linkage disequilibrium patterns of gene expression-modulating SNPs in three pro-inflammatory cytokine genes (*IL6*, *TNFA*, and *IL8*) across twenty-six populations belonging to five super-populations, namely African, admixed American, East Asian, European, and South Asian. These cytokines were selected because of their pro-inflammatory nature, significance in determining COVID-19 outcomes, and prospects as therapeutic targets for the disease. We aimed to determine (i) if there are any differences in the genetic architecture of those gene expression-associated SNPs across ethnic groups, (ii) how these differences may contribute to the ethnic disparities in COVID-19 outcomes, and (iii) how these differences may manifest as inter-ethnic variability in response to COVID-19 therapy.

Materials and Methods

Listing gene expression-modulating SNPs

Gene expression-modulating SNPs in *IL6*, *TNFA*, and *IL8* (p <5E-8, the default p-value for gene expression in PhenoScanner V2) were retrieved from the Gene Expression catalog of PhenoScanner V2 (Kamat et al., 2019). Duplicates were removed to retain only the unique reference SNP IDs (rs IDs). Chromosomal location (GRCh38/hg38), consequence, and associated trait for each of these SNPs were obtained through PhenoScanner V2.

Retrieving allele frequencies

Allele frequencies at the gene expression-modulating SNP loci in five super-populations and twenty-six constituent sub-populations were retrieved from the 1000 Genomes Project (1000 Genomes Project Consortium et al., 2015) via the Ensembl Genome Browser (Hunt et al., 2018). The 1000 Genomes Project reconstructed the genomes of individuals from 26 different populations of various ethnic backgrounds and geographic locations. Seven of these populations are from Africa, four from the admixed Americans, and five populations each from East Asia, Europe, and South Asia. Therefore, based on their geographical origins, the 26 populations are divided into 5 super-populations (as described by the 1000 Genomes Project), namely African (AFR), admixed American (AMR), East Asian (EAS), European (EUR), and South Asian (SAS). SNPs not present in the 1000 Genomes Project reference panel were excluded from further analysis. The correlation of these SNPs with gene expression was collected from the eQTLGen Consortium (Võsa et al., 2018).

Listing COVID-19 comorbidities associated with gene expression-modulating SNPs

Diseases associated with the gene expression-modulating SNPs were obtained from PhenoScanner V2 (Kamat et al., 2019) and DisGeNET v7.0 (Piñero et al., 2020). This list of diseases was matched with the list of known COVID-19 comorbidities enlisted by the Center for Disease Control and Prevention (CDC), USA (https://www.cdc.gov, Accessed: April 12, 2022). Only associations between gene expression-modulating SNPs and COVID-19 comorbidities were considered.

Assessing association with drug response

Any association of the gene expression-modulating SNPs with responses to therapies targeting IL-6, TNF-α, or IL-8, each rs ID was collected from the Pharmacogenomics Knowledgebase (PharmGKB) (Whirl-Carrillo et al., 2012).

Calculating haplotype frequencies and analyzing linkage disequilibrium pattern

Frequencies of haplotypes inferred by gene expression-associated SNPs in *IL6*, *TNFA*, and *IL8* genes in the five super-populations were calculated using the LDhap module of LDlink (Machiela and Chanock, 2015). Linkage disequilibrium patterns among those SNPs in five super-populations were obtained from the LDmatrix module of LDlink.

Statistical analysis

The difference in the variant allele frequencies (ΔVAF), which can be defined as the range of variant allele frequencies VAF (maximum VAF-minimum VAF) among the sub-populations belonging to a particular super-population, was calculated at each SNP locus as a measure of genetic diversity within each super-population. ΔVAF values of five super-populations were compared using the Kruskal-Wallis test followed by pairwise Wilcoxon rank sum test. p-values were adjusted using Holm's method. Allele frequency differences (AFDs) were calculated at each SNP locus to show pairwise comparisons among the super-populations (Berner, 2019). Calculations were conducted with LibreOffice Calc. All statistical analyses were performed in R. Boxplot, and bar plots were generated with the ggplot2 and ggsignif packages in R.

Results

Gene expression-modulating SNPs and their variant allele frequencies

Twenty-four gene expression-modulating variants exist in the *IL6*, *TNFA*, and *IL8* genes. Thirteen, six, and five variants are located in the *IL6*, *TNFA*,

and*IL8* genes, respectively. Among these, rs2069835 in *IL6* is absent in the 1000 Genomes Project reference panel. rs1799769 in *TNFA* is an INDEL variant. So, these two variants were excluded, and the remaining twenty-two SNPs were used in further analysis (Table 1 and supplementary Table 1). Five of these SNP loci have three alleles each. Only the variant with the highest frequency at the individual locus was considered in such cases. Correlations between these variant alleles and affected genes are listed in supplementary table 2. The relative distribution of VAFs at these loci in different super-populations is shown in Fig. 1. Nine of these SNPs have VAFs ≥ 0.4 in the European super-population. Variant alleles at these SNP loci also have high frequencies in the admixed American super-population. On the contrary, Africans and East Asians mostly carry the reference alleles at these loci. VAFs at rs1800796 and rs2066992 loci are > 0.7 in the East Asians, although the global VAFs at these loci are close to 0.3 (Table 1 and Supplementary Table 1). The variant allele atrs1800795 is highly prevalent in the European super- population (VAF = 0.416), although it is absent or rare in the East Asian populations (VAF = 0.001) (Table 1 and supplementary table 1). VAF at rs1800797 is also higher in the European super-population (VAF > 0.4) compared to the other super-populations (VAF < 0.2) (Table 1).

TNFA variants exhibit comparatively fewer interpopulation differences (Figure 2). Besides, these SNPs generally are not correlated with a higher risk of many COVID-19 comorbidities (Table 2). Compared to the variant alleles in *IL6* and *TNFA*, the variants in *IL8* have higher VAFs in all except the African super-population). At three SNP loci (rs2227306, rs2227543, and rs1126647), the VAFs in the African super-population are < 0.1, while those in the other super-populations are > 0.25 (Table 1 and supplementary Table 1). On the other hand, the global variant allele (G) at rs2227307 is the major allele (VAF = 0.791) in the African super-population.

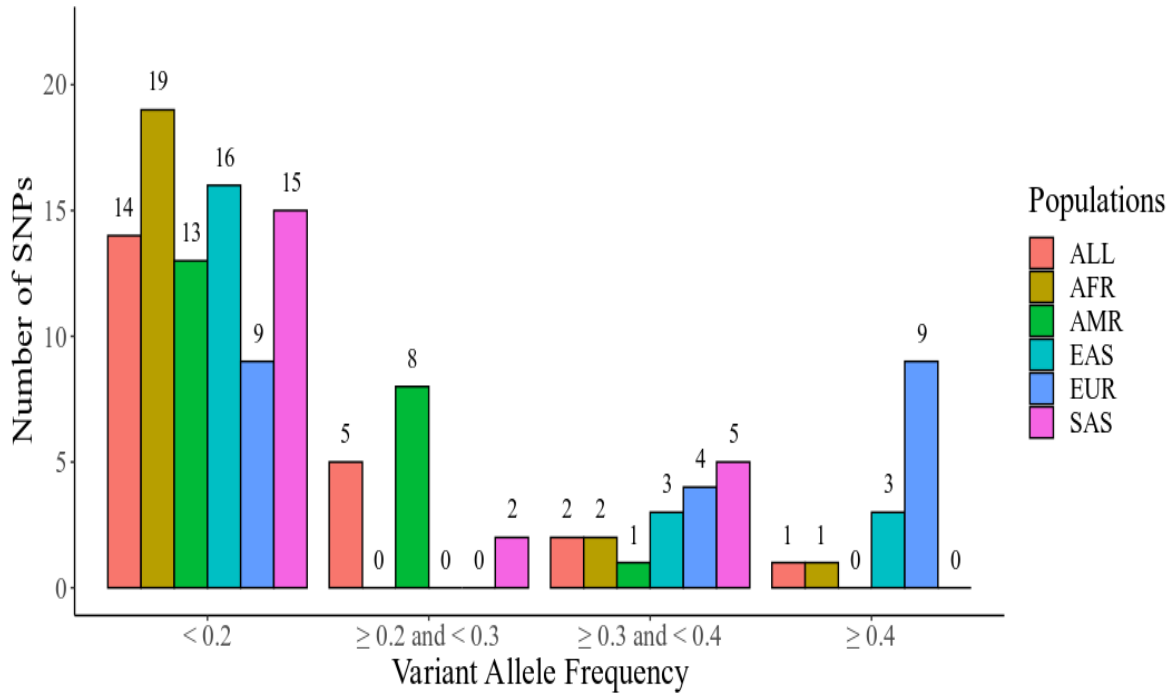

Fig. 1. Distribution of expression-modulating variant allele frequencies of *IL6, TNFA,* and *IL8* genes in different super-populations. ALL = global, AFR = African, AMR = Admixed American, EAS = East Asian, EUR = European, and SAS = South Asian.

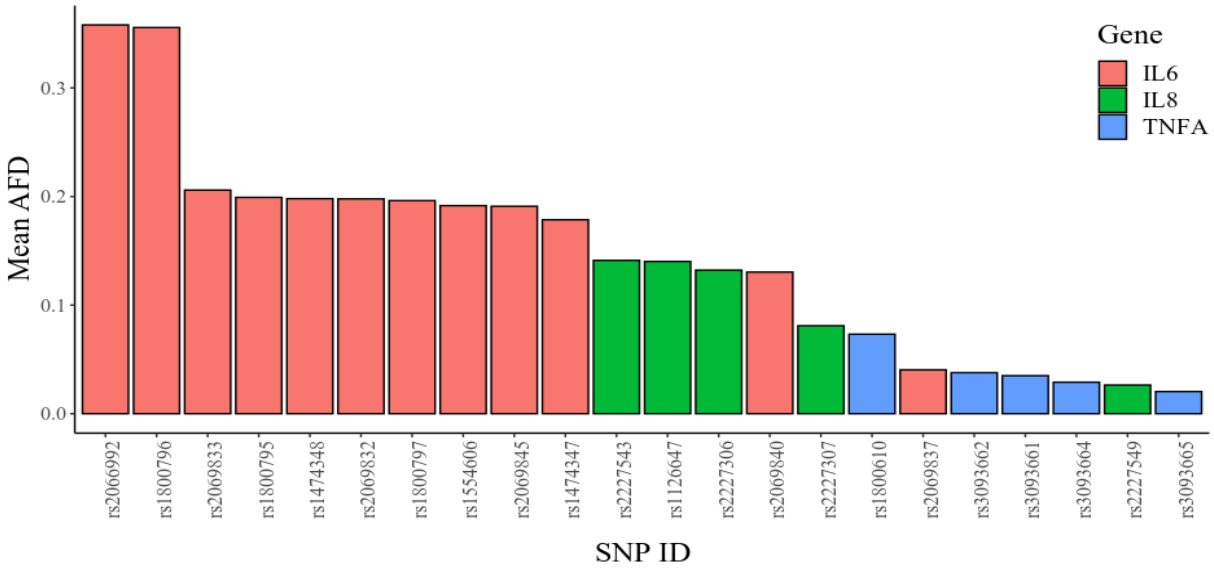

Fig. 2. Mean allele frequency differences (AFD) at each gene expression-associated SNPs in *IL6*, *TNFA*, and *IL8* across five super-populations.

Table 1. List of gene expression-modulating SNPs in *IL6*, *TNFA*, and *IL8* alongside their VAFs in five super-populations

Gene	SNP ID	Chromosomal location	Consequence	Reference allele	Variant allele	ALL*	AFR	AMR	EAS	EUR	SAS
IL6	rs1800797	chr7:22726602	Intron	G	A	0.138	0.017	0.184	0.001	0.408	0.134
	rs1800796	chr7:22726627	Intron	G	C	0.314	0.103	0.295	0.791	0.048	0.395
	rs1800795	chr7:22727026	Intron	G	C	0.141	0.018	0.184	0.001	0.416	0.139
	rs2069832	chr7:22727814	Intron	G	A	0.14	0.018	0.187	0.001	0.411	0.134
	rs2069833	chr7:22728045	Intron	T	C	0.14	0.017	0.187	0.001	0.411	0.138
	rs1474348	chr7:22728289	Intron	G	C	0.141	0.017	0.187	0.001	0.411	0.14
	rs2069837	chr7:22728408	Intron	A	G	0.12	0.12	0.081	0.141	0.089	0.156
	rs1474347	chr7:22728505	Intron	C	C	0.168	0.113	0.196	0.007	0.412	0.14
	rs2066992	chr7:22728630	Intron	G	T	0.308	0.085	0.293	0.788	0.048	0.395
	rs2069840	chr7:22728953	Intron	C	G	0.186	0.15	0.262	0.062	0.332	0.155
	rs1554606	chr7:22729088	Intron	T	T	0.249	0.311	0.287	0.009	0.432	0.199
	rs2069845	chr7:22730530	Intron	G	G	0.253	0.317	0.285	0.011	0.433	0.206
TNFA	rs3093661	chr6:31575981	Intron	G	A	0.052	0.03	0.056	0.031	0.048	0.105
	rs1800610	chr6:31576050	Intron	G	A	0.1	0.024	0.183	0.137	0.089	0.119
	rs3093662	chr6:31576412	Intron	A	G	0.08	0.077	0.11	0.031	0.084	0.108
	rs3093664	chr6:31576865	Intron	A	G	0.079	0.084	0.084	0.036	0.083	0.108
	rs3093665	chr6:31577614	3' UTR	A	C	0.019	0.039	0.027	0	0.021	0.003
IL8	rs2227307	chr4:73740952	Intron	T	G	0.424	0.518	0.337	0.414	0.417	0.374
	rs2227549	chr4:73741020	Intron	A	G	0.016	0.005	0.026	0	0.051	0.005
	rs2227306	chr4:73741338	Intron	C	T	0.259	0.097	0.269	0.338	0.388	0.259
	rs2227543	chr4:73742193	3' UTR	C	T	0.289	0.097	0.269	0.383	0.393	0.357
	rs1126647	chr4:73743328	3' UTR	A	T	0.285	0.096	0.265	0.384	0.387	0.349

***All populations (ALL), Africans (AFR), Admixed Americans (AMR), East Asian (EAS), European (EUR), and South Asian (SAS).**

Based on the data from the eQTLGen Consortium, it appears that the variant alleles at rs2066992 and rs1800796 are negatively correlated with the expression of a long non-coding RNA gene- *IL6-AS1* (GRCh38) or *AC073072.5* (GRCh37) (Gene ID: ENSG00000179428) (Supplementary table 2), which encodes an IL-6 antisense RNA, whereas rs2069833, rs1800795, rs1474348, rs2069832, rs1800797, rs1554606, rs2069845, and rs1474347 loci in *IL6* are positively correlated with IL6-AS1 expression.

Genetic diversity and population differentiation

We calculated the AFDs for each possible population pair at each SNP locus to assess genetic diversity and population differentiation. (Supplementary Table 3). We also calculated the mean of these pairwise AFDs at each SNP locus (Figure 3). The mean AFDs at half of the SNPs, *i.e.*, at eleven SNPs, are between 0.1 and 0.2. the values of the mean AFD at rs2066992 and rs1800796 are > 0.3, and at rs2069833 the value is 0.2059. On the opposite end, based on the distribution of ΔVAF values, more within-group variations are present among the admixed American populations than the constituent populations of the other super-populations (Figure 3). The East Asian populations appear to be genetically more uniform, with lower ΔVAF values.

Table 2. Association between gene expression-associated SNPs in three pro-inflammatory cytokine genes (*IL6, TNFA* and *IL8*) and COVID-19 comorbidities

Gene	SNP ID	COVID-19 comorbidities											
		Asthma	Cancer	Cystic fibrosis	Diabetes/ Hyperglycemia	Heart conditions	Hypertension	Kidney diseases	Liver disease	Neurological conditions	Obesity/BMI	Pulmonary/ Lung diseases	White blood cell count
IL6	rs1800797	√	√	-	√	√	-	√	√	√	√	-	√
	rs1800796	√	√	-	√	√	-	√	√	√	√	√	√
	rs1800795	√	√	-	√	√	√	√	√	√	√	√	√
	rs2069832	√	√	-	-	-	-	-	-	-	-	-	√
	rs2069833	-	-	-	-	-	-	-	-	-	-	-	-
	rs1474348	√	√	-	-	-	-	-	-	-	-	-	√
	rs2069837	-	√	-	-	-	√	√	-	√	-	√	-
	rs1474347	√	-	-	-	-	-	-	-	-	-	-	√
	rs2066992	-	√	-	-	√	-	-	-	√	-	-	√
	rs2069840	-	√	-	-	√	-	√	-	-	-	-	√
	rs1554606	√	-	-	-	-	-	-	-	-	√	-	√
	rs2069845	√	√	-	-	-	-	-	-	√	-	-	√
TNFA	rs3093661	-	-	-	-	-	-	-	-	-	√	-	√
	rs1800610	-	√	-	√	-	-	-	√	-	-	-	-
	rs3093662	-	-	-	-	-	-	-	-	√	√	√	√
	rs3093664	√	-	-	-	-	-	-	-	-	-	√	-
	rs3093665	-	√	-	-	-	-	-	-	-	-	-	√
IL8	rs2227307	-	√	√	-	-	-	-	-	-	-	√	√
	rs2227549	√	√	-	-	-	-	√	√	-	-	√	-
	rs2227306	-	-	-	-	-	-	-	-	-	-	-	√
	rs2227543	-	-	-	-	-	-	√	-	-	-	-	√
	rs1126647	-	√	-	-	-	√	-	-	√	-	-	√

√ indicates an association between the SNP and the corresponding COVID-19 comorbidity.

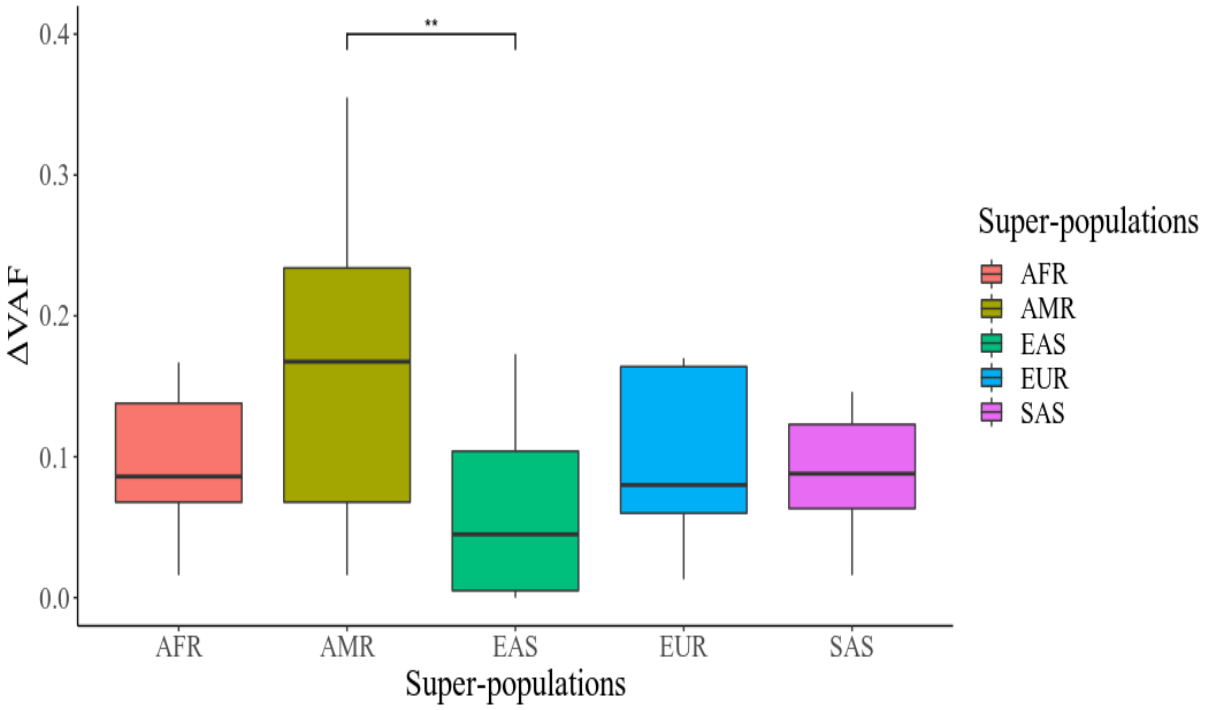

Fig. 3. Variant allele frequencies (ΔVAF) range in different super-populations. ΔVAF values indicate within-population variations. ΔVAFs were compared using the Kruskal-Wallis test and pairwise Wilcoxon rank sum test. p-values were adjusted using Holm's method. AFR = African, AMR = Admixed American, EAS = East Asian, EUR = European, and SAS = South Asian. **p < 0.01.

Disease and drug response associated SNPs

Twenty-one gene expression-associated SNPs correlate with at least two diseases or traits that can increase COVID-19 severity (Table 2). Altogether, these SNPs can modulate susceptibility to twelve COVID-19 comorbidities. Seventeen SNPs are associated with white blood cell count, *i.e.*, possible compromised immunity. SNPs in *IL6*, especially rs1800797, rs1800796, and rs1800795, are associated with more diseases than other SNPs.

Only one of those SNPs (rs1800795 in *IL6*) is associated with drug response. It can influence the efficacy (Level 3 clinical annotation) of TNF-α inhibitors, including adalimumab, etanercept, and infliximab (Dávila-Fajardo et al., 2014; Di Renzo et al., 2012).

Haplotype frequencies and linkage disequilibrium patterns

LD patterns could be illustrated among eleven of the twelve *IL6* SNP loci since one (rs2069833) has more than two alleles (Figure 4). Strong pairwise LD is maintained among rs1800797, rs1800795, rs2069832, and rs1474348; between rs2066992 and rs1800796; and between rs2069845 and rs1554606 in all super-populations. Strong pairwise LD exists among seven SNPs (rs1800797, rs1800795, rs2069832, rs1474348, rs1474347, rs1554606, and rs2069845) only in the European super-population. The highest number of strong pairwise LDs ($R^2 \geq 0.8$) is present in the European super-population. The African super-population has the lowest pairwise LDs with $R^2 \geq 0.8$, followed by the East Asian super-population. Similar LD patterns with $R^2 \geq 0.8$ exist in

the admixed American and South Asian super-populations. The haplotype comprising the variant alleles at rs1800797 and rs1800795, and the reference allele at rs1800796, is widespread (0.4086) in the European super-population. Twelve gene expression-modulating SNPs are located in *IL6* (Table 1). Since rs1800797, rs1800796, and rs1800795 in *IL6* are associated with multiple disease conditions, the frequencies of haplotypes comprising these SNPs are shown in Table 3. Haplotype ***A***_G_***C*** contains the variant alleles at rs1800797 and rs1800795. Among all the super-populations, this haplotype is present at the highest frequency (0.408) in the European one (Table 3). Haplotypes comprising variant alleles at rs1800797, rs1800795, rs2069832, rs1474348, rs1474347, rs1554606, and rs2069845 (which has the strongest LD in the European super-population) (***A_C_A_C_C_T_G***) has a frequency of 0.403 in the European super-population. In contrast, its frequency is only 0.134 in the global population (including the European super-population) and much lower, excluding the European super-population (0.067). On the contrary, the frequency of haplotype G_G_G_G_A_G_A, which contains the reference alleles at all of these seven SNP loci, is 0.989 in the East Asian super-population.

Table 3. Haplotypes comprising gene expression-associated SNPs in different super-populations

#	Gene	SNP ID	Haplotype[a]	Populations[b]					
				ALL	AFR	AMR	EAS	EUR	SAS
1	*IL6*	rs1800797_rs1800796_rs1800795	G_G_G	0.544	0.879	0.517	0.208	0.537	0.461
2			G_***C***_G	0.314	0.103	0.295	0.791	0.048	0.394
3			***A***_G_***C***	0.137	0.017	0.182	0.001	0.408	0.128
4			G_G_***C***	0.004	0.002	0.003	-	0.008	0.010
5			***A***_G_G	0.002	-	0.003	-	-	0.006
6			G_***C_C***	0.000	-	-	-	-	0.001
7	*TNFA*	rs3093661_rs1800610_rs3093662_ rs3093664_rs3093665	G_G_A_A_A	0.811	0.884	0.708	0.827	0.809	0.773
8			G_***A***_A_A_A	0.100	0.024	0.183	0.137	0.090	0.119
9			A_G_***G_G***_A	0.052	0.030	0.056	0.031	0.047	0.105
10			G_G_***G_G_C***	0.019	0.039	0.027	-	0.021	0.003
11			G_G_***G***_A_A	0.009	0.008	0.026	-	0.017	-
12			G_G_A_***G***_A	0.008	0.015	-	0.005	0.016	-
13	*IL8*	rs2227307_rs2227306_rs2227543_rs1126647	T_C_C_A	0.576	0.482	0.663	0.585	0.583	0.626
14			***G_T_T_T***	0.256	0.096	0.265	0.338	0.381	0.252
15			***G***_C_C_A	0.135	0.421	0.068	0.031	0.024	0.017
16			***G***_C_***T_T***	0.029	-	-	0.045	0.005	0.097

variant alleles are written in bold and italic letters

[b]ALL = Global, AFR = African, AMR = Admixed American, EAS = East Asian, EUR = European, SAS = South Asian.

Five gene expression-associated SNPs are located in *TNFA* (Table 1). Haplotype G_G_***G_G_C*** (at rs3093661, rs1800610, rs3093662, rs3093664, and rs3093665 loci, respectively) contains three variant alleles. This haplotype has the highest prevalence (0.0386) in the African super-population. It is, however, not present in the East Asian super-population because the global variant allele (C) at rs3093665 is absent in this super-population (Tables 1 and 3). The haplotype is present at a very low frequency (0.0031) in the South Asian super-population, too, and its frequencies in the admixed American and European super-populations are >0.02. The low VAFs at these loci in the East Asian and South Asian super populations are evident from their similar LD patterns (Figure 5). Strong pairwise LD ($R^2 \geq 0.8$) exists only among rs3093661, rs3093662, and rs3093664 in those two super-populations.

IL8 harbors five gene expression-associated SNPs (Table 1). Frequencies of haplotypes and LD patterns among four of these could be analyzed since one of the SNPs (rs2227549) is not biallelic. The haplotype ***G_T_T_T*** comprising the variant alleles at rs2227307, rs2227306, rs2227543, and rs1126647 loci are present at a high frequency (> 0.25) in all super-populations except the African (0.096). Haplotype ***G***_C_***T_T*** containing the variant alleles at three of the four SNPs is absent in the African and the admixed American super- populations and present at a very low frequency (0.005) in the European super-population. This haplotype is present at a relatively high frequency of (~0.1) in the South Asian super-population. The African super-population has the smallest extent of LD in this connection (Figure 6). In this super-population, rs2227307 does not maintain strong LD with any of the other three SNPs, even though strong LD exists among rs2227306, rs2227543, and rs1126647 (Figure 6). Compared with the African super-population, a larger extent of LD is observed among these four SNPs in the other super-populations. These SNPs have strong LD ($R^2 \geq 0.875$) with each other in the European super-population. A haplotype harboring the variant alleles at these four SNP loci is much less frequent (frequency < 0.1) in the African super-population compared to the other super-populations (frequency > 0.25) (Table 3).

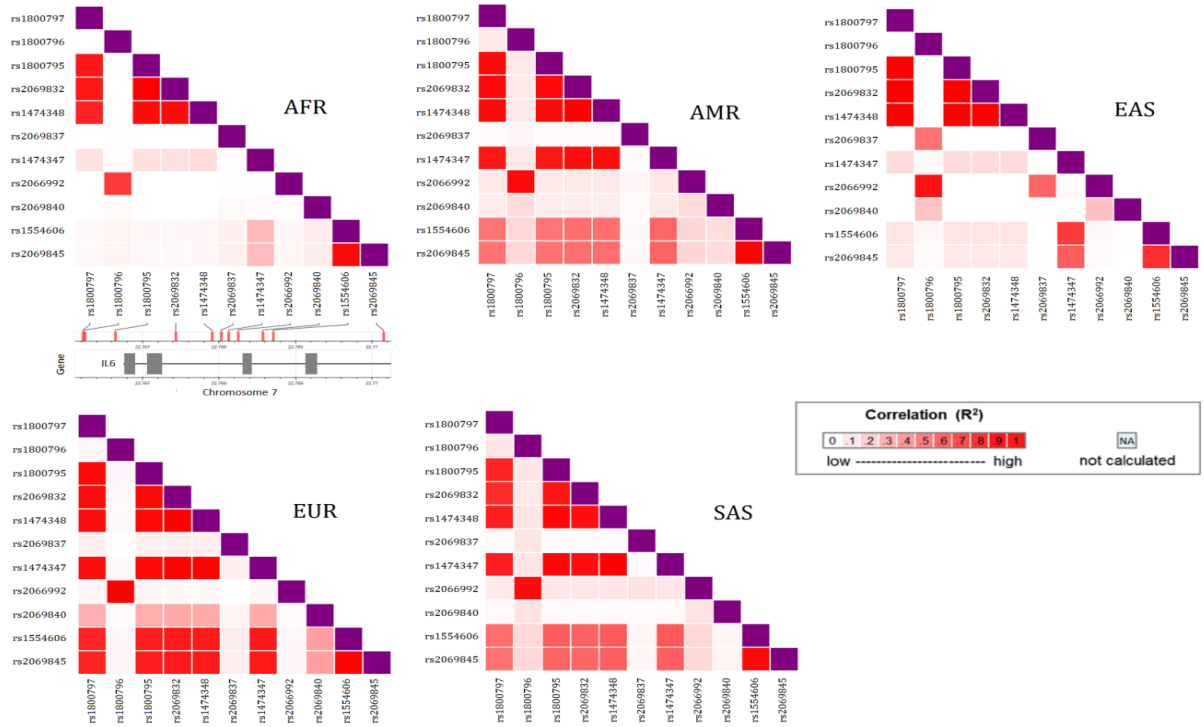

Fig. 4. Linkage disequilibrium (LD) patterns among *IL6* gene expression-associated SNPs in five super-populations. AFR = African, AMR = Admixed American, EAS = East Asian, EUR = European, and SAS = South Asian.

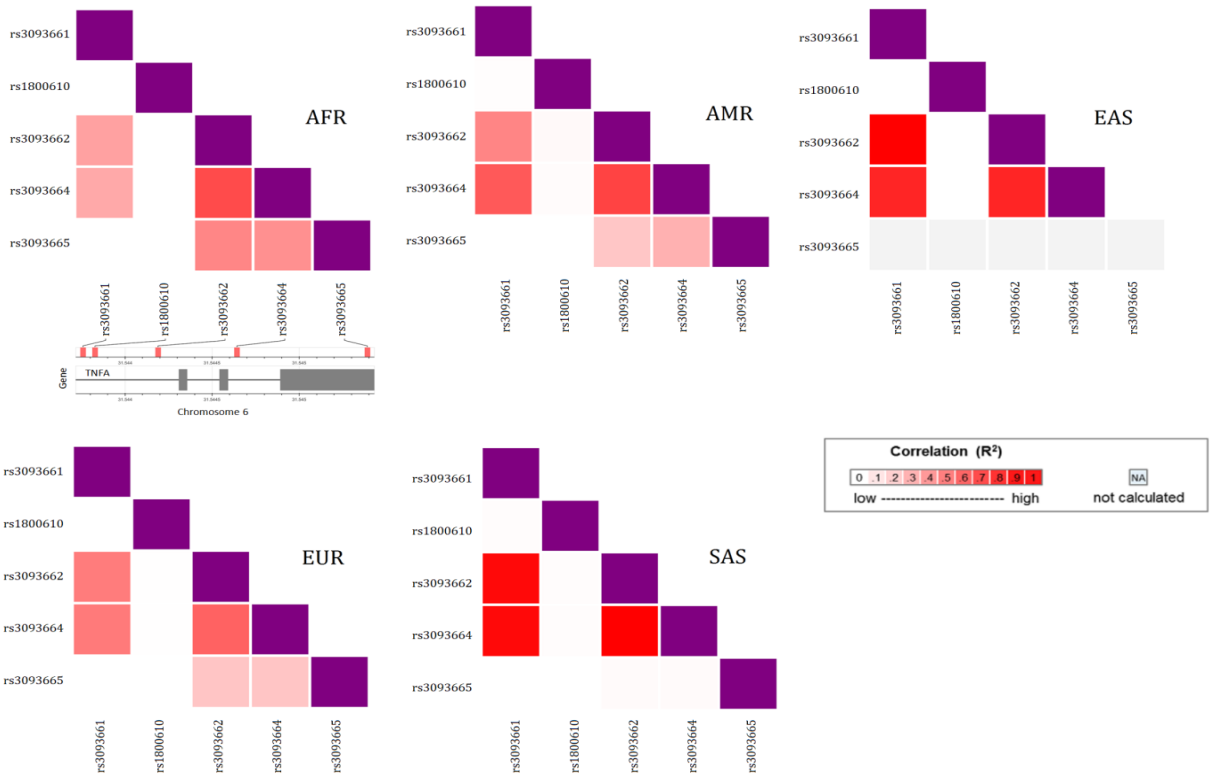

Fig. 5. Linkage disequilibrium (LD) patterns among *TNFA* gene expression-associated SNPs in five super-populations. AFR = African, AMR = Admixed American, EAS = East Asian, EUR = European, and SAS = South Asian.

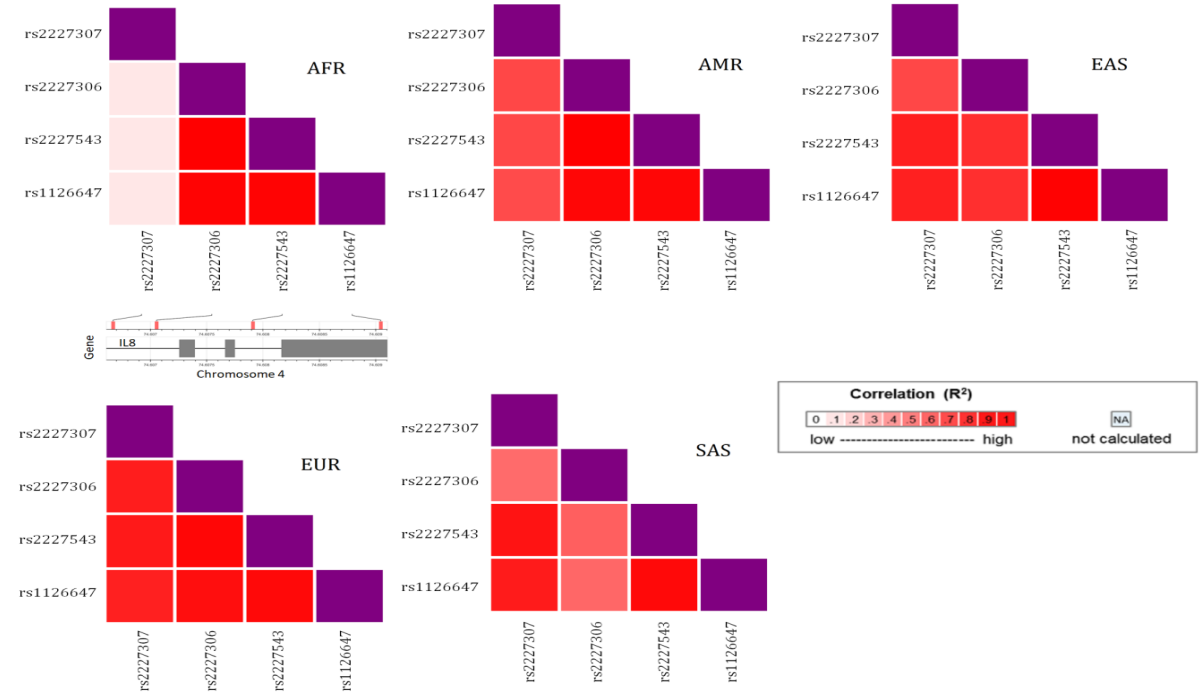

Fig. 6. Linkage disequilibrium (LD) patterns among *IL8* gene expression-associated SNPs in five super-populations. AFR = African, AMR = Admixed American, EAS = East Asian, EUR = European and SAS = South Asian

Discussion

There are substantial interethnic differences in gene expression-associated variant allele frequencies and linkage disequilibrium patterns in *IL6*, *TNFA*, and *IL8*. Since these variants are associated with susceptibilities to COVID-19 comorbidities, differences in allelic distribution might contribute to the interethnic variability in COVID-19 severity and mortality. In addition, these SNPs may be linked to dissimilarities in responses to therapies that target these cytokines.

Interethnic differences in pro-inflammatory cytokine expression

The picture the available literature provides concerning interethnic differences in IL-6 levels is not indubitable. A previous study reported that the differential distribution of alleles of cytokine genes in African American women, in contrast to American women with European ancestry, consistently up-regulates inflammation (Ness et al., 2004), which is consistent with almost 2.5 times higher number of age-adjusted COVID-19-related deaths in African-Americans (Wrigley-Field, 2020). Another study found significantly higher plasma levels of IL-6 in non-Hispanic blacks than Mexican Americans and non-Hispanic whites (Stowe et al., 2010). However, a more recent study could not find any significant difference in the plasma levels of IL-6 between African American and European American women (Yao et al., 2018). A comparison among Japanese, African American, and Caucasians showed that Japanese individuals had the lowest level of IL-6, and African Americans had the highest level of this pro-inflammatory cytokine (Coe et al., 2011). We could not find comparative studies on cytokine profiles incorporating South Asian populations.

Some SNPs at the *IL6* gene also correlate with the expression of the lncRNA *IL6-AS1* gene (supplementary table 2). The variant allele at rs2069833, rs1800795, rs1474348, rs2069832, rs1800797, rs1554606, rs2069845, and rs1474347 loci in *IL6* positively correlates with the expression of the lncRNA IL-6 antisense RNA. On the other hand, variant alleles at rs1800796 and rs2066992 loci are negatively correlated with IL6-AS1 as well as IL-6 expression. IL6-AS1 lncRNA has been found to be up-regulated in airway inflammation, which further promotes the expression of IL-6 by recruiting EBF1 and modulating histone methylation in the IL-6 promoter region. This lncRNA also acts as a competitive inhibitor of miR-149-5p and up-regulates IL-6 expression in the cytoplasm. The expression of IL-8 is also regulated by the IL6-AS1 lncRNA (Yi et al., 2021). An important question may be whether the interethnic variability in *IL6-AS1* expression correlates with differences in IL-6 levels and COVID-19 severities across the globe. Very little information is available regarding this regulatory RNA. A study on Chinese COVID-19 patients included the common Asian IL-6 haplotype defined by the rs1800796, rs1524107, and rs2066992 loci. They found that homozygous carriers of the C-T-T variant haplotype were less likely to develop severe COVID-19. The protective effect resulted from the disturbance of stimulus-dependent bidirectional transcription of the *IL-6/IL-6-AS1* locus through disruption of a conserved CTCF-binding locus at the enhancer elements of *IL-6-AS1*(Chen et al., 2021). In another study conducted on COVID-19 patients in the USA, the variant allele at rs1800795 was found to affect plasma IL-6 levels and confer higher expression levels of IL6-AS1. This allele may be a risk locus for higher mortality and earlier intervention in severe COVID-19 patients if confirmed with further replicative studies (Smieszek et al., 2021). Data from an NCBI BioProject (PRJEB4337) suggests that this gene is expressed in a variety of organs, including, but not limited to, the esophagus, lung, heart, liver, kidney, and small intestine (Fagerberg et al., 2014). These organs are susceptible to damage upon SARS-CoV-2 infection (Jain, 2020; Ma et al., 2020). Alterations in IL6-AS1 expression may thus have important clinical implications with respect to COVID-19.

Conflicting reports regarding differences in IL-6 levels exist for individual SNPs. For example, there are contradictory reports regarding the association

between elevated levels of IL-6 and genotypes at rs1800795, rs1800796, and rs1800797 (Ambreen et al., 2015; Fang et al., 2017; Guan et al., 2020; Koh et al., 2009; Li et al., 2016; Siniauskaya et al., 2020; Zakharyan et al., 2012; Zhang et al., 2016). These reports are indicative of a complicated regulation of *IL6* expression. A better understanding of the role of this lncRNA can shed more light on the pathogenesis of COVID-19. Further studies are needed to elucidate how this particular lncRNA plays a role in the outcome of COVID-19.

Almost all East Asians carry an *IL6* haplotype comprising rs1800797, rs1800795, rs2069832, rs1474348, rs1474347, rs1554606, and rs2069845 reference alleles, whereas Europeans carry haplotypes containing variant alleles at a disproportionately high frequency. Haplotype #1 in Table 3 consists of the reference alleles at the three SNP loci of the *IL6* gene. Despite the conflicting evidence of the relationship between genotype and IL6 level, the SNPs (rs1800797_rs1800796_ rs1800795) have evidence of higher serum IL6 levels in the presence of their G alleles. This G_G_G haplotype has a low frequency in the East Asian super-population compared to the others. Haplotype #3, which has two variant alleles at rs1800797 and rs1800795, is highly frequent (frequency 0.408) in the European super-population, whereas in other super-populations its frequency (0.13) is much lower. Many studies have reported the association of various *IL6* haplotypes, including variant alleles of rs1800797, rs1800796, and rs1800795, with diseases such as type 2 diabetes mellitus (Saxena et al., 2014), renal dysfunction (Ng et al., 2008), obesity (Boeta-Lopez et al., 2017), asthma (Lajunen et al., 2018), etc., all of which are COVID-19 comorbidities. Additionally, these promoter polymorphisms are associated with various cancer risks and prognoses, such as cervical cancer, colorectal cancer, breast cancer, prostate cancer, lung cancer, glioma, non-Hodgkin's lymphoma, Hodgkin's lymphoma, B-cell lymphoma, and diffuse large B-cell lymphoma (Peng et al., 2018).

Regarding *TNFA* expression, the variant alleles at rs3093661, rs1800610, rs3093662, and rs3093664 may be associated with elevated plasma levels of TNF-α (Zhang et al., 2020). Although VAFs at these SNP loci are < 0.2 in all super-populations, VAF at rs1800610 is > 0.2 in two admixed American populations (MXL and PEL) (Table 1). A previous study found a higher circulating TNF-α level in non-obese, non-diabetic Mexican Americans than non-Hispanic white adults (Ho et al., 2005). In addition, the strong LD maintained among rs3093661, rs3093662, and rs3093664 in the East Asian and South Asian super-populations could be interesting (Figure 5). These three SNPs are associated with the expression of multiple immune response genes such as *HLA-B*, *HLA-C*, *HLA-DRB5*, *HLA-DRB6*, *MICA*, *MICB*, *LST1*, *LTB*, and *LTA*, among others (Supplementary Table 2). Inflammatory conditions can induce the expression of *HLA* and *MICA*. Because of the interdependent nature of these genes, polymorphisms at the promoter of one gene can affect the expression of others (Jarduli et al., 2013). *HLA* variants may be associated with COVID-19 severity and likely explain some of the differences in the outcome of SARS-CoV-2 infections (Lorente et al., 2021; Tavasolian et al., 2021; Troshina et al., 2020). Hence, inter-ethnic differences in the expression level of *HLA* genes may contribute to variations in COVID-19 severity across ethnic groups. Variant alleles at rs3093661, rs3093662, and rs3093664 are negatively correlated with *MICA* expression level and positively correlated with *HLA-B* expression level (Supplementary Table 2). The variant allele at rs3093664 and the variant alleles at rs3093661 and rs3093662 are negatively correlated with *HLA-DRB5* and *HLA-DRB6* expressions, respectively.

Cells carrying the T_C haplotype at rs2227307 and rs2227306 significantly up-regulate the IL-8 expression at both transcriptional and translational levels (Benakanakere et al., 2016). Carriers of the T_C haplotype (#13 in Table 3) may have an increased influx of neutrophils in inflammatory lesions and can influence disease susceptibility

(Benakanakere et al., 2016). Variant alleles at these SNPs are positively correlated with *IL8* expression (Võsa et al., 2018). Although a previous study found African Americans to have a higher plasma level of IL-8 compared to Caucasians, the IL-8 mRNA level was not significantly different between those two groups (Mayr et al., 2007). This study, however, did not consider other variables such as body mass index, alcohol intake, smoking status, etc., which can influence IL-8 levels as well (Huang et al., 1999; Straczkowski et al., 2002; Wu et al., 2014).

Variant alleles at rs2227307, rs2227306, rs2227543, and rs1126647 are also positively correlated with the expression of three other chemokine genes, namely *CXCL1*, *CXCL2*, and *CXCL6* (Supplementary Table 2). CXCL1 and CXCL5 have neutrophil chemotactic activity (Wuyts et al., 1999). CXCL6 has neutrophil granulocyte chemotactic and antibacterial properties (Linge et al., 2008; Proost et al., 1993). These three chemokines are up-regulated in COVID-19 patients (Chu et al., 2020; Xiong et al., 2020). Therefore, rs2227307, rs2227306, rs2227543, and rs1126647 may contribute to the differences in COVID-19 severity across ethnic groups.

Regarding ΔVAF values, the East Asian populations show more genetic homogeneity, whereas the admixed American populations exhibit more genetic heterogeneity than the other population groups (Figure 2). This observation agrees with previous findings (Auton et al., 2009; Oota et al., 2002). Gene flow among the East Asian populations has decreased population differentiation and made these groups more homogeneous (Pan et al., 2020). Conversely, the high heterogeneity among the admixed American populations could be due to the admixture of genetic components from multiple ethnic origins (Montinaro et al., 2015). An intriguing observation of this study is the apparent low heterogeneity of the African populations at these SNP loci, even though Africa is a source of high genetic diversity (Campbell and Tishkoff, 2008; Rotimi et al., 2017).

Interethnic differences in susceptibility to COVID-19 comorbidities

Twenty-one of the studied SNPs are associated with at least two COVID-19 comorbidities (Table 2). Among the *IL6* variants, rs1800797, rs1800796, and rs1800795 are associated with most comorbidities, *e.g.*, asthma, cancer, diabetes, heart conditions, kidney disease, liver disease, neurological conditions, and obesity. Although the association of severe asthma and inflammation with elevated levels of IL-6 is already proven (Broide et al., 1992; Wong et al., 2001), one study also established that systemic IL-6-mediated inflammation, commonly occurring in obese patients, can worsen the severity of asthma (Peters et al., 2016). A high serum level of IL-6 is also associated with various cancers, including breast cancer (Knüpfer and Preiss, 2007; Kozłowski et al., 2003), colon and gastric cancer (Jones and Jenkins, 2018), ovarian cancer (Lane et al., 2011), etc. A higher IL-6 level may be associated with diabetes and its associated complications, like kidney disease and cardiovascular disease (Liu et al., 2006; Mihara et al., 1998; Shoily et al., 2021). Similarly, as IL-6 has a role in the physiological homeostasis of neural tissue, its overexpression and, consequently, the inflammatory condition lead to neurological damage, leading to many neuropathological changes and neurodegenerative diseases (Aarli, 2003; Rothaug et al., 2016).

It should be noted that variant-disease associations in this context are quite complex. First, there are some contradictory findings regarding such an association. For example, one meta-analysis did not find rs1800797 to be a risk factor for cancer (Qian et al., 2017). In contrast, another meta-analysis reported that rs1800797 is associated with a higher risk of cancer in Caucasians (Peng et al., 2018). Second, the association between SNP and a particular disease may depend on ethnicity. For example, rs1800795 and rs1800796 are associated with an elevated risk of cancer in Caucasians and Asians, but rs1800797 increases the risk of cancer only in Caucasians (Peng et al., 2018). Third, different alleles at the same SNP

locus can increase the risk of diseases. For example, the rs1800797 G allele (reference allele) may be associated with adult-onset asthma (Hamid et al., 2005). Conversely, rs1800797 A allele (variant allele) may be associated with major depressive disorder (Zhang et al., 2016). Nonetheless, based on the available resources and information, our study indicates that gene expression-modulating SNPs in *IL6* may contribute to interethnic differences in disease susceptibility.

Seventeen SNPs in this study are associated with white blood cell count (Table 2). Altered leukocyte counts, such as neutrophilia and lymphocytopenia, are important risk factors for COVID-19 mortality (Zhao et al., 2020). An abnormal elevation of IL-8 is possibly associated with COVID-19-induced neutrophilia (Coperchini et al., 2021). The crucial roles of TNF-α and IL-6 in neutrophil trafficking are known (Hashizume et al., 2011; Vieira et al., 2009). Severe COVID-19 patients (including those admitted to the ICU) have a rising neutrophil count and a falling lymphocyte count, accounting for a higher neutrophil-to-lymphocyte ratio (NLR) – a biomarker suggesting poor prognosis in COVID-19 (Borges et al., 2020). However, during the assessment of interethnic differences in leukocyte counts, it should be considered that individuals of African, Middle Eastern, and West Indian descent can have chronic neutropenia (Atallah-Yunes et al., 2019). This condition, known as benign ethnic neutropenia (BEN), does not increase the risk of infection (Atallah-Yunes et al., 2019).

Variability in drug response

We also investigated whether the genotype at any of the twenty-two SNP loci is correlated with altered response to therapies targeting IL-6, TNF-α, or IL-8. Rheumatoid arthritis patients with the *IL6* rs1800795 G allele may show an increased response to anti-TNF therapeutic antibodies, namely adalimumab, etanercept, and infliximab (Dávila-Fajardo et al., 2014). In contrast, psoriasis patients carrying rs1800795 G alleles may respond poorly to TNF-α blockers (Di Renzo et al., 2012). Anti-IL-6 inhibitors may not be a treatment option for all severe COVID-19 patients, even though IL-6 plays an essential role in the pathophysiology of disease progression. The differences in response may account for genetic variants and plasma IL-6 levels. As observed in trials conducted on Chinese (rs1800796 negatively associated with IL6-AS1 expression) and USA (rs1800795 positively associated with IL6-AS1 expression) COVID-19 patients, anti-IL-6 monoclonal antibodies such as tocilizumab and sarilumab may show improvement in response in some while failing in others (Chen et al., 2021; Smieszek et al., 2021). Several recent studies reported that immunosuppressant medications used to treat some autoimmune diseases may have a positive therapeutic effect in severe COVID-19 patients (Esmaeilzadeh and Elahi, 2021). Due to similarities in the cytokine response and damage of autoimmune diseases and COVID-19, the polymorphisms that affect autoimmune conditions might affect COVID-19 severity, too (Liu et al., 2021). High serum IL-6, IL-8, and TNF-α levels at the time of admission to the hospital are predictors of poor outcomes in COVID-19 patients (Del Valle et al., 2020). Again, patients who died of COVID-19 had significantly higher levels of the IL-2 receptor, IL-6, IL-8, IL-10, and TNF-α than those who recovered (Chen et al., 2020).

Similarly, between intensive care unit (ICU) and non-ICU patients, levels of pro-inflammatory cytokines were higher in those admitted to ICUs (Huang et al., 2020), suggesting increased cytokine mediated complications. Therefore, there is much evidence as to why anti-IL6, anti-IL8, and anti-TNF-α therapy could treat COVID-19 (Robinson et al., 2020). Hence, the polymorphisms that could interfere with the therapy should be given proper attention.

Context of our findings

Most of the data concerning differences in COVID-19 outcomes among individuals of different ethnic origins comes from studies on the US and UK populations, and there is a paucity of data regarding this issue from other regions of the world (Pan et al., 2020;Vahidy et al., 2020). Although ethnic minorities in these countries (such as blacks, Asians, and Hispanics, among others) are more susceptible to

COVID-19, it is still unclear if a certain ethnicity can be an independent poor prognostic factor for this disease (Burki, 2021; Pennington et al., 2020; Raharja et al., 2021). The higher burden of COVID-19 comorbidities and lower socio-economic status of these ethnic groups compared with individuals of European origin may explain these observed disparities in COVID-19 outcomes (Kopel et al., 2020). However, these disparities may still exist after adjusting for sociodemographic and comorbidity factors (Vahidy et al., 2020). Therefore, it is possible that genetic differences among ethnic groups can contribute to the differences in COVID-19 severity.

We acknowledge that associations between the SNPs included in our study and the expression levels of *IL6*, *TNFA*, and *IL8* upon SARS-CoV-2 infection must be elucidated before the role of these polymorphisms in COVID-19 severity can be confirmed. We also acknowledge that socio-economic factors may, directly and indirectly, play a bigger role in ethnic disparities in COVID-19 outcomes than genetic polymorphisms. However, our findings hint at the crucial roles played by differences in allele frequencies and LD patterns of gene expression-associated polymorphisms in pro-inflammatory cytokine genes in creating distinct COVID-19 outcomes across ethnic groups.

Conclusions

Gene expression-associated SNPs in *IL6*, *TNFA*, and *IL8* genes can influence the expression levels of multiple immune response mediators, modulate susceptibility to several COVID-19 comorbidities, and alter responses to COVID-19 therapy. Inter-ethnic differences in the genetic architecture of these SNPs can thus contribute to ethnic disparities in COVID-19 outcomes. However, due to the complex nature of cytokine expression and signaling regulation, conflicting reports regarding the effects of genotypes at these SNPs exist. Nevertheless, understanding the variations in the genetic architecture of gene expression-associated polymorphisms of cytokine genes across ethnic groups can, at least to some extent, explain differences in COVID-19 susceptibility and therapeutic outcomes.

Abbreviations

ACE2: Angiotensin-converting enzyme 2; AFDs: Allele frequency differences; COVID-19: Coronavirus disease 2019; eQTLs: Expression quantitative trait loci; INDEL: Insertion or deletion; IL-6: Interleukin-6, IL-8: Iinterleukin-8; LD: Linkage disequilibrium; SNP: Single nucleotide polymorphism; TNFA: Tumor necrosis factor alpha; VAF: variant allele frequencies.

Ethics approval and consent to participate

This study did not involve human or animal participants, so neither ethical approval nor consent is required.

Consent for publication

This study did not involve human participants, and no consent is required. All authors have read and approved the manuscript.

Availability of data and material

All data are provided in the manuscript.

Conflict of interest

There is no known conflict of interest.

Authors' contributions

TA,AAS- study design, TA, SSS, KF, ZH- data analysis, SSS, TA, KF, ZH- manuscript preparation, AAS- reviewed the manuscript. All authors have read and approved the manuscript.

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