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Mutations and polymorphisms in genes involved in the infections by covid 19: a review

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ABSTRACT

Covid19 is the third most aggressive coronavirus that spreads rapidly and kills many people. It is a multigenic and multifactorial disease with many genetic and environmental determinants. The identification of these factors is key to better understanding the etiology of Covid-19 and it can also help predict the risk and prevent Covid-19 infection.

Many predisposing factors have been described for this coronavirus such as advanced age, male gender, and geographic location. In addition to these elements, genetic factors have an important role in Covid19 infection. Interindividual variation in susceptibility to infection by Covid-19 has been associated with to the presence of genetic polymorphisms in many genes, especially in those that code for proteins implicated in the infection process. The present review gives a brief overview of different genes involved in the infection by SARS-CoV-2 and its association with disease severity.

The results of our research showed that many different genes are associated with a higher risk for COVID-19, notably those coding for proteins involved in coronavirus-cell entry and fusion such as ACE2 (angiotensin I converting enzyme 2), TMPRSS2 (transmembrane protease, serine 2) and CD26.

1. Introduction

The newly identified Coronavirus (Corona Virus Disease) is named after the year of the virus isolation 2019, "COVID-19" by the World Health Organization (WHO). The third most aggressive coronavirus is identified for the first time in Wuhan (China) at the end of the year 2019. It belongs to the beta-Coronaviridae family and it's similar to severe acute respiratory syndrome coronavirus (SARS-CoV), they share similar characteristics with an identity of more than 80%, so COVID-19 is also named SARS-CoV-2 (Alshami et al., 2020; de Wit et al., 2016). Worldwide, the number of confirmed cases and deaths linked to the Covid-19 pandemic dramatically increases every day, this virus has killed more than 881 K people to date (https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200501-covid-19-sitrep.pdf?sfvrsn=742f4a18_4).

COVID-19 can be either silent (asymptomatic) or associated with many symptoms, such as familiar cold symptoms (fever, stuffy nose, cough, Sore throat, weakness) bronchitis and pneumonia (Singhal, 2020).

Many Risk factors have been described for this coronavirus such as elderly age, male gender, race, obesity, hypertension, diabetes and

geographic region (COVID-19 Research Consortium et al., 2020; Scully et al., 2020). In addition to these elements, genetic factors also play a major role in Covid19 infection. Interindividual inherited differences in susceptibility to SARS-CoV-2 infection is linked to the presence of genetic polymorphisms (variants) in many genes especially in those that code for the host receptors involved in viral entry process. These DNA changes are transmissible from one generation to another, detectable in at least 1% of individuals in a population and could explain the differences between individuals in the susceptibility to some multigenic, complex diseases like Covid19 (Torres et al., 2004; Sieńko et al., 2020a). Two main approaches can be used in genetic epidemiology to establish a link between genetic variations and the risk of developing a disease: Genetic linkage analysis and Association studies (candidate gene and genome-wide association studies) (Tabor et al., 2002).

The aim of the present study was to provide an up-to-date view of the published results about genetic polymorphisms involved in the infection by SARS-CoV2. For that a bibliographic search was conducted on the electronic databases PubMed, Scopus and Google Scholar, by using the following keywords "Gene; polymorphism; mutation; risk; susceptibility; COVID-19; SARS-CoV-2; association; correlation". The selected studies were screened (by reading the title, the abstract and the entire

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article), studies linked to our subject were included in the current review while, duplicates, review articles, abstracts, non English studies, book chapter and studies that not meet the purpose of the research were excluded.

Our literature search results showed that many different genes are associated with a higher risk for COVID-19, notably those coding for the receptors ACE2 (angiotensin I converting enzyme 2), TMPRSS2 (transmembrane protease, serine 2) and CD26 [Table 1](#).

1.1. ACE gene (chromosome Xp22.2)

Angiotensin-converting enzyme (ACE) is the enzyme responsible for converting angiotensin-2 to Angiotensin (1–7) form ([Guo et al., 2020](#)). it is expressed in most organs such as, thyroid and lungs, heart, esophagus, kidney, adipose tissue, liver, retina, the vascular system, the small intestine, nasal and bronchial tissue, and alveolar type II epithelial cells ([Gheblawi et al., 2020](#); [Mariappan et al., 2020](#)).

ACE2 is also known as a host cell receptor that contributes to the viral infection by corona viruses. The COVID-19 virus binds to the target cells through ACE2 receptor which makes the COVID-19 attachment, invasion and penetration processes easier ([Delanghe et al., 2020a](#)). There are other receptors that can be used but, the virus has greater affinity for ACE2 and weaker affinities for two other receptors, CD147 and Grp78 (Glucose-Regulate Protein 78). ([Mariappan et al., 2020](#)).

ACE2 expression level has been reported to be significantly increased among men than women, which could explain the male predominance of COVID-19 ([Zhao et al., 2020a](#); [Gagliardi et al., 2020](#)). However, in another study ACE2 expression was not significantly associated with gender/disease severity bias among Covid-19 Italian patients ([Asselta et al., 2020](#)). Similar results were obtained by another author, who didn't observe a disparity between age groups and gender groups (male vs female) in ACE2 gene expression ([Cai, 2020](#)).

ACE2 is very polymorphic gene with about 1700 polymorphisms and their frequencies vary between populations, some of these polymorphisms were correlated with increased expression of ACE2 protein and were more frequent among the East-Asian populations ([Delanghe et al., 2020a](#); [Cao et al., 2020](#); [Chen et al., 2020a](#)). Not only that, ACE deletion allele that is linked to alterations of ACE expression, also influences the spread of the virus and outcomes of infection with COVID-19 especially in the Asian populations ([Sienko et al., 2020b](#); [Pati et al., 2020](#)).

Stawisk's study has indicated that many genetic variants in ACE2 gene (S19P, I21V, E23K, K26R, T27A, N64K, T92I, Q102P and H378R) are associated with the risk for COVID-19 ([Stawiski et al., 2020](#)).

Some polymorphisms present in ACE2 gene could also influence

Table 1
list of genes involved in the infection by Covid19.

Gene	Localisation	Polymorphism/mutation
ACE 2	Chromosome Xp22.2	ACE I/D, I21V, E23K, K26R, T27A, N64K, T92I, Q102P and H378R
TMPRSS2	Chromosome 21q22.3	rs112657409, rs11910678, rs77675406, rs713400 rs75603675, rs61735792 and rs61735794
CD26 (DPP4)	Chromosome 2	rs13015258
IFITM3	Chromosome 11	rs12252
HLA	Chromosome 6	HLA-B*46:01, HLA-A*24:02 alleles
ABO	Chromosome 9q34.2	-
SLC6A20	Chromosome 3p21.31	-
GSTT1	Chromosome 1p13.3	GSTT1 null genotype
DBP	Chromosome 4q11q13	rs7041
IL6	Chromosome 7p15.3	IL-6-174C allele

neurological complications rates in COVID-19 patients ([Strafella et al., 2020](#)). In contrast, Delanghe et al reported no relationship between the deletion allele frequency of ACE I/D polymorphism and COVID-19 infection and mortality rate in European, North-African and Middle East countries ([Delanghe et al., 2020b](#)). A Cohort study from Madrid, including 120 individuals showed a low frequency of polymorphisms in ACE2 gene among this population and an absence of association between this gene and SARS-CoV-2 ([Torre-Fuentes et al., 2020](#)).

The contradictory results of these studies could be explained by many factors such as genetic background, lifestyle, geographic and ethnic differences between populations, demographic characteristics of the population (gender, age), comorbidities.

1.2. TMPRSS2 gene (Chromosom21q22.3)

Another human receptors for virus is *TMPRSS2* that play an important role in the entry of the virus into the target cell. The analysis of *TMPRSS2* expression in human tissues revealed its high expression level in the lung tissue and the presence of four polymorphisms (rs464397, rs469390, rs2070788 and rs383510), it is thought that these variants could potentially influence the *TMPRSS2* expression and function ([Irham et al., 2020](#)).

Study by Cheng and colleagues, reported that two genetic variants in this gene (rs2070788 and rs383510) were highly associated with the risk for influenza ([Cheng et al., 2015](#)). In a large Italian cohort, *TMPRSS2* gene expression was found to be influenced by gender. Some genetic variants in this gene are associated with higher expression of *TMPRSS2* and correlated with the higher influenza risk. Others are regulated by androgens which could explain the gender bias in COVID-19 severity ([Asselta et al., 2020](#)). Through whole exome sequencing, study by Torre-Fuentes et al noted strong correlations between three variants in *TMPRSS2* gene (rs75603675, rs61735792 and rs61735794) and SARS-CoV-2 in individuals from Madrid ([Irham et al., 2020](#)).

In another study by SENAPATI et al., four polymorphisms in *TMPRSS2* gene (rs112657409, rs11910678, rs77675406 and rs713400) have been found to regulate *TMPRSS2* gene expression and to influence the risk of infection by COVID-19 ([Senapati et al., 2020](#)).

1.3. CD26 gene (Chromosom2)

CD26 is also known as Dipeptidyl peptidase-4 (DPP4), it is a cell receptor that governs SARS-CoV-2 entry into the human cell ([Senapati et al., 2020](#)). The evaluation of genetic susceptibility of CD26 (DPP4) for CoVid-19 showed a correlation between rs13015258 missense variant in *CD26* gene and the susceptibility to SARS-CoV-2 infection. The in silico prediction also suggests the intermolecular interactions between SARS-CoV-2 surface spike protein (S) and the receptors *TMPRSS2* and *CD26* ([Senapati et al., 2020](#)).

1.4. IFITM3 gene (Chromosome 11)

Interferon-induced transmembrane protein 3 (IFITM3) is an antiviral protein that prevents viral infection, by blocking entry of many viruses into the host cell. It inhibits the fusion of viral and cell membranes, by influencing cell membrane fluidity ([Zani and Yount, 2018](#)). Therefore, polymorphisms in this protein have been found to influence the risk and severity of respiratory infections, such as influenza and COVID-19 fluidity ([Everitt et al., 2012](#); [Allen et al., 2017](#)).

After sequencing the genetic variant rs12252 *IFITM3* gene, Zhang et al. found that 35% of all COVID-19 patients had the homozygous CC genotype and a higher association between the CC genotype and COVID-19 severity with an OR of 6.37 ($p < 0.001$) ([Zhang et al., 2013](#)).

1.5. HLA gene (chromosome 6)

Human leukocyte antigen (HLA) is a complex protein that plays an

important role in the transmission, progression and outcome of many infectious diseases. In a study by Wang et al., genotyping of 82 Chinese Han individuals with COVID-19 through next-generation sequencing (NGS) showed a positive association between many HLA alleles and the occurrence of COVID-19 (Wang et al., 2020). Nguyen et al. found that individuals with HLA-B*46:01 allele are more susceptible to COVID-19. These findings were confirmed by another study (Sanchez-Mazas, 2020; Nguyen et al., 2020).

Similarly, a study from Wuhan reported a positive correlation between HLA-A*24:02 and COVID-19 risk among the South Han Chinese population (van der Made et al., 2020).

1.6. ABO gene (chromosome 9q34.2)

Potential association between ABO blood groups and SARS-CoV-2 susceptibility has been detected in many studies. In these studies, blood group A was correlated with a higher risk of infection, while group O was associated with a lower risk (Li et al., 2020; Zhao et al., 2020b; Gérard et al., 2020).

A genome-wide association analysis of 1980 Covid-19 patients and 1394 Italian controls revealed two genetic segments on chromosome 3p21.31 and 9q34 as susceptibility loci for Covid-19 infection. The region 3p21.31 containing six important genes including that codes for the transporter Sodium/Imino-acid (proline) Transporter 1 t (SLC6A20 gene) that interact with ACE2 protein. The 9q34 region consisting of the ABO blood group locus, and a blood-group-specific analysis revealed a higher association between A-positive and risk of covid19. However, blood group O had a protective effect against covid19 (David et al., 2020).

1.7. GSTT1-M1 genes (chromosome 1p13.3 and chromosome 22q11.23)

Glutathione S-transferases (GSTs) family of enzymes involved in cellular detoxification. The *GSTT1* and *GSTM1* gene polymorphisms result in complete deletion of the gene (null genotypes) which leads to the total absence of GSTT1 and GSTM1 enzymes activity. Therefore, individuals with the deleted allele have a higher risk of developing many oxidative stress complex diseases such as respiratory infections (Bolt and Thier, 2006; Khomich et al., 2018; Henry et al., 2020).

Saadat et al. found that individuals carrying GSTT1 null had a high risk of COVID-19 in comparison to with GSTT1 present carriers and the higher numbers of COVID-19 cases and deaths were recorded in East-Asian countries which had lower frequency of the *GSTT1* null genotype (Saadat, 2020).

1.8. DBP gene (Chromosome 4q11q13)

Vitamin D binding protein (DBP) is a multifunctional glycoprotein which plays multiple physiological roles. It functions as, vitamin D transporter, actin-scavenger, controller of bone formation, macrophage-activating factor. Batur et al., found a Positive significant association between the prevalence and mortality from COVID-19 and TT and GT genotypes at rs7041 locus among different populations such as the populations of China, Japan, Nigeria, Kenya, Germany, Mexico, Italy, Czech, and Turkey (Batur and Hekim, 2020).

1.9. IL6 gene (Chromosome 7p15.3)

Interleukin 6 (IL6) is a pro-inflammatory cytokine, secreted by different types of cells such as fibroblasts keratinocytes mesangial cells and macrophages in response to tissue lesions and infections (Tanaka et al., 2014). The overexpression of this cytokine was associated with increased COVID-19 risk and death (Chen et al., 2020b; Ruan et al., 2020; Ulhaq and Soraya, 2020a). A meta-analysis evaluating the association between IL-6 gene polymorphism and COVID-19 showed a positive association between the IL-6-174C allele and pneumonia severity.

Also, it suggested that anti-IL-6R antibody could be an effective treatment for COVID-19. In a separate study, IL-6 polymorphisms have been proved to be an indicator of COVID-19 severity (Ulhaq and Soraya, 2020b; Kirtipal and Bharadwaj, 2020). While, Ravi et al. found that the IL-6 rs1800795 G allele was negatively associated with COVID-19 prevalence; and mortality (Ravi, 2020).

1.10. Other genes

A recent study of 3199 COVID-19 patients and controls, by Ellinghaus et al. has discovered a gene cluster on chromosome 3 as a major risk factor for COVID-19 at the genome-wide level. The risk is linked to a genomic fragment of around 50Kb in length, it's originated from Neanderthal population and its frequency varies between 63% in Bangladesh and less than 4% in East Asia (Hugo and Svante, 2020).

In another study from Nijmegen, the rapid whole-exome sequencing showed that loss-of-function variants of the X-chromosomal TLR7 among 4 COVID-19 male patients and their available family members. Genetic variation in the mediator of immune response against viruses, TLR7 was suggested as an explanation for Male predominance of COVID-19 because of its localization on the sexual chromosome X (van der Made et al., 2020).

2. Conclusion

COVID-19 seems to be a multigenic and multifactorial disease with many genetic and environmental determinants. The identification of the factors implicated in the infection by Covid-19 is key to better understanding the etiology and physiopathological mechanisms of Covid-19 infection. In addition, it can help predict the risk of Covid-19 infection for the better preventing. The results of the present review showed that many different genes present in coronavirus receptors and cell surface are associated with a higher risk for COVID-19.

Declaration of competing interest

I have no conflicts of interest and there has been no significant financial support for this work that could have influenced its outcomes. As corresponding author, I confirm that the manuscript has been read and approved for submission by all named authors.

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