REVIEW PAPER

Genetic Susceptibility to Coronavirus Disease 19 (COVID-19): A Review

Tajudeen O. Yahaya [a] **Esther O. Oladele** [b] **Aliyu A. Turaki** [c] **Kelechi Nnochiril** [a] **Haliru Abdullahi** [a] **Josephine Nathaniel** [a]

Coresponding author(s): yahaya.tajudeen@fubk.edu.ng

[a]Department of Biology, Federal University Birnin Kebbi, PMB 1157, Birnin Kebbi, Nigeria,[b]Biology Unit, Distance Learning Institute, University of Lagos, Nigeria, and [c]Department of Biochemistry and Molecular Biology, Federal University Birnin Kebbi, Nigeria

Certain gene polymorphisms are suspected to contribute to the geographic-specific susceptibility of people to coronavirus disease 19 (COVID-19), which may be used as therapeutic targets. Accordingly, this review articulates suspected COVID-19 susceptibility genes to assist researchers and medical practitioners to formulate effective drug and treatment procedures. Reputable electronic academic databases, including PubMed, SpringerLink, and Scopus were searched for relevant information on the subject. The search identified seven COVID-19 susceptibility genes, which are TICAM2, TLRs, ACE, ABO blood group gene, HLA, and TMPRSS2. Polymorphisms in ACE and TMPRSS2 may increase or decrease the binding of the virus to the human cell, while polymorphisms in TICAM2, TLRs, and HLA may enhance or compromise the immune system. Type O blood group seems to be the most protective ABO blood group because of its abundant antibodies and blood clothing inhibition, while type A blood group is the least protective. The distribution of the polymorphisms is influenced by geographical locations, which could contribute to the worldwide differential vulnerability of people to the disease. Most protective polymorphisms are prevalent among Africans and Asians, which could be the reason for their less susceptibility to the disease compared to Europeans and Americans. Most of these genes are X-linked, which could partly explain the dominance of the severe form of the disease among men than women. Overall, these show that polymorphisms in certain genes may modulate COVID-19 infectivity and severity. Thus, a thorough understanding of the biological mechanisms of these genes may help design a cure.

| COVID-19 | Gene | Immune system | Susceptibility | | X-chromosome |

The causative agent of coronavirus disease 19 (COVID-19) known as the severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) was first reported in Wuhan, China in December 2019 (1). Shortly after, the International Committee on Taxonomy of Viruses classified the virus as a member of the species of severe acute respiratory syndrome-related coronavirus (2). Phylogenetic analyses further indicated that SARS-CoV-2 belongs to the subgenus Sarbecovirus and genus Betacoronavirus as was severe acute respiratory syndrome (SARS-CoV) (3). These classifications bring to three the number of human coronaviruses (HCoV) that had emerged and spread in human populations in recent times. Aside from SARS-CoV mentioned above, the other HCoV that has emerged previously is the Middle East respiratory syndrome coronavirus (MERS-CoV). Being in the same genus, SARS-CoV and SARS-CoV-2 are more related (about 80% genetically compatible) than MERS-CoV, which belongs to the subgenus Merbecovirus (4, 5).

Coronaviruses are highly pathogenic with symptoms ranging from mild to moderate and severe respiratory illness, but SARS-CoV-2 could be asymptomatic in some cases. Coronaviruses spread primarily through saliva droplets and nasal discharges when coughing and sneezing, respectively (6). SARS-CoV-2 is particularly very pathogenic as evident in its transition to a global pandemic within a few months of the outbreak, affecting around 210 countries (7). The disease has caused a global lockdown of activities and unprecedented health burdens in recent times. As of June 14, 2020, cases and mortality of COVID-19 worldwide had reached 7,896,400 million and 432,887, respectively (8). In Nigeria, as of 13th June 2020, 15, 682 cases and 407 deaths have been recorded (9). The high incidence and mortality of COVID-19 have resulted in huge economic losses and gradually drifting the world into a recession. As of April 2020, the United States unemployment rate has risen to a record 14.7%, with over 20 million jobs lost in March (7). The European

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Union gross domestic product is predicted to drop by 7.5% during 2020 (7).

According to United Nations Economic Commission for Africa, around half of jobs in Africa could be lost to the COVID-19 outbreak (7). As of this date, the incidence and mortality of the disease are still increasing, indicating that its burden could be worse. Concerns are rife worldwide because up till this moment, no drug or treatment procedure has been certified safe and effective for the disease. This has put scientists in a frantic search for a cure and one area which some scientists opined can be leveraged on is the virus's selective infectivity and pathogenicity. Some people appear to be immune to the virus, while others are susceptible, suggestive of certain genetic and environmental predisposing factors. It is believed that these factors may be employed as therapeutic targets to develop drugs and vaccines. Understanding the selective infectivity of the virus may also help identify individuals that are at risk, which may be used as a preventive measure. It may also be used to prevent or manage the future occurrences of the disease. To this end, some researchers have identified certain genes whose polymorphisms or mutations may protect or predispose to the disease. This review was initiated to articulate the identified genes to guide researchers and medical practitioners in the search for a COVID-19 cure.

Material and Methods

Databases Searched and Search Terms

Academic databases searched for relevant information on the topic include Scopus, PubMed, SpringerLink. Search terms used to retrieve articles are 'coronavirus', 'COVID-19', 'severe acute respiratory syndrome', 'SARS-COV-2', 'genes predisposing to coronavirus diseases', and 'coronavirus susceptibility genes'. Other search terms used include 'coronavirus overview', 'incidence of COVID-19', 'prevalence of COVID-19', 'mortality of COVID-19', and 'economic burden of COVID-19'. The articles retrieved were pooled together and double citations removed using EndNote software.

Article Inclusion Criteria

- Research published in the English language.
- Research that focused on COVID-19.
- Studies that focused on the genetic basis of COVID-19.
- Studies that centered on the prevalence and mortality of COVID-19.

Article Exclusion Criteria

- Studies that are not available in the English language.
- Studies with only abstract available.
- Research that described COVID-19, but with no clear genetic mechanisms.

Genetic susceptibility to COVID-19

To infect a person, a virus invades the cell, hijacks the cellular mechanisms, and reconfigures the cell to produce copies of the virus, thus infecting more cells, and so on. Normally, when a virus infects human cells, the immune mechanism becomes activated, identifies the virus, and sends a subtype of white blood cells called cytotoxic T cells to destroy the infected cells and slow the infection (10). However, some individuals have different alleles of the genes that make up the immune system, some of which predispose to microbial infection (11), while some protect. Based on the foregoing, Darbeheshti and Rezaei (12) proposed three models of genetic variations among humans, which may produce differential susceptibility to COVID-19. These include common genetic variants in multiple loci with weak effects individually, but additively increase the infection risk and severity of individuals. Moderately rare variants in few genes may also combine to increase susceptibility to COVID-19. Some of these rare variants may be dominant and could be responsible for the severe infection noticed in some young patients expressing no underlying medical condition. Moreover, genetic and environmental factors such as smoking and pollution exposure increase an individual's susceptibility to COVID-19. This review identified seven genes whose polymorphisms or mutations may employ one or more of the above models to protect or predispose to COVID-19.

TICAM2 and TLRs

Toll-Like Receptor Adaptor Molecule 2 (TICAM2) codes for a protein that helps activate a family of receptors called toll-like receptors (TLRs) (13). Toll-Like Receptors (TLR) are important components of the innate immune system (14). They constitute a multigenic family of receptors, which collectively bind several types of exogenous and endogenous ligands (14). Studies show that TLRs functionally fight against infections and autoimmunity and thus can be viewed as a structurally distinct counterpart of major histocompatibility complex (MHC) (14). To date, 10 TLRs termed TLR1 to TLR10 have been described in human genomes (14). The TLRs recognize microbes by pairing with each other. The pairing of TLR1 and 2 or TLR2 and 6 recognizes bacteria, such as those that cause tuberculosis (15). The TLR3 recognizes certain viruses, while TLR4 recognizes certain molecules on bacteria found in the gastrointestinal tract such as E. coli (15). The TLR5 recognizes whip-like structures on bacteria called flagella, and TLR 7, 8, and 9 recognize certain viruses such as influenza and human immunodeficiency virus I (HIV-I) (15). After sensing a viral or microbial molecule, TLRs begin a series of chemical reactions that signal the innate immune cells to produce type I interferons (IFNs), other cytokines, and chemokines, killing the microbes (15,16). However, TLRs are highly polymorphic, some may hinder the recruitment of immune cells and predispose humans to microbial infection (14, 15), including coronaviruses.

Several instances in which mutations in TLRs predispose to infections have been reported. In a cross-mouse multi-parent population, strains with TICAM2 deletion, causing loss of function of TLRs, were highly susceptible to SARS-CoV infection (17). The mice exhibited increased weight loss and pulmonary hemorrhage than control mice (17). These results suggest an important role for TICAM2 in SARS-CoV disease (17). Given the genetic compatibility of SARS-CoV and SARS-CoV-2, it is expected that the gene will also contribute to the genetic susceptibility of individuals to SARS-CoV-2. Beyond this, the gene may help explain the observed high proportion of men who suffer from severe COVID-19 compared to women (13). Though behavioral and hormonal differences may be partly responsible for the differences, genetic factors, particularly mutation in the TLR7 gene, may also be involved (13). The gene is X-linked, thus making men more predisposed because men have one copy of the X chromosome, unlike women who carry two copies. It then follows that if one TLR7 gene is mutated in a female, the other will make up for it and prevent the infection.

ABO Blood Gene

Polymorphisms in the ABO blood gene are suspected to contribute to the differential susceptibility of humans to microbial infections, including SARS-CoV-2. The ABO gene contains three alleles, two of which encode different enzymes that coat the surface of red blood cells (RBC) with certain sugar molecules (glycoprotein). The sugar molecules are often referred to as antigens and tagged type A and B, respectively. The third allele is inactive and

thus lacks enzyme and sugar molecule on the surface of RBC and is referred to as type O. Based on the Mendelian principle, an individual can only inherit two alleles for a trait, so the possible ABO blood group genotype (allelic combination) of an individual are AA, AO, AB, BB, BO, or OO. Being inactive, type O is recessive, thus giving rise to four ABO blood group phenotypes, namely; type A (AA or AO), type B (BB or BO), type AB and type O. So, individuals expressing A antigen are type A, B antigen are type B, both A and B are type AB, and type O has neither antigen (16). Accordingly, the immune systems of type A blood develops antibodies for B antigen, type B has antibodies for A antigen, type O has antibodies for both, and AB type has none (18, 13). This shows that, in the ABO blood group system, type O blood is the richest in antibodies, possessing both antibodies A and B, whereas type AB blood has neither of them (13). This could explain, in part, the reason type O blood is protective against certain microbial infections, including SARS-CoV-2.

Furthermore, the spikes of SARS-CoV-2, which are important molecules the virus uses to infect cells, contain numerous sugars, which are bound using the host cell enzymes (18). As a result, the spike protein of coronavirus particles often carries the blood group sugar antigen of the infected host cells (18). So, when an infected person coughs or sneezes, viral particles coated in the blood type antigens of the person are released. If an individual with type A blood transmits the virus to a person with type O blood, the type O individual may resist it because it has numerous antibodies to fight the virus. However, if the person who inhaled the particles is also type A, he/she may not have antibody to resist it (18). This finding is corroborated by a study that monitored the transmission of SARS-CoV among 45 exposed healthcare workers in a Hong Kong hospital, China. Of the 19 people with type O blood, 8 became infected, but of the 26 people with other blood types, 23 became infected (19). The ABO blood group antibodies also react differently to the angiotensin-converting enzyme 2 (ACE2) receptor, which is necessary for SARS-CoV-2 to bind to the body cells. Guillon et al. (20) demonstrated that SARS-CoV spike protein's binding to ACE2 is inhibited by the anti-A antibody. Anti-A antibody is secreted by type B blood, which may point to the protective advantage of type B blood over type A if the latter lacks the property. However, the reaction of anti-B antibody could not be ascertained in the studies due to a lack of data. Aside from the effect of blood type antibodies, blood types also influence blood clotting, which is an important pathology of COVID-19. Studies show that COVID-19 often involves overactive blood clotting, which is suppressed by type O blood. People with type O blood have lower levels of proteins that promote blood clotting, which may lead to reduced severity of COVID-19 in the affected (18).

Most studies conducted on the association of ABO blood types with COVID-19 proved that type A blood is more susceptible, while type O is protective. In one study, researchers sequenced the genomes of 1,610 COVID-19 patients in Spain and Italy and compared their DNA to those of 2,245 healthy subjects (19). In all, the scientists analyzed 8,582,968 single-nucleotide polymorphisms (SNPs) and found two regions of DNA in which sequence variations were related to the severity of the disease. One of the regions is 9q34 which encodes ABO blood group genes, while the other is the 3p21.31 region that encodes the ACE2 gene. When the patients were grouped according to blood types, individuals with type A had a higher chance of developing severe respiratory failure compared with type O (21). In another study, a retrospective cohort study of SARS-CoV-2 patients in three hospitals in China also associated the prevalence and severity of the virus with blood types. In the study, the proportions of type A and O blood in SARS-CoV-2 patients were significantly higher and lower, respectively, than that in healthy controls (22). This shows that blood group A patients were at higher risk of hospitalization following SARS-CoV-2 infection, while blood group O patients had a lower risk (22). This further suggests that ABO blood types could be used as a biomarker to predict the risk of SARS-CoV-2 infection (22). However, no relationship was found between the ABO blood types and differential susceptibility to COVID-19 in the United States (18). Type O blood is more prevalent among African Americans in the United States, yet African Americans exhibited high incident rates (23). This suggests that blood types might contribute a minor effect to the variability observed in SARV-CoV-2 infectivity and severity (18) and that other factors might be involved. Most studies did not report an association between blood type B and AB, probably due to a lack of sufficient data (18). This may reflect the low prevalence of the blood types in human populations, particularly where some of these studies were carried out.

ACE

The ACE genes code for the angiotensin-converting enzymes (24). They are part of the renin-angiotensin system, which regulates blood pressure as well as body fluids and salts (24). The ACE enzymes can cleave proteins and, by cutting a protein called angiotensin I, the angiotensin-converting enzyme converts this protein to angiotensin II (24). Angiotensin II causes blood vessels to constrict, resulting in increased blood pressure (24). This protein also stimulates the production of the hormone aldosterone, which triggers the absorption of salt and water by the kidneys (24). The increased concentrations of fluid in the body also increase blood pressure (24). Proper blood pressure during fetal growth, which delivers oxygen to the developing tissues, is required for the normal development of the kidneys (24). Among the ACE gene family, in order of importance, angiotensin-converting enzyme 2 (ACE2) and angiotensin-converting enzyme 1 (ACE1) are associated with coronavirus infection and severity (13).

The receptor-binding domain of the COVID-19 spike-protein shows a strong interaction with the ACE2 receptor (25). It has been shown that similar to SARS-CoV, the SARS-CoV-2 spike protein binds to ACE2 to enter cells (26, 27). Spike glycoproteins comprise two major functional domains, which are the N-terminal domain (S1) for binding to the host cell receptor, and a C-terminal domain (S2) that is responsible for the fusion of the viral and cellular membranes (28). SARS-CoV-2 and SARS-CoV spike proteins share very high phylogenetic similarities, about 99% (29, 30). However, SARS-CoV-2's S-protein has accumulated mutations that increase its binding to ACE2 by about 10-15-fold compared to SARS-CoV's S-protein, making it more infectious (31). Considering the importance of ACE2 receptor to viral infection, genetic variants that affect its expression, conformation, and stability can alter genetic predisposition to COVID-19 (25). ACE2 is expressed on the surface of type II lung alveolar epithelial cells and its mRNAs are expressed in almost all organs, including the heart, blood vessels, kidney, and testis (27, 32). This indicates that loss of function of ACE2 gene due to massive binding of coronavirus can cause multi-organ damage as evidenced in COVID-19 [32, 36). Mouse experiments with ACE2 gene knockout expressed pulmonary vascular congestion, increased lung weight, congestive heart failure, and death (33). ACE2 differential cellular expression and polymorphisms have also been reported in humans, which could partly explain varied susceptibility to SARS-CoV-2 (26). Calcagnile et al. (27) identified two single-nucleotide polymorphisms (SNPs) of the ACE2 gene, which are S19P (common among Africans) and K26R (common among Europeans). The S19P decreases, while K26R increases the ACE2 binding to SARS-CoV-2 spike, suggesting that the S19P genetically protects, while K26R predisposes to more severe SARS-CoV-2 disease (27). This can partly explain varied ethnic and geographical

susceptibility to the disease. In a study that examines the binding of ACE2 allelic proteins with SARS-CoV-2 spike protein, again, S19P (rs73635825) allele and E329G (rs143936283) allele were found protective (34). However, in a study by Stawiski et al. (31), S19P was included among ACE2 variants that increase susceptibility to SARS-CoV-2; along with others such as I21V, E23K, K26R, T27A, N64K, T92I, Q102P, and H378R. Other ACE2 variants detected were protective, which include T92I K31R, N33I, H34R, E35K, E37K, D38V, Y50F, N51S, M62V, K68E, F72V, Y83H, G326E, G352V, D355N, Q388L, and D509Y (31).

Varied expression of ACE2 may also explain the COVID-19 differential susceptibility and severity of men versus women. Estrogen-induced overexpression of ACE2 may increase the susceptibility of some women to COVID-19, but less severe and often asymptomatic (27). Furthermore, the ACE2 gene is located on Xp22, in an area where genes may escape from X-inactivation, which further explains the increased susceptibility of some females (27). Generally, men showed higher incidences and mortality of COVID-19, probably due to underlying conditions such as cardiac, respiratory, and metabolic co-morbidities (27). The X-linked inheritance pattern of the ACE2 gene might also be another reason for the high prevalence and severity of COVID-19 in men than in women (35). However, regardless of sex, antihypertensive drugs, such as ACE inhibitors and sartans, which can increase ACE2 expression, may increase susceptibility and severity of COVID-19 (36). Environmental factors such as nitrogen dioxide exposure may overexpress ACE2 and increase susceptibility and severity of infection (36). In brief, ACE2 plays a dual role in infection mounting and pathogenesis. First, its overexpression promotes the entry of the virus into the cell as well as its replication. Second, its loss of function due to viral load causes accumulation of angiotensin II that further aggravates the acute lung injury observed in infected individuals (27). However, certain polymorphisms in the ACE2 gene such as the S19P mentioned earlier could reduce the spike affinity, subsequently lowering susceptibility to infection (27).

A close relative of ACE2 in blood pressure control is angiotensin-converting enzyme 1 (ACE1) (13). The ACE1D, one of the several genetic variants of the enzyme involving a deletion or insertion, reduces the expression of the ACE2 gene and thus prevents SARS-CoV infection (13). The frequency of ACE1D differs from one country to another, particularly in Europe, and reflects the global epidemiological incidence of the disease (13). Data from 25 countries, mainly Europe and Asia, showed that some variability in disease prevalence and mortality is explained by the frequency of the ACE1D variant (37). The study also noted that the ACE1D variant is less frequent in China and South Korea, which were severely hit by SARS-CoV-2 (37). However, an earlier study by Chan et al. (38) found no association between the ACE1D variant and the frequency and severity of SARS-CoV infection.

HLA

Some genetic susceptibility to COVID-19 may reside in the genes that encode human leukocyte antigens (HLAs), which is a set of proteins that prevent the immune system from attacking self-cells (13). Each individual has several alleles of the HLA genes and each allele codes for a different HLA protein (11). These proteins constitute the major histocompatibility complex (MHC), which distinguishes self from foreign antigens (13). The proteins bind to the peptides of foreign antigens and carry them to the cell surface, where they are killed by the immune system (11). The higher the number of virus peptides or other microbes a person's HLA genes can detect, the stronger the immune response (11). Given the role of HLA genes in immune maintenance, it is very likely a link exists between HLA genes and COVID-19 infectivity and pathogenicity. Indeed, some scientists, including Nguyen et al (8) have established a link between certain HLA gene variants and susceptibility to COVID-19. The scientists observed that, among other alleles, individuals expressing the HLA-B*46:01 variant were most at risk of SARS-CoV-2 infection, as was observed during the SARS-CoV epidemic (8). Whereas, individuals expressing the HLA-B*15:03 variant were the most protected. In a computer modeling experiment by Nguyen et al (10), some HLA alleles bind to numerous SARS-CoV-2 peptides while others bind to very few. This again suggests that the HLA genes of some individuals are genetically programmed to resist SARS-CoV-2 infections, while others may be genetically predisposed. When SARS-CoV-2 was compared with SARS-CoV retrospectively, the HLA gene alleles react the same way, which could be due to the genetic compatibility of the two viruses. The study again observed that the B46:01 allele increases susceptibility to both SARS-CoV-2 and SARS-CoV (11).

Though there is no scientific evidence yet linking HLA allele geographical distribution with the differential vulnerability of COVID-19 (39, 40), there are some evidence pointing along the direction. The predisposing allele, HLA-B*46:01 is prevalent among the Southeast Asian descent, and the Southeast Asia continent, a region that experienced a high incidence of COVID-19 (41). On the contrary, the predisposing allele is absent in regions with a low incidence of the disease such as India and Africa, and rarely present in Europe (40, 42). The protective allele, HLA-B*15:03 is absent among East Asians while it is the most dominant allele among African descent (40, 42). Another protective allele, HLA-A*02, is common among Indian and African populations, while a susceptibility allele, HLA-C*12:03, is the most frequent allele among European descent (40, 42). These show that HLA alleles might, in part, be responsible for the differential susceptibility of SARS-CoV-2 worldwide. According to Zahn (43), most people carry between three and six different HLA alleles that show geographically specific distributions.

TMPRSS2

The Transmembrane Serine Protease 2 (TMPRSS2) is an androgen-responsive serine protease that cleaves SARS-CoV-2 spike protein, facilitating viral entry and activation (44). TMPRSS2 is highly expressed in the lung (45) as well as cardiac endothelium, kidney, and digestive tract, suggesting that these organs may be targeted by SARS-CoV-2 (46). TMPRSS2 works synergistically with ACE2 to initiate and maintain infection. After the spike (S) protein on SARS-CoV-2 binds ACE2, transmembrane protease serine 2 primes the S protein to allow cellular uptake of the virus (45). Therefore, individual expression of TMPRSS2 may be an important determinant of SARS-CoV-2 susceptibility (45, 47). In a cohort study that investigated TMPRSS2 expression in the lungs of people from different continents, four variants, namely rs464397, rs469390, rs2070788, and rs383510 significantly affect TMPRSS2 expression (45). The results showed that TMPRSS2 upregulating variants (rs464397, rs383510, and rs469390) are present at higher frequencies among Europeans and Americans than in Asians, which implies that the former might be at increased risk of SARS-CoV-2 infection (45). Similar findings were observed in another study that compared the TMPRSS2 pulmonary expression between European and East Asia subjects. The European populations had higher levels of pulmonary expression of the TMPRSS2 gene, suggesting that the gene increased their vulnerability to SARS-CoV-2 (48). The findings of these studies suggest that the TMPRSS2 gene may be responsible for the higher prevalence and mortality of COVID-19 among European populations than eastern Asians. TMPRSS2 has also been observed to be modulated by sex steroids, which could have contributed to the worldwide reported increased vulnerability

of men to SARS-CoV-2 compared with women (49).

TMPRSS2 protein has no known indispensable function, thus, it could be considered a good therapeutic target for COVID-19 and related diseases (49). The therapeutic target of the gene is appealing because its inhibitors are available (49). In an in vitro study, an inhibitor of the protease activity of TMPRSS2, camostat mesylate, partially inhibited the entry of SARS-CoV-2 into the lung epithelial cells (44). Moreover, in a TMPRSS2 knockout model, mice infected with the H1N1 influenza virus showed a small viral load, mild symptoms, and no death compared with control (50). These make it tempting to speculate that androgen receptor{inhibitory therapies might reduce susceptibility to COVID-19 pulmonary symptoms and mortality (49).

Conclusion

The review discovered that polymorphisms in TICAM2, TLRs, ACE, ABO blood group gene, HLA, and TMPRSS2 may modify an individual's susceptibility to COVID-19. ACE and TMPRSS2 variants may affect the attachment of the virus's spike protein to the membrane of the human cell, increasing or reducing viral loads. Polymorphisms in TICAM2, TLRs, and HLA may disrupt or boost the innate immunity, increasing or decreasing susceptibility to COVID-19. Type O blood contains numerous antibodies, making it the most protective ABO blood type, while type A is the least protective blood type. Type O blood also inhibits blood clotting, reducing the severity of the disease. The frequency of the polymorphisms of each gene varies worldwide, which could, in part, explain the differential vulnerability of people to the disease. Africa and Asia have higher frequencies of the beneficial variants than Europe and the United States, which revealed why Africans and Asians are less susceptible. Some of the genes are X-linked, which could partly explain the dominance of the severe form of the disease among men than women. A proper understanding of the biological functions of these genes may provide information for designing effective drugs and treatment procedures.

Conflict of interest

Authors declare no conflict of interest.

Authors' contributions

TY conceptualized, did literature search, wrote the article, and did corresponding. EO and AT did literature search and proofreading. KN, HA, and JN did article sorting and referencing. All authors have read and approved the final document.

1. Zhu N, Zhang D, Wang W, et al. (2020). A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 382 (8):727{733.
2. Coronaviridae Study Group of the ICTV (2020). The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol 5:236{544.
3. Peng Z, Xing-Lou Y, Xian-Guang W, et al. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat Origin. Nature 579(7798):270{273.
4. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H. (2020). Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. The Lancet 395(10224):565{574.
5. Sironi M, Hasnain SE, Rosenthal B, et al. (2020). SARS-CoV-2 and COVID-19: A genetic, epidemiological, and evolutionary perspective. Infect Genet Evol 84:104384.
6. World Health Organization (2020). Coronavirus disease (COVID-19) outbreak. Available at https://www.who.int/health-topics/coronavirus tab=tab 1.
7. World Economic Forum (2020). The economic effects of COVID-19 around the world. Available at https://www.weforum.org/agenda/2020/02/coronavirus-economic-effects-global-economy-trade-travel/.
8. Worldometer (2020). Covid-19 Coronavirus Pandemic. Available at https://www.worldometers.info/coronavirus/?utm campaign=homeAdvegas1?%22%20%5CI%20%22.
9. Nairametrics (2020). COVID-19 Update in Nigeria.Available at https://nairametrics.com/2020/06/14/covid-19-update-in-nigeria/.
10. Nguyen A, David JK, Maden SK, et al. (2020). Human leukocyte antigen susceptibility map for severe acute respiratory syndrome coronavirus 2. J Virol 94:e00510-20.
11. Nguyen A, Nello A, Thompson R. (2020). Your genes could determine whether the coronavirus puts you in the hospital { and we're starting to unravel which ones matter. The Conversation-Academic rigour journalistic fair. Available at https://theconversation.com/your-genes-could-determine-whether-the-coronavirus-puts-you-in-the-hospital-and-were-starting-to-unravel-which-ones-matter-137145.
12. Darbeheshti F, Rezaei N. (2020). Genetic predisposition models to COVID-19 infection. Med Hypotheses 6:142.
13. Mangin L (2020). Do Your Genes Predispose You to COVID-19? Scientific America. Available at https://www.scientificamerican.com/article/do-your-genes-predispose-you-to-covid-19/ (Accessed June 11, 2020).
14. Georgel P, Macquin C, Bahram S. (2009). The Heterogeneous Allelic Repertoire of Human Toll-Like Receptor (TLR) Genes. PLoS ONE 4(11): e7803.
15. Immune Deficiency Foundation (2020). Innate Immune Defects. Available at https://primaryimmune.org/about-primary-immunodeficiencies/specific-disease-types/innate-immune-defects.
16. Mazaleuskaya L, Veltrop R, Ikpeze N, Martin-Garcia J, Navas-Martin S. (2012). Protective role of Toll-like Receptor 3-induced type I interferon in murine coronavirus infection of macrophages. Viruses 4(5):901-23.
17. Gralinski LE, Menachery VD, Morgan AP, et al. (2017). Allelic Variation in the Toll-Like Receptor Adaptor Protein Ticam2 Contributes to SARS-Coronavirus Pathogenesis in Mice. G3 7: 1653-1663.
18. Katsnelson A. (2020). Genetic study suggests that people's blood type may affect their COVID-19 risk. c en 98 (23). Available at https://cen.acs.org/biological-chemistry/infectious-disease/Genetic-study-suggests-peoples-blood/98/i23.
19. Cheng Y, Cheng G, Chui C, et al. (2005). ABO Blood Group and Susceptibility to Severe Acute Respiratory Syndrome. JAMA 293(12):1447-1451.
20. Guillon P, Clément M, Sebille V, et al. (2008). Inhibition of the interaction between the SARS-CoV Spike protein and its cellular receptor by anti-histo-blood group antibodies. Glycobiology 18 (12): 1085{1093.
21. Ellinghaus D, Degenhardt F, Bujanda L, et al. (2020). The ABO blood group locus and a chromosome 3 gene cluster associate with SARS-CoV-2 respiratory failure in an Italian-Spanish genome-wide association analysis. medRxiv (preprint).
22. Li J, Wang X, Chen J, Cai Y, Deng A, Yang M. (2020). Association between ABO blood groups and risk of SARS-CoV-2 pneumonia. British J Haematol 1-4.
23. Yancy CW. (2020). COVID-19 and African Americans. JAMA 323 (19):1891{1892.
24. Genetics Home Reference (2020). ACE gene. Available at https://ghr.nlm.nih.gov/gene/ACE.
25. Cao Y, Li L, Feng Z, Wan S, Huang P, Sun X. (2020). Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. Cell Discov 6(1):1{4.
26. Devaux CA, Rolain J-M, Raoult D. (2020). ACE2 receptor polymorphism: Susceptibility to SARS-CoV-2, hypertension, multi-organ failure, and COVID-19 disease outcome. J Microbiol Immunol Infect 53 (3): 425-435.
27. Calcagnile M, Forgez P, Iannelli A, Bucci C, Alifano M, Alifano P. (2020). ACE2 polymorphisms and individual susceptibility to SARS-CoV-2 infection: insights from an in silico study. bioRxiv (preprint)
28. Belouzard S, Millet JK, Licitra BN, Whittaker GR. (2012). Mechanisms of coronavirus cell entry mediated by the viral spike protein. Viruses 4: 1011-1033.
29. Walls AC, Park Y-J, Tortorici MA, Wall A, McGuire AT, Veesler D. (2020). Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell 181 (2): 281-292.e6.
30. Wrapp D, Wang N, Corbett KS, et al. (2020). Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 367: 1260-1263.
31. Stawiski EW, Diwanji D, Suryamohan K, et al. (2020). Human ACE2 receptor polymorphisms predict SARS-CoV-2 susceptibility. bioRxiv (preprint).
32. Tipnis SR, Hooper NM, Hyde R, Karran E, Christie G, Turner AJ. (2000). A human homolog of angiotensin-converting enzyme. Cloning and functional expression as a captopril-insensitive carboxypeptidase. J BiolChem 275:33238-33243.
33. Cirulli ET, Riffle S, Bolze A, Washington NL. (2020). Revealing variants in SARS-CoV-2 interaction domain of ACE2 and loss of function intolerance through analysis of >200,000 exomes. bioRxiv (preprint).
34. Hussain M, Jabeen N, Raza F, et al. (2020). Structural variations in human ACE2 may influence its binding with SARS-CoV-2 spike protein. J Med Virol 92(9):1580-1586.
35. Cai H. (2020). Sex difference and smoking predisposition in patients with COVID-19. Lancet Respir Med 8(4):e20
36. Alifano M, Alifano P, Forgez P, Iannelli A. (2020). Renin-angiotensin system at the heart of COVID-19 pandemic. Biochimie 174:30-33.

37. Delanghe JR, Speeckaert MM, De Buyzere ML. (2020). The host's angiotensin-converting enzyme polymorphism may explain epidemiological findings in COVID-19 infections. Clin Chim Acta 505:192-193.
38. Chan KA, Tang NL, Hui, DS, et al. (2005). Absence of association between angiotensin converting enzyme polymorphism and development of adult respiratory distress syndrome in patients with severe acute respiratory syndrome: a case control study. BMC Infect Dis 5:26.
39. Sanchez-Mazas A. (2020). HLA studies in the context of coronavirus outbreaks. Swiss Med Wkly 150: w20248.
40. Debnath M, Banerjee M, Berk M. (2020). Genetic gateways to COVID-19 infection: Implications for risk, severity, and outcomes. FASEB J 34 (7): 8787-8795.
41. González-Galarza F, Takeshita L, Santos E, et al. (2015). Allele frequency net 2015 update: new features for HLA epitopes, KIR and disease and HLA adverse drug reaction associations. Nucleic Acids Res 43: D784-D788.
42. Allele Frequency Databases (AFND) (2020). Allele Frequency in Worldwide Population. http://www.allelefrequencies.net/hla6006a.asp. (Accessed on June 20, 2020).
43. Zahn LM. (2020). HLA genetics and COVID-19. Science 368 (6493): 841.
44. Hoffmann M, Kleine-Weber H, Schroeder S, et al. (2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181(2):271-280.
45. Irham LM, Chou W-H, Calkins MJ, Adikusuma W, Shie-LiangHsieh S-L, Chang W-C. (2020). Genetic variants that influence SARS-CoV-2 receptor TMPRSS2 expression among population cohorts from multiple continents. Biochem Biophys Res Commun 529 (2): 263-269.
46. Bertram S, Heurich A, Lavender H, et al. (2012). Influenza and SARS coronavirus activating proteases TMPRSS2 and HAT are expressed at multiple sites in human respiratory and gastrointestinal tracts. PLoS One 7 (4):e35876.
47. Maya EAL, van der Graaf A, Lanting P, et al. (2020). Lack of Association Between Genetic Variants at ACE2 and TMPRSS2 Genes Involved in SARS-CoV-2 Infection and Human Quantitative Phenotypes. Front Genet 11:613.
48. dos Santos NPC, Khayat AS, Rodrigues JCG, et al. (2020). TMPRSS2 variants and their susceptibility to COVID-19: focus in East Asian and European populations. medRxiv (preprint).
49. Stopsack KH, Mucci LA, Antonarakis ES, Nelson PS, Kantoff PW. (2020). TMPRSS2 and COVID-19: Serendipity or Opportunity for Intervention? Cancer Discov 10 (6):779{82.
50. Hatesuer B, Bertram S, Mehnert N, et al. (2013). Tmprss2 is essential for influenza H1N1 virus pathogenesis in mice. PLoS Pathog 9:e1003774.