

REVIEW

Effects of Selected Inherited Factors on Susceptibility to SARS-CoV-2 Infection and COVID-19 Progression

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Summary

Genetic predispositions may influence geographical and interethnic differences in COVID-19 prevalence and mortality in affected populations. Of the many genes implicated in COVID-19 progression, a substantial number have no direct functional link on virus transfer/viability or on the host immune system. To address this knowledge deficit, a large number of *in silico* studies have recently been published. However, the results of these studies often contradict the findings of studies involving real patients. For example, the ACE2 has been shown to play an important role in regulating coronavirus entry into cells, but none of its variations have been directly associated with COVID-19 susceptibility or severity. Consistently was reported that increased risk of COVID-19 is associated with blood group A and with the *APOE4* allele. Among other genes with potential impacts are the genes for CCR5, IL-10, CD14, TMPRSS2 and angiotensin-converting enzyme. Variants within the protein-coding genes *OAS1* and *LZTFL1* (transferred to the human genome from Neanderthals) are understood to be among the strongest predictors of disease severity. The intensive research efforts have helped to identify the genes and polymorphisms that contribute to SARS-CoV-2 infection and COVID-19 severity.

Key words

Genetics • Population • Polymorphism • Susceptibility • SARS-CoV-2 • COVID-19

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Introduction

Severe acute respiratory syndrome RNA coronavirus 2 (SARS-CoV-2) infection causes the pneumonia-associated disease known as COVID-19 (Corona Virus Disease – 2019) (Coronaviridae Study Group 2020). First reported in Wuhan, China in December 2019, the disease has since spread rapidly to become a global pandemic (Liu *et al.* 2020). In comparison with previous coronavirus diseases such as MERS (Middle East Respiratory Syndrome) and SARS (Severe Acute Respiratory Syndrome), COVID-19 is characterised by relatively low mortality but being far more contagious (Petrosillo *et al.* 2020, Berekaa 2021).

Based on worldwide outcomes, it was quickly established that males, the elderly, obese and diabetics are typically at increased risk of COVID-19 morbidity and mortality (Hippisley-Cox *et al.* 2020).

Importantly, significant interethnic variability in COVID-19 prevalence, severity and associated mortality has been reported (Hastie *et al.* 2020, Lassale *et al.* 2020, Raisi-Estabragh *et al.* 2020). Accordingly, much attention has focused on the influence of genes with interethnic allelic differences on COVID-19 susceptibility and/or severity, irrespective of their involvement in the host immune system.

In fact however, hundreds of SNPs exhibit significant differences in allelic and genotype frequencies between ethnicities (Huang *et al.* 2015). It is estimated that about 15 % of all existing genetic variants within the human genome are population- or ethnicity-specific, and

even variants common within one ethnicity may be completely missing in others (Barbujani *et al.* 1997). Notable examples include variants within the genes for apolipoprotein L1, alcohol dehydrogenase, human homeostatic iron regulator protein (HFE) or genes predisposing to diabetes (Beckman *et al.* 1997, Borinskaya *et al.* 2009, Nadkarni *et al.* 2018, Hubáček *et al.* 2020).

Recently, there has been a rapid and significant increase in the publication of *in silico* studies. These studies used freely available ecological data on disease prevalence and severity as well as genotype distributions (coming often from small independent studies) within populations, but lack direct access to patient and control data. They typically compared the reported numbers of fatalities per million inhabitants, the total number of reported cases, or the number of total cases per million inhabitants. However, these data, collected from dozens of European and Asian countries during the first COVID-19 wave, often contradict the findings of case-control studies (see analysis of *ACE* and *ACE2* genes below), which evaluate samples collected directly from SARS-CoV-2-positive subjects in order to assess COVID-19 susceptibility and severity.

Simply, the fact that there are differences in disease prevalence at the population level are attributable not only to prevalence of risk factors or genetic predispositions (Vašků 2020, Ovsyannikova *et al.* 2020) but also to the imposition of government restrictions. For example, countries almost unaffected during the first wave in the spring of 2020, such as Czech Republic, Croatia and Poland, later experienced very high rates. And while countries like Belgium and France had two mortality peaks during the spring and winter of 2020, other countries such as Norway or Iceland reported relatively low COVID-19-associated mortality throughout the pandemic (online at [//covid19-country-overviews.ecdc.europa.eu](https://covid19-country-overviews.ecdc.europa.eu)). In this context, therefore, estimating the risk status of variants is dependent to a large degree on the exact dates of data collection.

Ethnic admixture plays another important role. As evidenced during the first wave, the highest mortality rates were in countries such as the UK, France, Italy and Spain where the proportion of non-European immigrants is very high. A number of studies have confirmed that ethnicity is one of the most important factors in disease susceptibility and severity (Hastie *et al.* 2020, Raisi-Estabragh *et al.* 2020, Lassale *et al.* 2020): Africans are considered at highest risk followed by Asians and then

Caucasians, the ethnic group at lowest risk.

This review presents the selected examples of associations between various genetic variants and COVID-19 susceptibility or severity.

AB0 blood groups

Rather surprisingly, the AB0 blood group system was the main subject of interest for studies investigating the association between inherited factors and COVID-19.

To date, there have been more than 40 reports and they were excellently summarized by Pendu *et al.* (2021) and within some meta analyses (Pourali *et al.* 2020, Wu *et al.* 2020 and Liu *et al.* 2020). Although largely heterogeneous and characterized by a number of discrepancies, almost all of these studies report lower risk of severe COVID-19 in subjects with blood group 0. Conversely, individuals with blood group A seem to be at highest risk according to these reports. Blood groups B and AB are generally evaluated as neutral, but with a slight increased risk of severe COVID-19 in populations around the Persian Gulf. However, given AB is by far the least common blood group (~5 %) regardless of ethnicity, no definitive conclusion on the association with AB blood group can be drawn.

Based on the evidence, the AB0 blood group system plays an important role in determining COVID-19 outcomes. It is in contrast with the fact that the highest frequency of blood group 0 usually occurs in Africans (~50 %) and Hispanics (~60 %). These ethnicities are at higher risk of COVID-19 risk compared to Caucasians, who have the lowest prevalence (~40 %) of blood group 0. In some European regions, however, blood group A is most common (Dean 2012).

In particular, according to one genome-wide association study (Severe Covid-19 GWAS Group 2020), significant signals within loci of the AB0 blood group system confirmed benefit in blood group 0 and increased risk in blood group A. Another study demonstrated that genetically determined plasma levels of AB0 proteins are causally associated with COVID-19 risk and severity (Hernández Cordero *et al.* 2021).

Apolipoprotein E

APOE (apolipoprotein E) is a protein-coding gene expressed in almost all human tissues. Exhibiting extreme pleiotropic complexity, *APOE* plays critical roles in lipid metabolism, cardiovascular disease and

Alzheimer's disease (Mahley 2016) as well as immune responses (Gale *et al.* 2014); or hypertension (Shi *et al.* 2018) which is understood to increase COVID-19 severity.

There are three major *APOE* alleles: *APOE2* (rs7412; Arg158>Cys), *APOE3* (the most common worldwide) and *APOE4* (an ancestral allele with deleterious effects on many diseases; rs429358; Cys112>Arg).

Associations with COVID-19 were first observed in subjects from the UK Biobank community cohort. This study found that *APOE4E4* homozygotes had an almost 2.5-fold increased risk of severe COVID-19, and association was valid even after excluding individuals with diabetes, hypertension and cardiovascular disease (Kuo *et al.* 2020). Similarly, Del Ser *et al.* (2021) found that elderly carriers (aged over 75 years) of *APOE4* alleles were at increased risk of developing mild or moderate COVID-19 symptoms. In a Czech study involving asymptomatic and symptomatic non-hospitalised subjects, carriers of at least one *APOE4* allele were significantly more common in symptomatic COVID-19 subjects than in general population controls. However, no differences between asymptomatic SARS-CoV-2-positive subjects and general controls were observed (Hubacek *et al.* 2021a).

Interestingly, all of the above studies are in agreement with an *in silico* study by Goldstein *et al.* (2020). They concluded that prevalence of the *APOE4* allele in black Africans (population frequency: ~30-40 %) compared to Caucasians (population frequency ~7-20 %) and Asians (population frequency: ~5-15 %) (Abondio *et al.* 2019) explains the high COVID-19 severity and mortality within this ethnic group.

ACE2 and TMPRSS2

The *ACE2* and *TMPRSS2* genes coding two proteins, serving as a SARS-Cov-2 entry gateway into the cell – ACE2 and TMPRSS2 – were the first had attracted great interest (Hoffmann *et al.* 2020).

Studies show that the TMPRSS2 (transmembrane protease, serine 2) enzyme activates the spread and pathogenesis of human coronaviruses in the infected host (Shirato *et al.* 2018) and ACE2 (angiotensin-converting enzyme 2) acts as a receptor, facilitating the entry of the COVID-19 virus into cells (Bourgonje *et al.* 2020).

Most studies conclude that the genetic variability

of *ACE2* in humans is lower than that of other genes, with no significant effects on COVID-19 progression. Even whole-exome sequencing analyses (Gómez *et al.* 2020, Torre-Fuentes *et al.* 2021) of *ACE2* coding regions have failed to identify a polymorphism that might influence disease risk or outcomes. Thus, albeit there is wide list of theoretical results from *in silico* studies that used molecular simulations, computational analyses, and different web-based tools to suggest interactions between different *ACE2* variants and protein functions, these were so far not confirmed *in vivo*.

TMPRSS2 has also attracted scientists to perform a list of *in silico* analysis (Srivastava *et al.* 2020) a number of promising *in vivo* studies have also been published. For example, a large Italian study detected an association between a cluster of five variants within the *TMPRSS2/MXI* gene loci and COVID-19 severity (Andolfo *et al.* 2021). In Spanish subjects, variability within *TMPRSS2* was also associated with COVID-19 severity (Torre-Fuentes *et al.* 2021). Altogether, *TMPRSS2* variability seems to exert more of an influence on COVID-19 progression than *ACE2*.

Angiotensin-converting enzyme

ACE (ACE1, angiotensin I-converting enzyme, alias kininase II) is a key member of the renin-angiotensin-aldosterone system (RAAS). Like ACE2, another RAAS family member, ACE acts as a receptor for SARS-CoV-2 (Hoffmann *et al.* 2020). Intron 16 of the ACE gene contains a functional insertion/deletion (I/D) polymorphism, 287 bp (rs4646994), the deletion of which is associated with increased enzyme activity and concentration (Cambien *et al.* 1988).

Polymorphisms within the ACE gene are among the heavily discussed variants with the potential to influence COVID-19 outcomes. However, most of the studies on this topic have been performed under *in silico* protocols. Unfortunately, also data on frequencies of ACE genotypes are often limited to small or non-representative samples, producing conflicting results.

The first large studies performed by Delanghe *et al.* (2020a and 2020b) identified the I/I genotype as deleterious. In contrast, studies by Bellone and Calvisi (2020) and Yamamoto *et al.* (2020) identified the D allele as a predictive marker of increased COVID-19 severity. Another study found no association between the ACE I/D polymorphism and SARS-2 infection or COVID-19 severity (Saadat 2020).

Unfortunately, even *in vivo* studies have failed to clarify these discrepancies. Verma *et al.* (2021) found an association between the D/D genotype and COVID-19 in an Asian population. Severe COVID-19 is also associated with the ACE D/D genotype in Spanish patients (Gómez *et al.* 2020). In contrast, our Central European study found an association between the I/I genotype and symptomatic progress of COVID-19 in non-hospitalised patients (Hubacek *et al.* 2021b).

The entire situation is here further complicated by the fact, that ACE inhibitors are some of the most prescribed blood pressure-lowering drugs. And while they have been shown to offer protection against both COVID-19 susceptibility and severity in Europeans, they pose significantly higher risk for Black Africans (Hippisley-Cox *et al.* 2020). To date, no study has examined the potential interaction between ACE inhibitors and ACE polymorphism in COVID-19 patients.

“Neanderthal” polymorphisms

Two variants with considerable effects on COVID-19 susceptibility and severity entered the human genome by gene flow from Neanderthals.

The rs35044562 (Zeberg and Pääbo 2020) polymorphism is located within the *LZTFL1* (leucine zipper transcription factor-like 1) loci and is associated with an approximate 70 % increased risk of hospitalisation due to COVID-19. Further genes located in identical loci (3p21.31) are associated with enhanced complement activation (Valenti *et al.* 2020). The chemokine receptors CCR9, CCR1 and CXCR6 are reported to have a potentially causal association with COVID-19. Additionally, the gene for FYCO1 (FYVE and coiled-coil domain-containing 1) and the gene for SLC6A20 (solute carrier family 6, proline IMINO transporter, member 20), which interacts with ACE2, are located in the same region (Severe Covid-19 GWAS Group 2020).

According to genome-wide association (GWA) studies, OAS-1 (oligoadenylate synthetase 1) is another protein of Neanderthal origin playing a role in immune responses against RNA viruses, with functional consequences for infection (Zhou *et al.* 2020, Pairo-Castineira *et al.* 2021). The OAS proteins OAS1, OAS2 and OAS3 activate RNAases, which in turn break down and eliminate endogenous as well as viral RNA (Kristiansen *et al.* 2010). Interestingly, variant within OAS1 has been previously associated with the

susceptibility to the SARS infection (He *et al.* 2006).

Although the above studies boast relatively high numbers of examined subjects and odds ratios, further independent studies are warranted.

Other mentioned genetic polymorphisms

Several other genes have been investigated using similar approaches as mentioned in details above. An *in silico* study found that human homeostatic iron regulator protein (*HFE*, Cys282Tyr polymorphism, rs1800562), which leads to iron overload and haemochromatosis, has no significant correlation with COVID-19 prevalence (Delange *et al.* 2020a). The other haemochromatosis-associated polymorphism Asp63His has yet to be examined.

Another extensive *in silico* analyses (Kim and Jeong 2020, Pati *et al.* 2021a) of publicly available data (mostly WHO and 1000 genome project), as well as *in vivo* study (Zhang *et al.* 2020) pointed on potential importance of the *IFITM* (interferon-induced transmembrane proteins, involved in restriction of both viruses entry as well as viruses replications, especially *IFITM3* seems to be of importance) gene family in determination of COVID-19 severity and fatality rate.

HLA (Human Leucocyte Antigen) complex is involved also in effective defense mechanism against viruses. Unfortunately, the genes coding the HLA proteins are among the most polymorphic in humans. So far performed studies were recently summarized (Fricke-Galindo and Falfán-Valencia 2021) and alleles associated with low risk (for example *-A*02:02* or *-C*12:03*) as well as with mortality (*C*05*, *-B*51:01* or *-DQB1*04*) were detected.

The functional rs2569190 polymorphism within the CD14 receptor gene has been intensively discussed in association with different infections (Guo *et al.* 2020, Zhao *et al.* 2013). One *in silico* study found an association between the T allele and SARS-CoV-2 infection and mortality in European populations (Pati *et al.* 2021b).

In UK Biobank subjects, the minor TT genotype of rs17775810 sigma-1 receptor (*SIR*, regulates inflammation due to cytokine production inhibition) was associated with lower death rates in comparison to carriers of at least one C allele (Lehrer and Rheinstein 2021).

In Czech subjects, the 32 bp deletion (rs333) allele within the *CCR5* (CC chemokine receptor 5) gene, which protects homozygote carriers against HIV infection

(Samson *et al.* 1996), was shown to protect against symptomatic COVID-19 progression (Hubacek *et al.* 2021c). Deletion allele was also less frequent in Spanish patients, hospitalized with COVID-19 (Cuesta-Llavona *et al.* 2021). In contrast, a large study of German stem-cell donors (Bernas *et al.* 2021) detected no association between this deletion and COVID-19 severity. Interestingly, *CCR5* is located within close proximity of the *LZTFL1* gene (see above).

Further COVID-19-associated signals within regions encoding genes for tyrosine kinase 2 (*TYK2*), dipeptidyl peptidase 9 (*DPP9*) and the interferon receptor gene (*IFNAR2*) have also been detected using the GWA model (Pairo-Castineira *et al.* 2021).

As vitamin D deficiency is much more common within the groups who are at highest risk of severe COVID-19 (Benskin 2020), vitamin D receptor (*VDR*) is another plausible candidate to study. Indeed, *in silico* study (Karcioglu Batur and Hekim 2021) suggest positive correlations between the prevalence and mortality rates and rs7041 variant within the *VDR* loci. Unfortunately, representative *in vivo* studies are missing so far.

The identical is valid for cytokines. Albeit cytokine variability (*IL-6*, *IL-10*, *IL1-RN*, *TNF- α* , ...) has definitely high potential to influence COVID-19 induced cytokine storm (Paim *et al.* 2021) relevant studies are generally missing.

Conclusions

It is clear that the causes of COVID-19 are multifactorial. Disease susceptibility, resistance and outcomes are characterized by high interindividual heterogeneity. The disease is not only influenced by accompanying factors such as obesity, hypertension and

diabetes, but also by important predictors such as ethnicity (Hippisley-Cox *et al.* 2020) and genetic predisposition (Vasku 2020, Ovsyannikova *et al.* 2020).

Thanks to the intensive efforts of many researchers worldwide, the genes and polymorphisms that contribute to SARS-CoV-2 infection and COVID-19 severity are now better understood. There is a long list of genes and variants with the potential to affect SARS-CoV-2 susceptibility. However, only a few genetic determinants of SARS-CoV-2 infection and COVID-19 severity seems to have consistent effects (Table 1), and many of *in silico* suggested associations were not conclusively examined and confirmed *in vivo*. This is definitely caused also by the fact, that number of examined subjects is often relatively low (not exceptions are studies with less than 30 subjects). COVID-19 association studies had collected and screened of magnitude less subjects than studies focused on other communicable or non-communicable diseases. Interestingly however, some of them overlap the candidates (for example *OAS-1* or *CD14*) associated with the previous SARS infection (Dos Santos *et al.* 2021).

It should also be noted that the inclusion criteria applied are highly variable, with SARS-CoV-2-positive cases ranging from asymptomatic through mild-to-severe to fatalities. Finally, ethnic differences in disease susceptibility and severity highlight the heterogeneity of the genes and variants involved.

Over-activation of the immune system is an acknowledged hallmark of severe COVID-19 cases (Mehta *et al.* 2020, Paces *et al.* 2020). However, not all of the genes of interest thus far described are known to have important or at least some roles in the immune system.

Table 1. Brief summary of selected examples of COVID-19 associated genes.

Gene	Effect
<i>ABO</i> blood groups	Lower risk is associated with the blood group 0, increased risk with blood group A
<i>APOE</i>	<i>APOE4</i> (rs429358) allele is associated with increased risk
<i>ACE</i>	Controversial roles – insertion (rs4646994) allele seems to be risky in Caucasians, deletion allele in Asians
<i>OAS1</i>	Cluster of polymorphisms associated with increased risk – effect due to the activation of RNAses
<i>LZTFL1</i>	rs35044562 polymorphism increases the risk, detailed mechanism unknown, possible association with neighboring chemokine receptor alleles

Therefore, it cannot be discounted that they serve as markers in high linkage disequilibrium for some adjacent clustering genes with causal variants.

A simple, quick and inexpensive test aimed at predicting symptomatic COVID-19 based on individual DNA polymorphisms would be helpful both in distinguishing between subjects at high and low risk and importantly, also in estimating disease severity. Such a test would require a wide list of polymorphisms to be examined simultaneously. Similarly to other diseases (Talmud *et al.* 2015, Mistry *et al.* 2018) creation of the (poly)genetic risk score (Choi *et al.* 2020) reflecting the host ability to affect the individual's sensitivity to COVID-19 could be important.

Further studies aimed at elucidating the complex role played by genetic predispositions are needed in order to improve timely detection in at-risk subjects and management of the ongoing COVID-19 pandemic.

Conflict of Interest

There is no conflict of interest.

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