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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 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](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; Sienko 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
TMPSRS2	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. TMPSRS2 gene (Chromosom21q22.3)

Another human receptors for virus is TMPSRS2 that play an important role in the entry of the virus into the target cell. The analysis of TMPSRS2 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 TMPSRS2 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, TMPSRS2 gene expression was found to be influenced by gender. Some genetic variants in this gene are associated with higher expression of TMPSRS2 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 TMPSRS2 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 TMPSRS2 gene (rs112657409, rs11910678, rs77675406 and rs713400) have been found to regulate TMPSRS2 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 TMPSRS2 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.

## References

- Allen, E.K., Randolph, A.G., Bhangale, T., Dogra, P., Ohlson, M., Oshansky, C.M., et al., 2017. SNP-mediated disruption of CTCF binding at the IFITM3 promoter is associated with risk of severe influenza in humans. *Nat. Med.* 23, 975–983. <https://doi.org/10.1038/nm.4370>.
- Alshami, A., Douedi, S., Varon, J., 2020. Coronavirus in the arena: one more time. *Curr Resp Med Rev* 16, 1.
- Asselta, R., Paraboschi, E.M., Mantovani, A., Duga, S., 2020. ACE2 and TMPRSS2 variants and expression as candidates to sex and country differences in COVID-19 severity in Italy. *medRxiv*. <https://doi.org/10.1101/2020.03.30.20047878>.
- Batur, L.K., Hekim, N., 2020. The role of DBP gene polymorphisms in the prevalence of new coronavirus disease 2019 infection and mortality rate [published online ahead of print, 2020 Aug 8]. *J Med Virol*. <https://doi.org/10.1002/jmv.26409> doi: 10.1002/jmv.26409.
- Bolt, H.M., Thier, R., 2006. Relevance of the deletion polymorphisms of the glutathione S-transferases GSTT1 and GSTM1 in pharmacology and toxicology. *Curr Drug Metab.* 7, 613–628 [PubMed] [Google Scholar].
- Cai, G., 2020. Bulk and single-cell transcriptomics identify tobacco-use dis-parity in lung gene expression of ACE2, the receptor of 2019-nCoV. *medRxiv*. <https://doi.org/10.1101/2020.02.05.20020107>.
- Cao, Y., Li, L., Feng, Z., Wan, S., Huang, P., Sun, X., et al., 2020. Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. *Cell Discov* 6, 11.
- Chen, J., Jiang, Q., Xia, X., Liu, K., Yu, Z., Tao, W., et al., 2020a. Individual variation of the SARS-CoV2 receptor ACE2 gene expression and regulation. *Preprints* 2020030191.
- Chen, G., Wu, D., Guo, W., et al., 2020b. Clinical and immunologic features in severe and moderate coronavirus disease 2019. *J. Clin. Invest.* 130 (5), 2620–2629.
- Cheng, Zhongshan, Zhou, Jie, Kelvin Kai-Wang To, Chu, Hin, Li, Cun, Dong, Wang, Dong, Yang, Zheng, Shufa, Hao, Ke, Bossé, Yohan, Obeidat, Ma'en, Brandsma, Corry-Anke, Song, You-Qiang, Yu, Chen, Zheng, Bo-Jian, Li, Lanjuan, Yuen, Kwok-Yung, 15



- October 2015. Identification of TMPRSS2 as a susceptibility gene for severe 2009 pandemic A(H1N1) influenza and A(H7N9) influenza. *The Journal of Infectious Diseases* 212 (8), 1214–1221. <https://doi.org/10.1093/infdis/jiv246>.
- COVID-19 Research Consortium, Barnaby, D.P., Becker, L.B., Chelico, J.D., Cohen, S.L., Cookingham, J., Coppa, K., Diefenbach, M.A., Dominello, A.J., Duer-Hefe, J., Falzon, L., Gitlin, J., Hajizadeh, N., Harvin, T.G., Hirschwerk, D.A., Kim, E.J., Kozel, Z.M., Marrast, L.M., Mogavero, J.N., Osorio, G.A., Qiu, M., Zanos, T.P., 2020. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA* 323, 2052e2059. <https://doi.org/10.1101/2020.05.31.20114991>.
- David, E., Frauke, D., Luis, B., Maria, B., Agustin, A., Pietro, I., Javier, F., 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*. <https://doi.org/10.1101/2020.05.31.20114991>.
- de Wit, E., van Doremalen, N., Falzarano, D., Munster, V.J., 2016. SARS and MERS: recent insights into emerging coronaviruses. *Nat Rev Microbiol.* 14 (8), 523–534. <https://doi.org/10.1038/nrmicro.2016.81>.
- Delanghe, J.R., Speckaert, M.M., De Buyzere, M.L., 2020a. The host's angiotensin-converting enzyme polymorphism may explain epidemiological findings in COVID-19 infections. *Clin. Chim. Acta* 505, 192–193.
- Delanghe, J.R., Speckaert, M.M., De Buyzere, M.L., 2020b. COVID-19 infections are also affected by human ACE1 D/I polymorphism. *Clin. Chim. Lab. Med.* 58 (7), 1125–1126.
- Everitt, A.R., Clare, S., Pertel, T., John, S.P., Wash, R.S., Smith, S.E., et al., 2012. IFITM3 restricts the morbidity and mortality associated with influenza. *Nature*. 484, 519–523. <https://doi.org/10.1038/nature10921>.
- Gagliardi, M.C., Tieri, P., Ortona, E., Ruggieri, A., 2020. ACE2 expression and sex disparity in COVID-19. *Cell Death Discov.* 6, 37. Published 2020 May 26. <https://doi.org/10.1038/s41420-020-0276-1>.
- Gérard, C., Maggipinto, G., Minon, J.M., 2020. COVID-19 and ABO blood group: another viewpoint. *Br. J. Haematol.* 190 (2), e93–e94. <https://doi.org/10.1111/bjh.16884>.
- Gheblawi, M., Wang, K., Viveiros, A., et al., 2020. Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2. *Circ. Res.* 126 (10), 1456–1474. <https://doi.org/10.1161/CIRCRESAHA.120.317015>.
- Guo, J., Huang, Z., Lin, L., et al., 2020. Coronavirus disease 2019 (COVID19) and cardiovascular disease: a viewpoint on the potential influence of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers on onset and severity of severe acute respiratory syndrome coronavirus 2 infection. *J. Am. Heart Assoc.* 9, e016219.
- Henry, B.M., Vikse, J., Benoit, S., Favaloro, E.J., Lippi, G., 2020. Hyperinflammation and derangement of renin-angiotensin-aldosterone system in COVID-19: a novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis. *Clin. Chim. Acta* 507, 167–173. [https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200501-covid-19-sitrep.pdf?sfvrsn=742f4a18\\_4](https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200501-covid-19-sitrep.pdf?sfvrsn=742f4a18_4).
- Hugo, Z., Svante, P., 2020. The major genetic risk factor for severe COVID-19 is inherited from Neandertals. *bioRxiv*. <https://doi.org/10.1101/2020.07.03.186296>.
- Irham, L.M., Chou, W.H., Calkins, M.J., et al., 2020 Aug. Genetic variants that influence SARS-CoV-2 receptor TMPRSS2 expression among population cohorts from multiple continents. *Biochem. Biophys. Res. Commun.* 529 (2), 263–269. <https://doi.org/10.1016/j.bbrc.2020.05.179>.
- Khomich, O., Kochetkov, S., Bartosch, B., Ivanov, A.V., 2018. Redox biology of respiratory viral infections. *Viruses*. 10, 392.
- Kirtipal, N., Bharadwaj, S., 2020. Interleukin 6 polymorphisms as an indicator of COVID-19 severity in humans. *J. Biomol. Struct. Dyn.* 1–4. <https://doi.org/10.1080/07391102.2020.1776640>.
- 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. *Br J Haematol.* <https://doi.org/10.1111/bjh.16797> [Epub ahead of print]. [CrossRef] [Google Scholar].
- Mariappan, V., Balakrishna, S.R.R., Pillai, A., 2020 Dec. Angiotensin-converting enzyme 2: a protective factor in regulating disease virulence of SARS-CoV-2. *IUBMB Life* 72 (12), 2533–2545. <https://doi.org/10.1002/iub.2391>. Epub 2020 Oct 8. 33031602.
- Nguyen, A., David, J.K., Maden, S.K., et al., 2020. Human leukocyte antigen susceptibility map for SARS-CoV-2. *J Virol.* <https://doi.org/10.1128/JVI.00510-20>. [CrossRef] [Google Scholar].
- Pati, Abhijit, et al., 2020. ACE Deletion Allele Is associated with susceptibility to SARS-CoV-2 infection and mortality rate: an epidemiological study in the asian population. *Clinica Chimica Acta; International Journal of Clinical Chemistry* 510, 455–458.
- Ravi, P.R., 2020. Genetic polymorphisms mediating behavioural and immune response to pathogens may moderate the impact of the COVID-19 pandemic: a pilot study. *medRxiv*. <https://doi.org/10.1101/2020.06.03.20120998>, 06.03.20120998.
- Ruan, Q., Yang, K., Wang, W., Jiang, L., Song, J., 2020. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan. *China. Intensive Care Med.* 46 (5), 846–848.
- Saadat, M., 2020. An evidence for correlation between the glutathione S-transferase T1 (GSTT1) polymorphism and outcome of COVID-19. *Clin. Chim. Acta* 508, 213–216. <https://doi.org/10.1016/j.cca.2020.05.041>.
- Sanchez-Mazas, A., 2020. HLA studies in the context of coronavirus outbreaks. *Swiss Med. Wkly.* 150, w20248.
- Scully, E.P., Haverfield, J., Ursin, R.L., Tannenbaum, C., Klein, S.L., 2020. Considering how biological sex impacts immune responses and COVID-19 outcomes. *Nat Rev Immunol.* 20 (7), 442–447. <https://doi.org/10.1038/s41577-020-0348-8>.
- Senapati, S., Kumar, S., Singh, A.K., Banerjee, P., Bhagavatula, S., 2020. Assessment of risk conferred by coding and regulatory variations of TMPRSS2 and CD26 in susceptibility to SARS-CoV-2 infection in human. *J. Genet.* 99 (1), 53. <https://doi.org/10.1007/s12041-020-01217-7>.
- Sienko, J., Kotowski, M., Bogacz, A., et al., 2020a. COVID-19: the influence of ACE genotype and ACE-I and ARBs on the course of SARS-CoV-2 infection in elderly patients. *Clin Interv Aging* 15, 1231–1240. Published 2020 Jul 21. <https://doi.org/10.2147/CIA.S261516>.
- Sienko, J., Kotowski, M., Bogacz, A., et al., 2020b. COVID-19: the influence of ACE genotype and ACE-I and ARBs on the course of SARS-CoV-2 infection in elderly patients. *Clin Interv Aging* 15, 1231–1240. Published 2020 Jul 21. <https://doi.org/10.2147/CIA.S261516>.
- Singhal, T., 2020. A review of coronavirus disease-2019 (COVID-19). *Indian J. Pediatr.* 87 (4), 281–286. <https://doi.org/10.1007/s12098-020-03263-6>.
- Stawiski, E.W., Diwanji, D., Suryamohan, K., et al., 2020. Human ACE2 receptor polymorphisms predict SARS-CoV-2 susceptibility. *bioRxiv*. <https://doi.org/10.1101/2020.04.07.024752>, 2020.04.07.024752.
- Strafella, C., Caputo, V., Termine, A., et al., 2020. Analysis of ACE2 genetic variability among populations highlights a possible link with COVID-19-related neurological complications. *Genes (Basel)* 11 (7), 741. Published 2020 Jul 3. <https://doi.org/10.3390/genes11070741>.
- Tabor, H.K., Risch, N.J., Myers, R.M., 2002. Candidate-gene approaches for studying complex genetic traits: practical considerations. *Nat Rev Genet* 3, 391–397.
- Tanaka, T., Narazaki, M., Kishimoto, T., 2014 Sep 4. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb Perspect Biol.* 6 (10), a016295.
- Torre-Fuentes, L., Matias-Guiu, J., Hernández-Lorenzo, L., Montero-Escribano, P., Pytel, V., Porta-Etessam, J., Gómez-Pinedo, U., Matias-Guiu, J., 2020. ACE2, TMPRSS2, and Furin Variants and SARS-CoV-2 Infection in Madrid, Spain. *Journal of Medical Virology*.
- Torres, M.M., Acosta, C.P., Sicard, D.M., et al., 2004. Susceptibilidad genética y riesgo de cáncer gástrico en una población del Cauca. *Biomedica.* 24, 153–162.
- Ulhaq, Z.S., Soraya, G.V., 2020a. Interleukin-6 as a potential biomarker of COVID-19 progression. *Med. Mal. Infect.* 50 (4), 382–383.
- Ulhaq, Z.S., Soraya, G.V., 2020b. Anti-IL-6 Receptor Antibody Treatment for Severe COVID-19 and the Potential Implication of IL-6 Gene Polymorphisms in Novel Coronavirus Pneumonia (May 2, 2020). SSRN: <https://ssrn.com/abstract=3592878> or. <https://doi.org/10.2139/ssrn.3592878>.
- van der Made, C.I., Simons, A., Schuurs-Hoeijmakers, J., et al., 2020. Presence of genetic variants among young men with severe COVID-19. *JAMA.* 324 (7), 663–673. <https://doi.org/10.1001/jama.2020.13719>.
- Wang, W., Zhang, W., Zhang, J., He, J., Zhu, F., 2020. Distribution of HLA allele frequencies in 82 Chinese individuals with coronavirus disease-2019 (COVID-19). *HLA.* 96 (2), 194–196. <https://doi.org/10.1111/tan.13941>.
- van der Made, C.I., Simons, A., Schuurs-Hoeijmakers, J., et al., 2020. Presence of Genetic Variants Among Young Men With Severe COVID-19. *JAMA* 324 (7), 1–11. <https://doi.org/10.1001/jama.2020.13719>.
- Zani, A., Yount, J.S., 2018. Antiviral protection by IFITM3 in vivo. *Curr Clin Microbiol Rep.* 5, 229–237. <https://doi.org/10.1007/s40588-018-0103-0>.
- Zhang, Y.H., Zhao, Y., Li, N., et al., 2013. Interferon-induced transmembrane protein-3 genetic variant rs12252-C is associated with severe influenza in Chinese individuals. *Nat. Commun.* 4, 1418. <https://doi.org/10.1038/ncomms2433>.
- Zhao, Y., Zhao, Z., Wang, Y., Zhou, Y., Ma, Y., Zuo, W., 2020a. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCoV. *bioRxiv*. <https://doi.org/10.1101/2020.01.26.919985>.
- Zhao, J., Yang, Y., Huang, H., Li, D., Gu, D., Lu, X., et al., 2020b. Relationship between the ABO Blood Group and the COVID-19 Susceptibility. *MedRxiv*. <https://doi.org/10.1101/2020.03.11.20031096> [Epub ahead of print]. [CrossRef] [Google Scholar].