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REVIEW

Genetic Risk of Different Populations in COVID-19 Susceptibility and Severity

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Abstract: The coronavirus disease 2019 (COVID-19) pandemic has created challenges by threatening public health and triggering the largest global economic crisis in recent history. While environmental factors and social activities influence the clinical outcome of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exposure and COVID-19 severity, the host genetic background and variants are increasingly recognized as vital players in individual susceptibility to SARS-CoV-2 infection, ranging from asymptomatic infection to lethal COVID-19. A plethora of genome-wide association meta-analyses have been provided and will continue to provide genetic determinants of the heterogeneity of COVID-19 outcomes. Such discoveries undoubtedly deepen our understanding of the biological underpinnings of SARS-CoV-2 infection and COVID-19 disease, paving the way for the development of more efficient SARS-CoV-2 prevention strategies and drug repurposing. Here, we provide a brief overview of studies regarding host susceptibility to COVID-19 and its clinical outcomes, focusing on the identification of genome-wide significant loci from different ancestral populations.

Keywords: COVID-19, SARS-CoV-2, genetic risk, susceptibility, severity, populations

Introduction

Since late December 2019, the emergence of COVID-19, elicited by SARS-CoV-2 infection, has posed a global health and economic crisis,[1] resulting in a cumulative 0.774631 billion infections and claiming approximately 7.031 million deaths.[2] Globally, approximately 13.64 billion (Source: World Health Organization) doses of vaccines-including inactivated/attenuated virus vaccines, mRNA vaccines, and DNA vaccines-have been administered, with many individuals receiving one or two doses.[3,4] Concurrently, numerous small-molecule inhibitors and drugs have been developed. These therapeutics target either host factors, such as angiotensin-converting enzyme 2 (ACE2), which functions as the receptor for SARS-CoV-2 viral entry, or transmembrane serine protease-2 (TMPRSS2), which primes the SARS-CoV-2 spike protein or viral proteins, including RNA-dependent RNA polymerase (RdRp), NSP3/papain-like protease, and NSP5/3C-like protease.[5–7] Many are in clinical use or under development. However, the world continues to face the COVID-19 pandemic due to newly evolved SARS-CoV-2 variants, particularly Omicron and its sub-variants, which employ alternative strategies to evade neutralizing antibodies targeting the ancestral virus or acquire mutations conferring resistance to inhibitors/drugs.[8,9] In addition, it has been proved that the SARS-CoV-2 spike protein plays a pivotal role in mediating the entry of the virus into host cells,[10] making it an ideal target for the development of neutralizing antibodies and drugs. But after several rounds of modifications and alterations, the spike gene has undergone mutations, determining the enhanced early replication and immune evasion capability of the SARS-CoV-2 Omicron-BA.1 clone and some other relative mutants. The new SARS-CoV-2 variants, due to the spike gene mutation became pandemic in

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Lebanon and other regions in the world,[11–13] further challenged the development of efficient drugs or antibodies against the SARS-CoV-2.

Intensive studies from immunological, biochemical, and cell biological perspectives have elucidated SARS-CoV-2 infection mechanisms and host responses.[14,15] As knowledge of SARS-CoV-2–host interactions increases, factors such as viral exposure risk, individual immune status, age, blood groups, and pre-existing medical conditions have been investigated to determine their influence on SARS-CoV-2 infection risk, COVID-19 susceptibility, and disease severity.[16,17] Besides, mental problems (fear of contagion, depression, anxiety disorders) and awareness of the COVID-19 pandemic via digital media may play roles in determining COVID-19 susceptibility and severity,[18,19] however, efficient and precision medicine strategies development based on in-depth study of SARS-CoV-2 infection mechanism and populations genetic risks would significantly alleviate the situation. The COVID-19 Host Genetics Initiative and other global efforts have conducted large-scale investigations using genome-wide association studies (GWAS) to characterize population genetic heterogeneity in response to SARS-CoV-2 exposure.[20,21] A recent GWAS meta-analysis by the COVID-19 Host Genetics Initiative, encompassing up to 125,584 cases and over 2.5 million controls across 60 studies from 25 countries, identified 23 genome-wide significant loci associated with SARS-CoV-2 infection or susceptibility to or severity of COVID-19.[22] These analyses provide valuable insights into population-level SARS-CoV-2 infection risk and COVID-19 outcomes.

In this review, we summarize recent studies on the genetic basis of host susceptibility to and severity of COVID-19, focusing specifically on the identification of genome-wide significant loci across different ancestral populations, such as European, Asian, and African.

Genetic Risk Loci Associated with COVID-19 in European Populations

The world has suffered from the COVID-19 pandemic for almost three years. An early reported age-specific COVID-19-associated modelling framework, by analyzing data from 45 countries and 22 seroprevalence studies, declared consistency of age distribution of deaths in younger age groups (less than 65 years of age).[23] However, with more COVID-19 cases reported and data available, age, gender or higher body-mass index alone could not explain all of the variability in disease susceptibility and severity outcome.[24,25]

In the search for key players determining susceptibility to SARS-CoV-2 infection and differential COVID-19 outcomes, human genetic heterogeneity has attracted significant scientific attention. Using detailed stratified GWAS analyses, candidate variants (including rs35731912, rs11085725, rs687289, rs8065800, and rs12512667) were identified in populations from Italy, Spain, Norway, and Germany/Austria, highlighting the contribution of these loci to COVID-19 severity in these European populations.[26] Moreover, to identify genetic determinants of COVID-19 susceptibility and severity, the "COVID-19 Host Genetics Initiative" (COVID-19 HGI) was launched in Finland to share and analyze human genetic data across continents. The COVID-19 HGI initially mapped the human genetic architecture of COVID-19 using data from 46 studies across 19 countries, comprising 49,562 cases and 2 million controls. Subsequently, the study expanded to 125,584 cases and over 2.5 million controls across 60 studies from 25 countries.[20,22] Due to the geographical locations of the contributing studies and recruited participants, populations of European ancestry constitute the majority (approximately 78% of total effective samples) within the COVID-19 HGI. Key lead variants associated with SARS-CoV-2 infection susceptibility or COVID-19 severity are summarized in Table 1. Notably, the COVID-19 HGI identified and reported 23 genome-wide significant loci and over 70 proximal genes linked to disease susceptibility and severity. Among these, seven loci (rs2271616, rs11919389, rs912805253, rs4801778, rs148063273, rs2071351, and rs190509934) were categorized as conferring susceptibility to SARS-CoV-2 infection, while the others were associated with COVID-19 severity.

During SARS-CoV-2 infection, angiotensin-converting enzyme 2 (ACE2) functions as the receptor mediating viral entry into host cells. Horowitz et al further found that the expression level of ACE2, whose gene is located near the rs190509934 locus (Table 1), negatively correlates with COVID-19 risk.[29] Given ACE2's vital role in mediating SARS-CoV-2 infection, its function is likely universal across all populations regarding infection susceptibility. Investigations have established that the rs11385942 variant at locus 3p21.31 (Table 1) is associated with COVID-19 severity.[27,28,30] *SLC6A20*, located near the rs2271616 locus within the 3p21.31 region, encodes a protein that functionally interacts with

Table 1 Summarized Lead Variants That May Function in SARS-CoV-2 Infection Susceptibility or COVID-19 Severity

rsid	Chromosome (b38)	Position (b38)	Reference Allele	Effect allele	Suggested Phenotypic Impact	Genes	Ref.
rs2271616	3	45796521	G	T	Infection susceptibility	*SLC6A20*	[20,22]
rs11919389	3	101705614	T	C	Infection susceptibility	*ZBTB11, RPL24, CEP97, NXPE3*	
rs912805253	9	133274084	C	T	Infection susceptibility	*ABO*	
rs4801778	19	48867352	G	T	Infection susceptibility	*PLEKHA4, PPP1R15A, TULP2, NUCB1*	
rs148063273	1	155127096	C	T	Infection susceptibility	*EFNA1,SLC50A1,DPM3,KRTCAP2,TRIM46,MUC1,THBS3,MTX1,GBA, FAM189B,SCAMP3,CLK2,HCN3,PKLR,FDPS,RUSC1,ASH1L,MSTO1*	
rs2071351	6	33076153	A	G	Infection susceptibility	*HLA-DPA1,HLA-DPB1*	
rs190509934	23	15602217	T	C	Infection susceptibility	*ACE2*	
rs10490770	3	45823240	T	C	Disease severity	*LZTFL1*	
rs1886814	6	41534945	A	C	Disease severity	*FOXP4*	
rs72711165	8	124324323	T	C	Disease severity	*TMEM65*	
rs10774671	12	112919388	G	A	Disease severity	*OAS1, OAS3, OAS2*	
rs1819040	17	46142465	T	A	Disease severity	*ARHGAP27, PLEKHM1, LINC02210-CRHR1, CRHR1, SPPL2C, MAPT, STH, KANSL1, LRRC37A, ARL17B, LRRC37A2, ARL17A, NSF, WNT3*	
rs77534576	17	49863303	C	T	Disease severity	*KAT7, TAC4*	
rs2109069	19	4719431	G	A	Disease severity	*DPP9*	
rs74956615	19	10317045	T	A	Disease severity	*ICAM1, ICAM4, ICAM5, ZGLP1, FDX2, RAVER1, ICAM3, TYK2*	
rs13050728	21	33242905	T	C	Disease severity	*IFNAR2*	
rs67579710	1	155203736	G	A	Disease severity	*EFNA1,SLC50A1,DPM3,KRTCAP2,TRIM46,MUC1,THBS3,MTX1,GBA, FAM189B,SCAMP3,CLK2,HCN3,PKLR,FDPS,RUSC1,ASH1L,MSTO1*	
rs721917	10	79946568	A	G	Disease severity	*SFTPD*	
rs35705950	11	1219991	G	T	Disease severity	*MUC5B*	
rs766826	11	34507219	C	T	Disease severity	*ELF5*	
rs12809318	12	132564254	T	C	Disease severity	*FBRSL1*	
rs117169628	16	89196249	G	A	Disease severity	*ACSF3,CDH15,SLC22A31*	
rs1405655	19	50379362	T	C	Disease severity	*NAPSA,NR1H2,POLD1*	
rs114301457	1	155066988	C	T*	Not determined	*EFNA4*	[21]
rs7528026	1	155175305	G	A*	Not determined	*TRIM46*	
rs73064425	3	45859597	C	T*	Not determined	*LZTFL1*	
rs9271609	6	32623820	T*	C	Not determined	*HLA-DRB1*	
rs2496644	6	41515007	A*	C	Not determined	*LINC01276*	
rs28368148	9	21206606	C	G*	Not determined	*IFNA10*	

(*Continued*)

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Table 1 (Continued).

rsid	Chromosome (b38)	Position (b38)	Reference Allele	Effect allele	Suggested Phenotypic Impact	Genes	Ref.
rs2532300	17	46152620	T*	C	Not determined	*KANSL1*	
rs12610495	19	4717660	A	G*	Not determined	*DPP9*	
rs34536443	19	10352442	G	C*	Not determined	*TYK2*	
rs368565	19	48697960	C	T*	Not determined	*FUT2*	
rs17860115	21	33230000	C	A*	Not determined	*IFNAR2*	
rs11385942	3	45834967	G	GA	Disease severity	*SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6, XCR1*	[27]
rs657152	9	133263862	A	C	Disease severity	*ABO*	
rs13078854	3	45861932	A	G	Not determined	*SLC6A20 - LZTFL1*	[28]
rs35044562	3	45909024	A	G	Not determined	*LZTFL1 - CCR9*	
rs2531743	3	45838300	A	G	Not determined	*SLC6A20 - LZTFL1*	
rs147771334	X	80484529	C	T	Not determined	*SH3BGRL*	
rs57801596	X	106714575	D	I	Not determined	*PIH1D3 - FRMPD3*	
rs142658912	7	66344650	D	I	Not determined	*RABGEF1 - TMEM248*	
rs117479047	10	79829561	A	G	Not determined	*RPS24 - ZMIZ1*	
rs10180974	2	207266781	A	T	Not determined	*ZDBF2 - ADAM23*	

Note: asterisk (*) indicates the risk allele.

ACE2 and has been implicated in SARS-CoV-2 infection susceptibility.[20,22] Additionally, several other variants have been consistently associated with SARS-CoV-2 susceptibility and differential COVID-19 outcomes, including: rs2109069 in the dipeptidyl peptidase 9 (DPP9) gene (chr. 19p13.3); rs10735079 in a gene cluster encoding antiviral restriction enzyme activators (OAS1, OAS2, and OAS3) (chr. 12q24.13); and rs74956615 near the tyrosine kinase 2 (TYK2) gene (chr. 19p13.2).[20–22,30] Furthermore, findings indicate that the inverted H2 form of human chromosome 17q21.31 appears to be under positive selection in Europeans,[31,32] and the rs1819040 variant in KANSL1 (chr. 17q21.31) (Table 1) is reported to confer protection against COVID-19 risk.[20,22] However, as previously noted limitations inherent to the recruited case/control cohorts-including underrepresentation of diverse ancestries-necessitate the verification of these recently identified loci and genes in specific, larger populations. Sustained international efforts are therefore required to further validate genetic risk loci associated with COVID-19 in European and other ancestry populations.

Genetic Risk Loci Associated with COVID-19 in Asian or African Populations

Literature reviews on host genetic factors underlying COVID-19 susceptibility and severity reveal that most studies rely on samples from populations of European ancestry, while few utilize cases/controls from Asian or African populations. To some extent, the COVID-19 HGI addresses this limitation by including studies and samples from Asian and African ancestry populations, providing insights into potential genetic risk loci associated with COVID-19 in these populations. Among the 23 genome-wide significant loci reported by the COVID-19 HGI, the majority of cases and controls originate from populations of European ancestry; consequently, most loci are likely primarily associated with COVID-19 risk and outcomes in this ancestry group.

However, rs1886814 (Table 1) has an allele frequency of approximately 15% in Southeast Asian populations, compared to less than 3% in European populations.[20,22] Furthermore, the *FOXP4* variant linked to rs1886814 is common

among East Asian participants (32%), admixed American participants (20%), and Middle Eastern participants (7%) in the COVID-19 HGI data, but occurs at a frequency of only about 3% in most populations of European ancestry.[20] In addition, Shanru Li et al reported that Foxp1 and Foxp4 cooperatively regulate lung secretory epithelial cell fate and regeneration,[33] suggesting that the association of FOXP4 with COVID-19 susceptibility represents an attractive biological target, though further investigation is needed.

Moreover, the rs72711165 locus (Table 1) has been reported to have an allele frequency of approximately 8% in Southeast Asian populations—roughly threefold higher than in European populations (less than 3%).[20,22] *TMEM65*, associated with the rs72711165 locus, is implicated in regulating cardiac conduction and connexin 43 function.[34,35] The association of *TMEM65* with COVID-19 risk and outcomes, and whether this association is specific to Asian ancestry, require further investigation. Additionally, data indicate that the rs190509934 allele (Table 1) is approximately 10 times more common in South Asians than in Europeans,[22] underscoring the importance of including diverse populations in genetic discovery. This finding also suggests a potentially stronger association between rs190509934 and COVID-19 risk in Asian populations. In addition, by using whole exome sequencing strategy, Badla et al reported that variants in interferon (*IFNA4, IFNA10, IFNA14, IFNAR1*) and stimulated genes (*IFI27L1, IFI44, IFIH1*), and toll-like receptor genes (*TLR4, TLR6*) may determine clinical COVID-19 outcomes in young Asian and Middle Eastern patients,[36] though extending studies on larger population are necessary to clarify the significance.

The first confirmed COVID-19 case in South Africa was reported on 5 March 2020. To date, approximately 9.4 million COVID-19 cases have been confirmed in the WHO African Region.[37] However, the identification of genetic risk loci associated with severe COVID-19 in African populations remains limited. This is due to factors including technological constraints, high reagent costs, Africa's exceptional genetic diversity, and other challenges.[38,39] Enhanced scientific collaboration is crucial to map the genetic architecture of COVID-19 across African populations.

Conclusion

Age, gender, environment, social activities, and immune status influence an individual's susceptibility to SARS-CoV-2 infection and the clinical symptoms and severity following exposure. Confirmed cases continue to increase worldwide, particularly in European and American countries and other regions, partly due to divergent pandemic prevention policies. This underscores the potential role of human genetic factors in determining SARS-CoV-2 susceptibility and differential COVID-19 outcomes.

Genome-wide analyses have revealed genome-wide significant loci and proximal genes associated with COVID-19 susceptibility and severity. Consistent with the mechanisms of SARS-CoV-2 infection and host immune responses, many identified loci and related genes are implicated in lung, autoimmune, or inflammatory diseases. Some loci and genes identified by the COVID-19 HGI appear ancestry-specific; however, future studies with larger, balanced cohorts representing diverse ancestries are essential for validation. Furthermore, investigating all potentially relevant genes and biological mechanisms is crucial to advance our understanding of human susceptibility to COVID-19.

To be concluded, though the present study was limited by not included sufficient enough data, and due to the end of COVID-19 as a global health emergency, some data may not reflect the real situations, the important information summarized in the review suggest that joint efforts by including global studies and diverse populations, and combining multiple strategies, such as cell biology, immunology, etc, are needed to discover ancestry-specific loci and genes, to identify at-risk individuals and more potentially druggable targets for the pandemic infection disease and for future potential infectious diseases.

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