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LETTER TO THE EDITOR

WILEY

The impact of certain genetic variants (single nucleotide polymorphisms) on incidence and severity of COVID-19

Dear Editor,

The incidence of novel coronavirus disease (COVID-19) varies considerably between different countries and continents and, so far, there has been no clear explanation for this observation. Furthermore, there is a variation in disease severity, ranging from asymptomatic carriers and mild symptoms to a life-threatening illness that requires intensive care unit (ICU) admission and mechanical ventilation.[1] A few factors are linked to the severity of COVID-19, such as old age, multiple comorbidities and male sex.[2] However, severe illness has been observed in patients who do not have the above risk factors. Therefore, we would like to review whether genetic factors such as single nucleotide polymorphisms (SNPs) in certain genes could possibly have an impact on the variation in disease incidence and severity.

Novel coronavirus (SARS-CoV-2) enters the cells by binding with angiotensin-converting enzyme 2 (ACE2) receptor. This binding is facilitated by the activity of a human enzyme: type 2 transmembrane serine protease (TMPRSS2).[3] Therefore, SNPs in ACE2 gene that alter the structure of the proteins or the rate of ACE2 receptor expression could have an impact on the susceptibility to and severity of COVID-19. Calcagnile *et al.*[4] identified two ACE2 SNPs that affect the affinity of SARS-CoV-2 viral proteins to bind with ACE2 receptors. S19P SNP (rs73635825), which is common in Africans, decreases the binding affinity, whereas K26R SNP (rs1299103394), which is common in Europeans, increases the binding affinity.[4] Although this is not sufficient evidence, these findings could explain the considerable low incidence of COVID-19 in Africa compared to Europe. Hussain *et al.*[5] found that S19P variant has the lowest binding affinity to SARS-CoV-2 viral proteins compared to other ACE2 polymorphisms. They also found that S19P and E329G ACE2 SNP (rs143936283) increase the resistance to SARS-CoV-2 infection.[5] Moreover, Wooster *et al.*[6] identified that six SNPs in the ACE2 gene region that increase the expression level of ACE2 receptors are significantly associated with a higher risk of hospitalisation in patients with COVID-19. Interestingly, the expression of the TMPRSS2 gene increases in response to androgen hormone levels.[2] This could explain the higher risk of disease severity in male compared to female patients. There are three SNPs in TMPRSS2 (rs2070788, rs9974589 and rs7364083) that increase the expression level of TMPRSS2 and could be linked with an increased susceptibility to and severity of COVID-19.[2] The frequency of these genetic variants is significantly higher in Europeans.[2]

The excessive release of cytokines (known as a cytokine storm) in response to COVID-19 infection is the main pathological mechanism leading to lung injury and multi-organ damage.[3] SNPs in cytokine genes are linked to a higher chance of development of sepsis and septic shock.[7] Tumour necrosis factor (TNF)-2, a polymorphism in the promotor region of the TNF-α gene, can result in higher TNF-α levels, which subsequently increases the chance of development of septic shock and death.[8] Another polymorphism in the promotor region of TNF-α gene (G-308) increases the incidence and severity of infection in patients with COVID-19.[9] Furthermore, TNF-α promotor region variants were found to increase the risk of femoral head necrosis in patients who recovered from SARS-CoV infection.[10] An interleukin (IL)-1A genetic variant (rs1946518) was associated with increased nasopharyngeal viral shedding in patients infected with SARS-CoV.[11] An increased nasopharyngeal viral load is a marker that indicates the severity of infection in SARS disease. On the other hand, an SNP (rs315952) in the IL-1 receptor antagonist (IL-1 RN) gene increases the serum level of IL-1 receptor antagonist (IL-1 RA), which blocks the action of IL-1.[12] This polymorphism decreases the risk of development of acute respiratory distress syndrome and improves survival from septic shock,[12] which are the two main causes of ICU admission and mortality in COVID-19. The G1082A SNP in the IL-10 gene and the 174c polymorphism in the IL-6 gene are associated with higher IL-6 and IL-10 serum levels and an increased risk of pneumonia severity.[13,14] A high serum level of IL-6 is associated with severity of infection in COVID-19.[15] A meta-analysis showed that pharmacological IL-6 receptor antagonist was effective in the management of COVID-19.[14] This was evident as a result of a reduction in the serum level of C-reactive protein and an improvement of clinical symptoms following treatment. Indeed, SNPs in cytokine genes, particularly in IL-1A, TNF-α and IL-6, could increase the severity of infection in COVID-19. On the other hand, polymorphisms in the IL-1 RN gene might have a protective effect.

Mutations in other gene loci could have an impact on disease severity in COVID-19. Four genetic variants were detected in toll-like receptor 7 (TLR-7), which plays an important role in the innate antiviral immune response, in four young male patients with no significant past medical history who were admitted to the ICU with severe COVID-19.[16] These mutations suppressed the production of interferon, which subsequently weakened the immune response against the viral infection and predisposed to severe disease.[16] In addition to the TMPRSS2 gene, the expression of ACE2 gene is also androgen dependent.[17] It has been proposed that the length of the CAG repeat polymorphism in the androgen receptor is inversely linked with disease severity in COVID-19.[17] So far, this link has not been established, and McCoy *et al.*[17] are planning to conduct a clinical

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study to test this possibility. Indeed, four genetic variants identified in certain protease genes that alter the structure and function of the encoded protease proteins, which consequently cleave SARS-CoV-2 protein to facilitate viral cell entry, could be protective against and decrease the severity of COVID-19 infection.[18]

In conclusion, SNPs in ACE2, TMPRSS2, cytokines, TLR-7, androgen receptor and protease genes could have a significant impact on incidence and severity of COVID-19. Performing genetic analysis in patients with COVID-19 to detect these variants could help in risk stratification of patients to plan their management accordingly.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

A. Abobaker designed the article and drafted the initial manuscript. T. Nagib and A. Alsoufi reviewed and revised the manuscript for important intellectual content.

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