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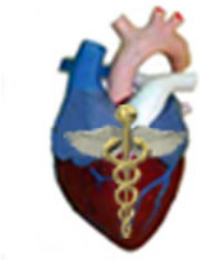

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EDITORIAL

COVID-19 Genetics: Current Status

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Abstract

Interindividual clinical variability characterizes COVID-19 infection SARS-CoV-2 infection, ranging from no or mild symptoms in >95% of individuals to severe and life-threatening acute respiratory distress syndrome with bilateral pneumonia requiring intensive care unit monitoring in <0.5% of infected individuals. The host genetic background seems to determine the susceptibility and outcome in COVID-19 patients. Several relevant genetic variants and risk genes have been identified, relating to blood type, HLA system, angiotensin converting enzyme and other proteins, cytokines, and other host genetic signals and immune system's specific response. On the other hand, emerging new variants of the COVID-19 virus with enhanced transmissibility/infectivity and immune escape ability pose new risks, especially if they are going to have an impact on the efficacy of currently available vaccines. All these issues relating to the impact of genetics on COVID-19 selectivity are herein reviewed. ***Rhythmos 2021;16(3): 48-56***.

Key Words: COVID-19; SARS-CoV-2; COVID vaccines; genetic susceptibility; COVID-19 variants; ACE-2 polymorphisms; spike glycoprotein; mutations; innate immunity; adaptive immunity; blood type; HLA system

Abbreviations: ACE = angiotensin converting enzyme; ARDS = acute respiratory distress syndrome; COVID-19 = corona virus disease 2019; DNA = deoxyribonucleic acid; GWAS = genome-wide association study; HLA – human leucocyte antigen; ICU = intensive care unit; IL = interleukin; miR = microRNA; SARS-CoV-2 = severe acute respiratory syndrome-corona virus-2; TMPRSS2 = transmembrane protease serine 2

Introduction

Interindividual clinical variability characterizes human infection, including SARS-CoV-2 infection, the course of which exhibits wide interindividual phenotype characterization or clinical variability, ranging from asymptomatic or mild infection in >95% of individuals to severe and life-threatening acute respiratory distress syndrome (ARDS) with bilateral pneumonia requiring intensive care unit (ICU) monitoring in <0.5% of infected individuals.[1, 2] The impact of genetics on this strange selectivity of COVID-19 is herein reviewed.

Genetic Risk Factors

Identification of major risk factors associated with COVID-19 including advanced age, male gender and pre-

existing medical conditions, do not fully explain why some people experience no or mild symptoms whereas others become critically ill.[1, 3, 4] Thus, genetic risk factors have been considered to play a role in the severity and progression of the virus.[2, 5, 6] Studies of the genetics of people exposed to the SARS-CoV-2 virus have begun identifying links between developing the disease and variations in specific parts of host DNA, thus shedding light on the role of genetics in individual susceptibility to COVID-19.

Identifying genetic markers associated with the susceptibility or clinical outcome of COVID-19 could provide an essential contribution to the knowledge of this disease, as different genes are implicated or related to the susceptibility or severity of COVID-19.[7]

A recent genome-wide association study (GWAS) identified a gene cluster on chromosome 3 (*3p21.31*) as a genetic susceptibility/risk locus for respiratory failure after infection with SARS-CoV-2 and confirmed a potential involvement of the ABO blood-group system.[8] Genes in this region include SLC6A20, which produces a protein that interacts with ACE2, the protein used by SARS-CoV-2 to enter its host cells, and genes for chemokine receptors, which are involved in inflammation. Variation in this region of DNA is associated with worse clinical outcomes as ACE2 and inflammation characterize severe COVID-19 infection.

Another study (COVID-19 Host Genetics Initiative) comprising 3,199 hospitalized patients with COVID-19 and controls showed that this cluster is the major genetic risk factor for severe symptoms and need for hospitalization in patients with COVID-19.[9]

A subsequent study showed that a major genetic risk factor associated with severe COVID-19 infection is inherited from Neandertals.[10] This risk is conferred by a genomic segment of 49.4 kilobases in size that is inherited from Neanderthals and is carried by ~50% of people in south Asia and ~16% of people in Europe.

On the other hand, the same investigators reported a protective locus on chromosome 12 that was associated with reduced risk of intensive care for COVID-19 patients.[11] This protective haplotype differs from the risk haplotype in that it has a more moderate effect and occurs at substantial frequencies in all regions of the world outside Africa. The genes in this region, called OAS ("original antigenic sin"), control the activity of an enzyme that degrades viral genomes, and the Neandertal variant of the enzyme seems to do this more efficiently. Both of these genetic variations are believed to be inherited from Neanderthals, human ancestors that became extinct over 40,000 years ago. Much of their DNA remains prominent in the human genetic code and is carried by ~50% of people in South Asia and ~16% of people in Europe.

Recently emerged COVID-19 variants show several mutations at the receptor binding domain in the spike (S) glycoprotein and contribute to immune escape and enhanced binding with angiotensin-converting enzyme 2 (ACE2). ACE2 and transmembrane protease serine 2 (TMPRSS2) play important roles in SARS-CoV-2 entry into the cell.[12] Mutations leading to genetic variation in these host entry-related proteins have been found to enhance viral transmission and infectivity and/or contribute to immune escape.[13]

Thus, complex molecular mechanisms seem to underly inherited predispositions to COVID-19-disease phenotypes; however, recent studies have provided some insight into the genetic factors contributing COVID-19 disease susceptibility and severity (**Table 1**).[14, 15] In addition to host genetic variation, clinically relevant variation in the expression of COVID-19-related genes seems to be also associated with other host factors and environmental exposures.[16] Furthermore, host genetic variants associated with critical illness may identify mechanistic targets for therapeutic intervention.

The Blood Type Association?

Genetic data have suggested that blood group A has been associated with a higher risk than non-A blood groups, whereas blood group O confers a lower risk of acquiring Covid-19 than that in non-O blood groups.[17, 18]

A review of 23 studies indicates that blood type O may serve as a protective factor against COVID-19.[19] Blood type O individuals are less susceptible to infection, or they are asymptomatic at higher rates and therefore do not seek out testing. As mentioned, studies have found a strong association between a locus on a specific gene cluster on chromosome 3 (chr3p21.31) and outcome severity, such as respiratory failure. Cellular models have suggested an explanation for blood type modulation of infection, evidencing that spike protein/ACE2-dependent adhesion to ACE2-expressing cell lines was specifically inhibited by monoclonal or natural human anti-A antibodies, so individuals with non-A blood types, specifically O, or B blood types, which produce anti-A antibodies, may be less susceptible to SARS-CoV-2 infection due to the inhibitory effects of anti-A antibodies.[19]

Nevertheless, there is some controversy about the link between COVID-19 and blood type. Observational US data on 14,112 individuals tested for SARS-CoV-2 with known blood type to assess the association between ABO and Rh blood types and infection, intubation, and death, showed a slightly increased infection prevalence among

non-O types. [18] Risk of intubation was decreased among A and increased among AB and B types, compared with type O, while risk of death was increased for type AB and decreased for types A and B. The investigators estimated Rh-negative blood type to have a protective effect for all three outcomes.

Table 1. **Genetic Variants for COVID-19 Susceptibility and Severity** [7, 13]

Variants in Immune System-Related Genes

HLA Gene Complex, examples:

- HLA-C*07:29 and -B*15:27 alleles found more frequently among patients than in controls
- HLA-DRB1*15:01, -DQB1*06:02, and -B*27:07 alleles associated with COVID-19 susceptibility
- HLA-A*02:01 associated with increased risk for COVID-19
- HLA-A*11:01, -B*51:01, and -C*14:02 alleles were related to worst outcome among a Chinese population sample
- HLA-A*11, -C*01, and -DQB1*04 associated with higher mortality in Spaniards
- HLA-DRB1*08 was correlated with mortality of COVID-19 in the Italian population
- HLA-B*15:03 was considered a protector allele

Cytokine Genes

- 7 variants in interleukin 6 (IL6) (rs140764737, rs142164099, rs2069849, rs142759801, rs190436077, rs148171375, rs13306435) and 5 variants in IL6R (rs2228144, rs2229237, rs2228145, rs28730735, rs143810642) have been predicted to alter the expression and interaction of IL6 and IL6R, implicated in the pathogenesis of COVID-19 and its complications
- Increased thrombotic risk for homozygous carriers of the IL1RN haplotype 5 GTGTA
- Inborn errors of Toll-like receptor 3 (TLR3, HGNC:11849)– and interferon regulatory factor 7 (IRF7, HGNC:6122)–dependent type I interferon (IFN) immunity related to life-threatening COVID-19 pneumonia
- Wide inter-ethnic variability in cytokine gene variants' frequencies (IL2, IL6, IL10, TNF, TGFB1, and IFNG)

Variants in Coding Genes for Receptors of COVID-19

ACE2 and TMPRSS2

- Higher allele frequencies of variants (e.g., rs143695310) associated with elevated expression of ACE2 among East Asian populations, suggesting higher susceptibility to COVID-19
- ACE2 variants (e.g. p.Arg514Gly) in African/African-Americans associated with cardiovascular and pulmonary conditions
- Genetic predisposition for the lowest TMPRSS2 (HGNC:11876) expression levels was observed for Africans and the highest for East Asians
- Variants in TMPRSS2 (e.g., p.Val160Met, rs12329760) associated with COVID-19 susceptibility
- Significant differences in TMPRSS2 expression levels among males and females have been reported

Mutations in S Glycoprotein

Recently emerged variants exhibit several mutations in the S protein, especially in the receptor binding domain (RBD) *:

- UK variant (B.1.1.7) carries 8 mutations in the S glycoprotein: H69/V70 deletion (DH69/V70), Y144 deletion (DY144), N501Y, A570D, P681H, T716A, S982A, and D1118H
- South Africa variant (B.1.351) carries 3 mutations in the RBD region: K417N, E484K, and N501Y
- Brazil variant (B.1.1.28; P.1 and P.2 lineages) exhibits a different pattern of mutations (P.1 has same RBD mutations as South Africa; P.2 has the spike E484K mutation)
- North America variant (B.1.429) includes 3 mutations in the S protein: S13I & W152C in the S1 domain and L452R in the RBD
- India variant (B.1.617.2 or Delta) has 13 mutations in the S glycoprotein (15 or 17 according to some sources, depending on whether more common mutations are included); 4 of them are of particular concern: D614G, T478K, L452R, P681R

Variants in Other Genes

- Associations of LZTFL1 (HGNC:6741) rs11385942, at ***locus 3p21.31***, and ***ABO*** (HGNC:79) rs657152, at locus 9q34.2, with genetic susceptibility to COVID-19
- Association with COVID-19 severity of the gene locus located in TMEM189 (PEDS1, HGNC:16735)–UBE2V1 (HGNC: 12494), involved in the IL-1 signaling pathway
- Significant associations found in several other loci:
  - in a gene cluster that encodes antiviral restriction enzyme activators OAS1 (HGNC:8086), OAS2 (HGNC:8087), and OAS3 (HGNC:8088)
  - near the gene that encodes tyrosine kinase 2 (TYK2, HGNC:12440)
  - within the gene that encodes dipeptidyl peptidase 9 (DPP9, HGNC:18648)
  - in the interferon receptor gene IFNAR2 (HGNC:5433)
- In the ***anticoagulant pathways***, variants in *protein C gene* (PROC, HGNC:9451), *factor V Leiden* (F5, HGNC:3542), and deficiencies of *antithrombin* (SERPINC1, HGNC:775) have been related to an impaired function of the coagulation
- Variants in the serpin *plasminogen activator inhibitor 1* (SERPINE1, HGNC:8583) could impact the encoded protein levels, considered one of the main inhibitors of fibrinolysis, related to ***DIC*** (disseminated intravascular coagulation) development

*These variants have caused a severe increase in SARS-CoV-2 infections since December 2020. / Notably, the N501Y mutation, which is located in the RBD and has been found in most of the variants, is believed to enhance the transmissibility of SARS-CoV-2. The aforementioned variants all have the D614G mutation, though this is expected due to the predominance of D614G since the early pandemic

Similarly, a study by the genetic testing company 23andme found evidence that blood type has an impact on COVID-19 infection (https://medical.23andme.com/23andme-finds-evidence-that-blood-type-plays-a-role-in-covid-19/). Preliminary information from the blood and genetic profiles of >750,000 participants suggests that O blood type appears to be protective against COVID-19; individuals with O blood type tested positive for COVID-19 are 9-18% less likely than other individuals; these findings hold true when adjusted for other variables, like age, sex, BMI, ethnicity and comorbidities. Although another study, as mentioned, found the blood group O to be protective only across rhesus positive blood types,[18] this finding did not pan out in the 23andMe data.

However, a recent observational study comprising 107,796 individuals newly infected with the SARS-CoV-2 virus, found that blood type was not associated with disease susceptibility or severity, including viral positivity, hospitalization, or ICU admission.[20]

A meta-analysis of 7 studies, including a total of 13 subgroups of populations (7503 SARS-CoV-2 positive cases and 2962160 controls), indicated that SARS-CoV-2 positive individuals are more likely to have blood group A (pooled OR 1.23) and less likely to have blood group O (pooled OR = 0.77).[21]

Another meta-analysis of 4 studies comprising 31,100 samples indicated that compared to other ABO blood type, there was an increased odds of infecting COVID-19 among individuals with A blood group (OR: 1.249, $P < 0.001$) and a decreased odds of infecting COVID-19 among individuals with blood group O (OR: 0.699, $P < 0.001$).[22] Also, individuals with blood group AB seem to have a higher risk to COVID-19 severity (OR: 2.424) and demise (OR: 1.348). In contrast, individuals with O blood group had lower risk to COVID-19 severity (OR: 0.748), and individuals with B blood group were likely to relate a lower risk to COVID-19 demise.

A recent meta-analysis of 21 studies comprising 29649 individuals showed that, overall, individuals with group O had a lower infection rate compared to individuals of non-O group (OR: 0.81).[23] However, the difference in the effect size was lower in cohort studies compared to case control studies. No evidence was found indicating an effect of the O type on the disease severity in the infected patients.

Finally, genetic variation at a multigene cluster at chromosome 3p21.31 and the ABO blood group have been associated with the risk of developing severe COVID-19; as alluded to earlier, the 3p21.31 chromosome region and variants in the ABO gene have recently been identified in two different GWAS including diverse populations;[8, 24, 25] however, further studies elucidating the role of the proteins encoded by the identified genes in the COVID-19 and their association in other populations is still warranted.

Human Leukocyte Antigen (HLA) System

Human leukocyte antigens (HLA) are proteins encoded by the human major histocompatibility complex (MHC) genes, which are highly polymorphic in the human genome. Individual human HLA alleles, characterized by interethnic variability in their frequencies, can affect both the susceptibility and the severity of viral infections.[26] The HLA system, with its highly polymorphic nature (3-6 different *HLA* alleles in each individual with a variable distribution in the ethnic populations), organizes immune regulation and can affect clinical outcomes in multiple infectious diseases, including COVID-19 infection.[27] Several correlations have been suggested between the expression of a specific HLA allele/haplotype and susceptibility, clinical course and severity of SARS-CoV-2 infection; protective (e.g., patients possessing HLA-B*15:03 genotype may become immune to the infection) and harmful HLA variants have been reported in both mild and severe forms of COVID-19, albeit with some degree of confusion and contradiction, considering the large number of existing variants.[27-30] Nevertheless, as variation in HLA alleles may affect the course of COVID-19, HLA typing may contribute information on how COVID-19 might manifest in an individual, identify individuals at high risk and even guide therapeutic options and/or prioritize vaccination.

DNA polymorphisms in ACE2 and TMPRSS2

ACE2 and TMPRSS2 are the two key host factors of SARS-CoV-2. A study investigated genetic susceptibility to COVID-19 by examining DNA polymorphisms in ACE2 and TMPRSS2 from ~ 81,000 human genomes.[31] ACE2 polymorphisms were found to be associated with cardiovascular and pulmonary conditions by altering the angiotensinogen-ACE2 interactions, such as p.Arg514Gly in the African/African-American population. Unique but prevalent polymorphisms (including p.Val160Met (rs12329760), an expression quantitative trait locus (eQTL)) 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. The authors concluded that ACE2 or TMPRSS2 DNA polymorphisms are likely associated with genetic susceptibility of COVID-19. These polymorphisms could guide effective treatments (i.e., hydroxychloroquine and camostat) for COVID-19.

SARS-CoV-2 uses the SARS-CoV receptor ACE2 for entry and TMPRSS2 for S protein priming.[32, 33] Hitherto, a total of 21 genetic variants of TMPRSS2 and 33 variants

of ACE2 gene have been reported affecting susceptibility to SARS-CoV-2.[13, 34] A recent systematic review indicates that people with ACE2 polymorphism who have TMPRSS2 are at high risk of SARS-CoV-2 infection.[6] Also, other studies have shown that males are more likely to become infected with SARS-CoV-2 than females, as males seem to express higher ACE2 levels in their type II pneumocytes.[35, 36]

S Glycoprotein Mutations / SARS-CoV-2 Variants

Mutations in the S glycoprotein have produced several SARS-CoV-2 variants, shown to enhance viral transmissibility/infectivity and immune escape ability; however, no current mutations increase viral pathogenicity or COVID-19 severity (**Table 2**).[13, 37, 38] The recent emergence of SARS-CoV-2 variants of concern with increased transmissibility include the UK variant (B1.1.7 or *alpha*), the South African variant (B.1.351 or *beta*), the Brazilian variant (B.1.1.28), the USA variant (B.1.429; prevalent in California) and the Indian variant (B.1.617 or *delta*) which have several mutations in the S glycoprotein, especially within the receptor binding domain (RBD).

Current COVID-19 vaccines seem to remain effective for B.1.1.7 (UK variant), however, a sharp decrease in neutralization activity for the South African variant (B.1.351) has been reported using sera from vaccinee and monoclonal antibodies.[13, 39] The decrease of neutralizing activity is believed to be caused by a specific mutation in S glycoprotein. Most likely, this unfortunate development will require new or modified vaccines to combat the new variants.[37]

Complement

Complement activation has been associated with COVID-19 severity. A study in 72 unrelated European hospitalized patients found that the rs11385949 G>GA variant, tagging the chromosome 3 gene cluster variation and predisposing to severe COVID-19, is associated with enhanced complement activation, both with C5a and terminal complement complex, while non-O blood group with C5a levels.[40] The authors concluded that these findings provide a link between genetic susceptibility to more severe COVID-19 and complement activation.

Critical Illness

New genetic associations with critical illness in COVID-19 have been discovered. Some of these associations lead directly to potential therapeutic approaches to augment interferon signalling, antagonize monocyte activation and infiltration into the lungs, or specifically target harmful inflammatory pathways.[15] The investigators identified several new genome-wide significant associations; on chromosome 12q24.13 (rs10735079) in a gene cluster that encodes antiviral restriction enzyme activators; on chromosome 19p13.2 (rs74956615) near the gene that encodes tyrosine kinase 2 (TYK2); on chromosome 19p13.3 (rs2109069) within the gene that encodes dipeptidyl peptidase 9 (DPP9); and on chromosome 21q22.1 (rs2236757) in the interferon receptor gene IFNAR2. They found evidence that low expression of IFNAR2, or high expression of TYK2 or of the monocyte-macrophage chemotactic receptor CCR2, are associated with life-threatening or severe COVID-19 disease.[15] These mechanisms may be amenable to targeted treatment.

Cytokine Storm / Cytokine Genes. Some COVID-19 patients may become critically ill by developing a ***cytokine storm***, a hyperinflammatory condition, that may have a fatal outcome.[3, 4] Genetic and non-genetic factors could explain the uncontrolled inflammatory response that characterizes a cytokine storm.[41, 42] Thus, the study of cytokine genes with adequate co-variables adjustment could lead to the identification of genetic markers related to COVID-19 outcome, and explain why some individuals are particularly vulnerable to a severe cytokine storm. It has been suggested that deficient innate immunity marked by reduced levels of inflammatory markers at baseline, with ensuing secondary overactive adaptive immune response may account for a higher genetic risk for cytokine storm.[42] Variants in certain cytokine genes could be related to disease susceptibility and cytokine storm, and/or COVID-19 complications.[7]

Several gene variants in interleukin (*IL) 6* with differential cytokine expression and with different disorders have been reported; some alleles (e.g., rs1800795, rs1800796) have been associated with higher IL-6 plasma levels; high levels of IL-6 can activate the coagulation pathway and vascular endothelial cells, contributing to disease's poor prognosis.[7] Genetic variants in the regulatory regions of other cytokine genes have also been reported; several of these variants have been related to infectious disease susceptibility, cytokine storm, and venous thrombosis. The inheritance of certain cytokine gene polymorphisms is strongly associated with ethnicity.[43]

Variants of primary immunodeficiency (PID)-related genes, including defects in innate and adaptive immunity, have been suggested to dysregulate host inflammatory responses to infection, and some of them have been shown to contribute to the development of cytokine storms.[44-46] A recent study analyzed the association between PID gene variants with severe cytokine storms in 233 hospitalized COVID-19 patients and identified 4 PID gene (UNC13D,

AP3B1, RNF168, DHX58) variants significantly enriched in COVID-19 patients experiencing severe cytokine storms.[46]

Table 2. Classification of SARS-CoV-2 Variants
(SARS-CoV-2 Variant Classifications and Definitions (cdc.gov)**)**

I) **Variants of Interest (**a variant with specific genetic markers associated with changes to receptor binding, reduced neutralization by antibodies generated against previous infection or vaccination, reduced efficacy of treatments, potential diagnostic impact, or predicted increase in transmissibility or severity**)**

Selected Characteristics of SARS-CoV-2 Variants of Interest:

● ***B.1.427 (epsilon*****;** first identified: California**)** / **Spike Protein Substitutions**: L452R, D614G / **Name**: 20C/S:452R
Attributes:
- ~20% increased transmission
- Modest decrease in susceptibility to the combination of bamlanivimab and etesevimab; however, the clinical implications of this decrease are not known. Alternative monoclonal antibody treatments are available.
- Reduced neutralization by convalescent and post-vaccination sera
- Deescalated from a variant of concern on June 29, 2021 due to the significant decrease in the proportion of B.1.427 lineage viruses circulating nationally and available data indicating that vaccines and treatments are effective against this variant

● ***B.1.429 (epsilon*****;** first identified: California**)** / **Spike Protein Substitutions**: S13I, W152C, L452R, D614G / **Name**: 20C/S:452R
Attributes:
- ~20% increased transmission
- Reduced susceptibility to the combination of bamlanivimab and etesevimab; however, the clinical implications of this decrease are not known. Alternative monoclonal antibody treatments are available.
- Reduced neutralization by convalescent and post-vaccination sera.
- Deescalated from a variant of concern on June 29, 2021 due to the significant decrease in the proportion of B.1.429 lineage viruses circulating nationally and available data indicating that vaccines and treatments are effective against this variant

● ***B.1.525 (Eta***; first identified: UK/Nigeria**)** / **Spike Protein Substitutions**: A67V, 69del, 70del, 144del, E484K, D614G, Q677H, F888L / **Name**: 20A/S:484K
Attributes:
- Potential reduction in neutralization by some Emergency Use Authorization (EUA) monoclonal antibody treatments
- Potential reduction in neutralization by convalescent and post-vaccination sera

● ***B.1.526 (Iota***; first identified: New York**)** / **Spike Protein Substitutions**: L5F, (D80G*), T95I, (Y144-*), (F157S*), D253G, (L452R*), (S477N*), E484K, D614G, A701V, (T859N*), (D950H*), (Q957R*) / **Name**: 20C/S:484K
Attributes:
- Reduced susceptibility to the combination of bamlanivimab and etesevimab monoclonal antibody treatment; however, the clinical implications of this are not known. Alternative monoclonal antibody treatments are available.
- Reduced neutralization by convalescent and post-vaccination sera
- B.1.526.1 sublineage consolidated with this parent lineage

● **B.1.617.1 (Kappa;** first identified: India**)** / **Spike Protein Substitutions**: (T95I), G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H / **Name**: 20A/S:154K
Attributes:
- Potential reduction in neutralization by some Emergency Use Authorization (EUA) monoclonal antibody treatments
- Potential reduction in neutralization by post-vaccination sera

● **B.1.617.3 (**first identified: India**)**
Spike Protein Substitutions: T19R, G142D, L452R, E484Q, D614G, P681R, D950N / **Name**: 20A
Attributes:
- Potential reduction in neutralization by some EUA monoclonal antibody treatments
- Potential reduction in neutralization by post-vaccination sera

● **P.2** (**Zeta**; first identified: Brazil**)** / **Spike Protein Substitutions**: E484K, (F565L*), D614G, V1176F / **Name**: 20J
Attributes:
- Potential reduction in neutralization by some EUA monoclonal antibody treatments
- Reduced neutralization by post-vaccination sera

II) Variants of Concern (A variant for which there is evidence of an increase in transmissibility, more severe disease (e.g., increased hospitalizations or deaths), significant reduction in neutralization by antibodies generated during previous infection or vaccination, reduced effectiveness of treatments or vaccines, or diagnostic detection failures**)**
Possible attributes of a variant of concern:
In addition to the possible attributes of a variant of interest
- Evidence of impact on diagnostics, treatments, or vaccines
  - Widespread interference with diagnostic test targets
  - Evidence of substantially decreased susceptibility to one or more class of therapies
  - Evidence of decreased neutralization by antibodies generated during previous infection or vaccination
  - Evidence of reduced vaccine-induced protection from severe disease
- Evidence of increased transmissibility
- Evidence of increased disease severity

Selected Characteristics of COVID-19 Variants of Concern:

● **B.1.1.7 (Alpha;** first identified: UK**)** / **Spike Protein Substitutions**: 69del, 70del, 144del, (E484K*), (S494P*), N501Y, A570D, D614G, P681H, T716I, S982A, D1118H (K1191N*) / **Name**: 20I/501Y.V1
Attributes:
- ~50% increased transmission
- Potential increased severity based on hospitalizations and case fatality rates
- No impact on susceptibility to EUA monoclonal antibody treatments

- Minimal impact on neutralization by convalescent and post-vaccination sera

● **B.1.351 (Beta;** first identified: South Africa) / **Spike Protein Substitutions**: D80A, D215G, 241del, 242del, 243del, K417N, E484K, N501Y, D614G, A701V / **Name**: 20H/501.V2
Attributes:
- ~50% increased transmission
- Reduced susceptibility to the combination of bamlanivimab and etesevimab monoclonal antibody treatment, but other EUA monoclonal antibody treatments are available
- Reduced neutralization by convalescent and post-vaccination sera

● **B.1.617.2 (Delta;** first identified: India) / **Spike Protein Substitutions**: T19R, (G142D*), 156del, 157del, R158G, L452R, T478K, D614G, P681R, D950N / **Name**: 20A/S:478K
Attributes:
- Increased transmissibility
- Potential reduction in neutralization by some Emergency Use Authorization (EUA) monoclonal antibody treatments
- Potential reduction in neutralization by post-vaccination sera

● **P.1 (Gamma;** first identified: Japan/Brazil) / **Spike Protein Substitutions**: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I / **Name**: 20J/501Y.V3
Attributes:
- Reduced susceptibility to the combination of bamlanivimab and etesevimab monoclonal antibody treatment, but other EUA monoclonal antibody treatments are available
- Reduced neutralization by convalescent and post-vaccination sera

III) Variants of High Consequence (A variant of high consequence has clear evidence that prevention measures or medical countermeasures (MCMs) have significantly reduced effectiveness relative to previously circulating variants)
Possible attributes of a variant of high consequence:
In addition to the possible attributes of a variant of concern
- Impact on Medical Countermeasures (MCM)
  - o Demonstrated failure of diagnostics
  - o Evidence to suggest a significantly reduction in vaccine effectiveness, a disproportionately high number of vaccine breakthrough cases, or very low vaccine-induced protection against severe disease
  - o Significantly reduced susceptibility to multiple EUA or approved therapeutics
  - o More severe clinical disease and increased hospitalizations

Currently there are no SARS-CoV-2 variants that rise to the level of high consequence

Comorbidities

Genetically increased body mass index (BMI) has been causally associated with testing positive for COVID-19 and a higher risk of COVID-19 hospitalization.[47]

Polymorphisms of alpha-1 anti-trypsin (*AAT)* and ACE genes have been associated with various comorbidities, such as cardiovascular disease, hypertension, diabetes, chronic kidney disease, and obesity. Investigators have hypothesized that people with comorbidities may have a genetic predisposition that makes them more vulnerable to various factors; including SARS-CoV-2.[5] As comorbidities are associated with chronic inflammation and are closely related to the renin-angiotensin-aldosterone system (RAAS), these individuals may already have a mild ACE1/ACE2 imbalance before viral infection, which increases their risk for developing severe cases of COVID-19.

Innate and Adaptive Immunity

Analysis of data on 406 SARS-CoV-2-negative individuals as part of a UK population study against corresponding genotype data from a large genome-wide association study (GWAS) of severe COVID-19 revealed that a higher genetic risk for severe COVID-19 was associated with lower blood levels of interferon gamma (IFN-γ), vascular endothelial growth factor D (VEGF-D) and tumor necrosis factor alpha (TNF-α).[42] Inflammatory profiles of those with high genetic risk increasingly diverge from the norm in association with age and obesity. The authors allege that these results support the notion that individuals at risk of severe COVID-19 have a deficient innate immunity characterized by lower levels of inflammatory markers at baseline, including IFN-γ, VEGF-D and TNF-α; they hypothesize that a secondary overactive adaptive immune response may subsequently explain the high levels of cytokines observed in COVID-19 patients.

According to the results of the GenOMICC (Genetics Of Mortality In Critical Care) GWAS in 2,244 critically ill patients with COVID-19 from 208 UK intensive care units, critical illness may be related, among other mechanisms, to innate antiviral defenses, known to be important early in disease (interferon receptor gene IFNAR2 and antiviral restriction enzyme activators OAS genes), and host-driven inflammatory lung injury, a key mechanism of late, life-threatening COVID-19 (dipeptidyl peptidase 9-DPP9, tyrosine kinase 2-TYK2 and C-C chemokine receptor type 2-CCR2).[15]

MicroRNA

MicroRNAs (miRs) are gene expression regulators; their role, function, and/or association in COVID-19 infection is slowly being elucidated.[48] Several miRs have been identified to target SARS-CoV-2 specific genes, possibly acting by interfering with their cleavage and/or translation process. In addition, other miRs regulate the expression levels of the ACE2 and TMPRSS2 proteins, which are pivotal for the virus entry into the host cells.

Finally, relevant studies indicate the potential use of miRs as therapeutic targets against COVID-19. It is suggested that SARS-CoV-2 can adsorb host immune-related miR, which leads to immune system dysfunction of the host.[49] Furthermore, SARS-CoV-2 encodes its own miRs, which can enter host cell eluding detection by the host's immune system, and attack host function genes causing illness.

In this context, inflammation and cardiac myocyte-specific miRs, upregulated in critically ill COVID-19 patients, may be able to differentiate between severely ill, mechanically-ventilated Influenza-ARDS and COVID-19 patients, indicating a rather specific response and cardiac involvement of COVID-19. [50] Garg Finally, employing miR mimics to inhibit production of proteins involved in the cytokine storm might be important for the development of therapeutic approaches to combat COVID-19 induction of inflammatory responses.[51] Indeed, recent experimental data have suggested a miR candidate (miR-200c) that can target ACE2 in cardiomyocytes and thus employed as a preventive strategy to treat cardiovascular complications of COVID-19.[52]

Conclusion

The host genetic background seems to determine the susceptibility and outcome in COVID-19 patients. Mutations in the spike (S) glycoprotein of SARS-CoV-2 have been shown to enhance viral transmissibility and immune escape ability. Several relevant genetic variants and risk genes, potentially related to the inter-individual variability of COVID-19 susceptibility and/or severity, have been identified. They relate to blood type, HLA system, ACE-2 and TMPRSS2 proteins, cytokines, and other host genetic signals and immune system's response.

Thus, genetic and other association studies may assist the global scientific community and health care workers better understand how and why symptoms vary among COVID-19 patients and what role our DNA plays in whether we contract COVID-19 infection and how severe our symptoms might be. Furthermore, the results of such genetic studies relating to key host defense mechanisms against the virus and mediators of inflammatory organ damage, may lead to and/or guide targeted treatment with existing or new drugs. However, there is dire need for randomized clinical trials to evaluate such an approach.

Finally, the emerging new variants of the COVID-19 virus pose new risks relating to transmissibility and infectivity, and immune escape ability, albeit not to viral pathogenicity and COVID-19 severity (as yet), while they may have an impact on the efficacy of currently available vaccines. In the long run, "stopping the spread at the source remains key" while scaling up global vaccination (The effects of virus variants on COVID-19 vaccines (who.int)).

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