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Letter to the Editor

LETTER TO THE EDITOR

Genes, COVID-19 and phenotype

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The novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19) has caused worldwide devastation. Pre-existing comorbidities greatly influence COVID-19 severity and mortality rates in various populations [1], raising interest in the association between the underlying genetic component of comorbidities and COVID-19 and the opportunity to link host genomic factors to the highly variable clinical manifestations of SARS-CoV-2 infection, with the aim of translating these findings into improved patient care.

Recently, a *3p21.31* gene cluster as a genetic susceptibility locus in patients in parts of Italy and Spain with COVID-19 with respiratory failure was identified [2] and confirmed a potential involvement of the ABO (A, B, O antigens) blood group system [1], adding a piece to the nascent genetic knowledge of SARS-CoV-2 [3].

Genomic distribution varies by geography. COVID-19 infection is strangely—and tragically—selective. Most patients with COVID-19 exhibit no or mild to moderate symptoms, but ∼15% progress to severe pneumonia and ∼5% eventually develop acute respiratory distress syndrome, septic shock and multiple organ failure [4]. Although most of the critically ill are elderly and have comorbid diseases, some killed by the disease are previously young and healthy. Furthermore, the mortality rates related to COVID-19 vary among countries, generally known to be significantly higher in European and North American countries than in Asian or African countries [5].

We reviewed and summarize the literature on associations between specific genetic loci or genes, which may well differ based on their geographic distribution, and COVID-19 (Table 1) [2, 4, 6–24].

Human genetic factors may contribute to the extremely high transmissibility of SARS-CoV-2 and to the relentlessly progressive disease. The genetic landscape of an individual in particular and a population in general seems to play a pivotal role in shaping COVID-19 dynamics. We need to embrace and evaluate patients' genome analyses to provide a better understanding of disease phenotype and severe disease high-risk identification and personalize COVID-19 treatment [25].

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Table 1. Associations between human genes and COVID-19 [2, 4, 6–24]

Population involved	Predominant genetic association/loci (OMIM; loci; chromosome location)	COVID-19 association
African descent	ACE1 (106 180, 17q23.3), DD genotype	Acute respiratory distress syndrome
	ACE2 (300 335, p. Arg514-Gly, Xp22.2)	Cardiovascular and pulmonary conditions
	ApoE (107 741; rs429358-C-C; 19q13.32)	4-fold increase in disease mortality. Comorbid risk factors (atherosclerosis and HTN)
	ApoL1 (603 743; 22q12.3)	COVIDAN
	G1 haplotype (c.1024A>G; p.Ser342Gly)	Focal segmental glomerulosclerosis
	G2 variant (c.1164_1169del; p.Asn388_Tyr389del)	Susceptibility to non-diabetic end-stage renal disease
	Common variable ion channels	
	(p.Asp85Asn-KCNE1; 21q22.12)	Increased risk of DI-LQTS, DI-TdP and DI-SCD
	(p.Ser1103Tyr-SCN5A; 3p22.2)	Hypoxia/acidosis and increased risk of VA and SCD
	HLA class I (142 800; 6p22.1)	
	HLA A02:01; A11:01	Increased risk for SARS-CoV-2 infection and fatality rates, respectively
	HLA B15:03	Cross-protective T cell–based immunity
Asian descent	ACE1 (106 180; 17q23.3), II genotype	Higher SARS-CoV-2 infection prevalence and mortality rate
	ApoE (107 741; rs429358-C-C; 19q13.32)	4-fold increase in disease mortality. Comorbid risk factors (atherosclerosis, HTN)
	HLA class I (142 800; 6p22.1)	
	HLA A02:01; A11:01	Increased risk for SARS-CoV-2 infection and fatality rates, respectively
	HLA B46:01	Vulnerable to disease. Appear to be linked to olfactory receptor gene
	IFITM3 (605 579; rs12252-C/C; 11p15.5)	Mild to moderate disease requiring hospitalization
	IFIH1 (606 951; rs1 990 760 (C>T, aaA946T); 2q24.2)	Lower risk of SARS-CoV-2 infection and more resistant to SARS- CoV-2 infection Autoimmune diseases (type 1 diabetes, lupus erythematosus and vitiligo)
	TLR7 (300 365; g.12 905 756_12 905 759del and g.12 906 010G>T; Xp22.2)	Severe disease
European descent	Blood group A (616 093; rs657 152A or C SNP; 9q34.2)	Severe COVID-19 disease (respiratory failure) than in other blood groups
	ACE1 (106 180; 17q23.3), DD genotype	Acute respiratory distress syndrome
	ApoE (107 741; rs429 358-C-C; 19q13.32)	4-fold increase in disease mortality. Comorbid risk factors (atherosclerosis, HTN)
	DBP gene (rs7041 and rs4588)	rs7041 locus, GT genotype: higher prevalence and mortality rates rs7041 locus, TT genotype: lower prevalence and mortality rates rs4588 locus: no significant correlation
	HLA class I (142 800; 6p22.1), HLA C12:03	
	IFIH1 (606 951; rs1 990 760 (C>T, aaA946T); 2q24.2)	Lower risk of SARS-CoV-2 infection and more resistant to SARS- CoV-2 infection Autoimmune diseases (T1D, LE and vitiligo)
	TMPRSS2 (602 060; p.Val160Met (rs12 329 760); 21q22.3)	Increased susceptibility to disease and for risk factors, e.g. cancer and high-risk group of male patients[a]

[a]Polymorphisms including p.Val160Met (rs12329760) in *TMPRSS2* offer potential explanations for differential genetic susceptibility to COVID-19 as well as for risk factors, including those with cancer and the high-risk group of male patients [11].

OMIM, Online Mendelian Inheritance in Man; ACE2, angiotensin-converting enzyme 2; AGT, angiotensinogen; APOE, apolipoprotein E; HLA: human leukocyte antigen; IFITM3, interferon-induced transmembrane protein 3; IL-10, interleukin-10; MHC, major histocompatibility complex; COVIDAN, COVID-associated nephropathy; TLR7, toll-like receptor 7; TMEM189, transmembrane protein 189; UBE2V1, ubiquitin-conjugating enzyme E2 variant 1; TMPRSS2, the transmembrane protease serine 2; IFIH1, interferon-induced helicase 1; MDA5, melanoma differentiation-associated protein 5; VA, ventricular arrhythmia; SCD, sudden cardiac death; T1D, type 1 diabetes; LE, lupus erythematosus; HTN, hypertension; DI-LQTS, drug-induced long QT syndrome; DI-TdP, drug-induced torsades de pointes; DI-SCD, drug-induced sudden cardiac death.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interests.

Each author has participated in the writing of the manuscript and has seen and approved the submitted version.

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