Germline Genetic Variants of Viral Entry and Innate Immunity May Influence Susceptibility to SARS-CoV-2 Infection: Toward a Polygenic Risk Score for Risk Stratification

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The ongoing COVID-19 pandemic caused by the novel coronavirus, SARS-CoV-2 has affected all aspects of human society with a special focus on healthcare. Although older patients with preexisting chronic illnesses are more prone to develop severe complications, younger, healthy individuals might also exhibit serious manifestations. Previous studies directed to detect genetic susceptibility factors for earlier epidemics have provided evidence of certain protective variations. Following SARS-CoV-2 exposure, viral entry into cells followed by recognition and response by the innate immunity are key determinants of COVID-19 development. In the present review our aim was to conduct a thorough review of the literature on the role of single nucleotide polymorphisms (SNPs) as key agents affecting the viral entry of SARS-CoV-2 and innate immunity. Several SNPs within the scope of our approach were found to alter susceptibility to various bacterial and viral infections. Additionally, a multitude of studies confirmed genetic associations between the analyzed genes and autoimmune diseases, underlining the versatile immune consequences of these variants. Based on confirmed associations it is highly plausible that the SNPs affecting viral entry and innate immunity might confer altered susceptibility to SARS-CoV-2 infection and its complex clinical consequences. Anticipating several COVID-19 genomic susceptibility loci based on the ongoing genome wide association studies, our review also proposes that a well-established polygenic risk score would be able to clinically leverage the acquired knowledge.

Keywords: SARS-CoV-2, COVID-19, genetic susceptibility, genotype-phenotype association studies, viral entry, innate immunity, polygenic risk score, risk stratification
INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the virus responsible for the ongoing pandemic COVID-19 has yet infected more than 108 million people worldwide with a reported mortality rate between 0.5 and 10% in different countries (1). SARS-CoV-2 is a novel coronavirus originally detected in China. The specific mechanism by which it infects humans and affects human health is not fully understood. The clinical characteristics of COVID-19 usually incorporates fever, fatigue, dry cough, and dyspnea, while severe infections may result in bilateral pneumonia, and life-threatening acute respiratory distress syndrome (ARDS). Although severe complications usually manifest in elderly patients with concurrent chronic diseases (e.g., high blood pressure, diabetes) young, healthy individuals might also suffer from critical consequences of the disease, requiring intensive care. The wide range of disease susceptibility especially in younger patients suggests that difference in genetic background of individuals might contribute to these alterations. In fact, the analysis of previous, unrelated infectious diseases provides clear evidence that specific protective genetic variations are enriched in populations where certain infections are endemic. For instance, sickle cell trait and carrying specific HLA antigens in African populations confer diminishing susceptibility against malaria infection (2, 3). Another example, Δ32, a 32-base pair deletion of the CCR5 gene prevents cellular viral entry of human immunodeficiency virus (HIV) resulting in effective resistance against HIV infection in individuals homozygous regarding this variation (4).

In the present review we aim to summarize previously published genotype-phenotype studies of genes which might play a role in the susceptibility to COVID-19. The associations between various single nucleotide polymorphisms (SNPs) and certain traits were studied using targeted and genome-wide approaches. In the case of targeted approach, hypothesis-driven selection of specific genes/SNPs were analyzed in cases and controls while during genome-wide association studies (GWASs) detection of novel genomic loci with susceptibility to various traits/diseases are possible. Our examination focuses on genetic variants of 2 key processes in the initiation of the disease: viral entry and recognition by the innate immune system. Also, as several international collaborations are ongoing to provide large-scale genomic susceptibility data, we propose that a well-established polygenic risk score would be able to optimally leverage the acquired knowledge.

VIRAL ENTRY

Large emphasis has been directed to decipher how SARS-CoV-2 is incorporated in human cells. Key data in this regard originate from studies focusing on SARS-CoV, responsible for the SARS epidemic of 2002–2003, which shares 79.6% sequence identity with SARS-CoV-2 (5). In fact, the spike protein of SARS-CoV binds to angiotensin-converting enzyme 2 (ACE2) that serves as a receptor for the virus (6), and recent data confirmed that SARS-CoV-2 also binds ACE2 in vitro (7–9). Further analyses revealed that the spike protein of SARS-CoV-2 is cleaved by transmembrane protease serine 2 (TMPRSS2) (7), facilitating viral entry. Also of note, both ACE2 and TMPRSS2 are primarily expressed in bronchial transient secretory cells (10), elucidating the predilection of the lower airways. Additionally, proprotein convertase FURIN was shown to pre-activate the viral entry of SARS-CoV-2 (11), while additional factors as PIKfyve, TPCN2 and cathepsin L (CTSL) are also critical in this process (12).

Table 1 summarizes genetic variants of the aforementioned genes with suggested genotype-phenotype findings. The main physiological function of ACE2 is catalyzing the hydrolysis of angiotensin I and angiotensin II into angiotensin (1–9) and angiotensin (1–7), respectively, contributing to blood pressure regulation (34). Therefore, numerous SNP association studies were directed to ascertain the role of ACE2 genetic variants on certain cardiovascular and metabolic traits. Throughout several populations, ACE2 polymorphisms have been associated with susceptibility to cardiovascular and metabolic diseases including hypertension and type 2 diabetes mellitus underlining the potential functional impact of these SNPs on ACE2 expression and/or function (13–21). A TMPRSS2 SNP has been linked to TMPRSS2-ERG genetic fusion which is a frequent molecular event in prostate cancer (22, 23). More importantly, a study examining patients of the 2009 swine flu pandemic caused by the H1N1 influenza virus found that TMPRSS2 SNP rs2070788 is associated with severity of the disease (24). Additionally, genotype-specific TMPRSS2 expression was confirmed in human lung tissues regarding rs2070788 and rs383510, the latter being tagged to the former polymorphism. Mechanistically, rs383510 was found to enhance the transcription of TMPRSS2 mRNA, and these 2 SNPs were also found to associate with susceptibility to the H7N9 influenza virus (24).

Certain high throughput screening studies identified rs4702, a common genetic variant of proprotein convertase FURIN as susceptibility factor for schizophrenia and hypertension (25, 26), while other studies correlated another SNP rs17514846 with other various traits including coronary artery disease, metabolic syndrome and longevity (27–29).

While we found no SNP association studies for PIKfyve, certain variants of the TPCN2 gene coding for cation-selective ion channel were found to be associated with type 2 diabetes mellitus (T2DM) and hair color (30, 31). In the case of CTS1, two studies performed on different populations confirmed that a promoter polymorphism correlates with hypertension in Asian and American populations (32, 33).

INNATE IMMUNITY

After SARS-CoV-2 successfully infected cells, a complex immune response initiates, in which the rapid and coordinated response of the innate immunity is pre-requisite (35). Following infection, the innate immune system recognizes viral antigens mainly by RIG-I-Like Receptors (RLRs) and Toll-Like Receptors (TLRs) (35). In the first step in RLR-dependent immune response, cytoplasmic RNA sensors RIG-I and MDA5 recognize viral RNA, after which interaction with mitochondrial antiviral signaling protein (MAVS) initiate signaling changes activating interferon
| Chromosome | Gene ID | Transcript ID | Gene | SNP | MAF   | Position | Exon(E)/intron(I) | Observed association                                                                 |
|------------|---------|---------------|------|-----|-------|----------|------------------|-------------------------------------------------------------------------------------|
| X          | ENSG00000130234 | ENST00000427411.1 | ACE2 | rs2074192 | 0.36   | 15564667   | I17–18           | Left ventricular hypertrophy (LVH) in females Chinese Han (13)                       |
|            |         |               |      | rs4648176  | 0.07   | 15569381   | I15–16           | Essential hypertension (EH) in females Chinese Han (16)                             |
|            |         |               |      | rs4648155  | 0.06   | 15579386   | I9–10            | Essential hypertension (EH) in females Chinese Han (16)                             |
|            |         |               |      | rs2106809  | 0.32   | 15599938   | I2–3             | Left ventricular hypertrophy (LVH) in females Chinese Han (13)                      |
|            |         |               |      | rs1514283  | 0.11   | 15564624   | I17–18           | Lone atrial fibrillation Chinese Han (17)                                           |
|            |         |               |      | rs2285666  | 0.35   | 15592225   | I4–5             | Essential hypertension (EH) in females Chinese Han (16)                             |
|            |         |               |      | rs879922   | 0.32   | 15572684   | I12–13           | Cardiovascular death in females Chinese Han European (18)                           |
|            |         |               |      | rs1978124  | 0.21   | 15599940   | I2–3             | Optional T2DM Uygur (14)                                                            |
|            |         |               |      | rs2048683  | 0.20   | 15590376   | I5–6             | Optional T2DM Uygur (14)                                                            |
|            |         |               |      | rs233575   | 0.14   | 15564843   | I17–18           | Optional T2DM Uygur (14)                                                            |
|            |         |               |      | rs4240157  | 0.32   | 15568841   | I15–16           | Optional T2DM Uygur (14)                                                            |
|            |         |               |      | rs4648156  | 0.20   | 15578920   | I9–10            | Optional T2DM Uygur (14)                                                            |
|            |         |               |      | rs4648188  | 0.04   | 15583220   | I8–9             | Optional T2DM Uygur (14)                                                            |
|            |         |               |      | rs6832677  | 0.02   | 15596749   | I2–3             | Structural atrial fibrillation in males Chinese Han (19)                            |
|            |         |               |      | rs714205   | 0.31   | 15565781   | I17–18           | Diabetic retinopathy within female T2DM patients Chinese (15)                       |

(Continued)
| Chromosome | Gene ID          | Transcript ID | Gene    | SNP              | MAF | Position     | Exon(E)/intron(I) | Observed association                                                                 |
|------------|-----------------|---------------|---------|------------------|-----|--------------|-------------------|-------------------------------------------------------------------------------------------------------------------|

| 21 | ENSG000000184012 | ENST00000332149.10 | TMPRSS2 | rs12329760       | 0.26 | 41480570     | E6                | N TMPRSS2-ERG fusion in patients with prostate cancer                                                                 |
|     |                 |               |         |                  |      |              |                   | N TMPRSS2-ERG fusion by translocation, multiple copies of the gene fusion                                                                 |
| 15 | ENSG00000140564 | ENST00000268171.8 | FURIN   | rs4702           | 0.35 | 90883330     | E16               | O Systolic and diastolic blood pressure                                                                                     |
| 11 | ENSG00000162341 | ENST00000294309.8 | TPCN2   | rs1551305        | 0.34 | 69087765     | I24–25            | O T2DM                                                                                                                      |
|     |                 |               |         | rs35264875       | 0.10 | 69078931     | E16               | O Hair color (blond vs. brown)                                                                                               |
|     |                 |               |         | rs3829241        | 0.18 | 69087885     | E25               | O Hair color (blond vs. brown)                                                                                               |
| 9  | ENSG00000135047 | ENST00000343150.10 | CTSL    | rs3118869        | 0.43 | 87725948     | 5’ upstream       | O Essential hypertension (EH)                                                                                               |
|     |                 |               |         |                  |      |              |                   | O Hypertension, systolic blood pressure, diastolic blood pressure                                                      |

Regarding locus specifications genome build GRCh38.p13 was used and for minor allele frequency (MAF) of the second most frequent allele in 1,000 Genomes Phase three combined population is demonstrated, where available. SNP, single nucleotide polymorphism; MAF, minor allele frequency; T2DM, type 2 diabetes mellitus. A, autoimmune; I, infectious; N, neoplastic; O, other.
regulatory factor IRF3 and IRF7, resulting in type I IFN (IFN-α and IFN-β) production and antiviral response (35–38).

**Supplementary Table 1** summarizes the SNP association studies concerning the agents implicated in viral recognition and response by the innate immune system. Several RIG-I SNPs were found to be associated with neutralizing antibody levels after measles and rubella vaccinations while other studies found RIG-I SNPs to be associated with nasopharyngeal carcinoma and EV71-induced hand, foot, and mouth disease (39–43). MDA5 genetic variants were thoroughly investigated in relation to autoimmunity with several associations being found with psoriasis, systemic lupus erythematosus (SLE), type 1 diabetes mellitus (T1DM), hypothyroidism and multiple sclerosis (MS) (44–53). Polymorphisms in MAVS were analyzed regarding inflammatory response finding that rs7269320 associated with osteoarthritis (54). Moreover, in an African American cohort, where rs11905552 of the MAVS gene was much more frequent compared to European Americans, this SNP associated with low type I IFN production in patients with SLE (55). Studies focusing on genetic variants of IRF3 and IRF7 found associations with SLE and systemic sclerosis (56–59), while IFN-α genetic variants were found to be associated with mixed connective tissue disease and prognosis in glomerulonephritis patients (60, 61).

During TLR-mediated immune response, TLR3, TLR7, TLR8, and TLR9 sense intracellular, while TLR2 and TLR4 detect extracellular, cell surface-associated viral antigens (35, 62). TLRs transduce the signal by binding MyD88 and TRIF, which in turn stimulate IRF3, IRF7, and NF-κB enhancing type I IFN response (35, 63–65).

A multitude of case-control studies analyzed the role of TLR-associated SNPs in health and disease. TLR3 SNPs were associated with infectious, autoimmune, and neoplastic diseases. Certain studies demonstrated association of TLR3 polymorphisms with hepatitis B and C virus (HBV and HCV), herpes simplex virus (HSV), HIV infections (66–72), while SNPs rs3775291, rs3775292, rs5743312, and rs7657186 were associated with vaccine-induced immunity to serogroup C meningococcal vaccine as defined by virus-specific IgG persistence (73). rs3775291 was also associated with various autoimmune disorders including SLE, rheumatoid arthritis (RA), and sarcoidosis (74–76). Regarding neoplastic diseases, TLR3 genetic variants were linked to breast, colorectal and nasopharyngeal cancers, while also serving as prognostic factors in colorectal cancer (CRC) and melanoma malignum (MM) (42, 77–81). Several lines of evidence supported the association between SLE and TLR7 SNPs in various populations (82–85), while additional studies found correlation between TLR7 polymorphisms and susceptibility to HCV and chikungunya virus infection, asthma, and age-related macular degeneration (86–89). The association between rs3764880 of TLR8 and tuberculosis susceptibility in males has been confirmed in European, Russian, and Chinese populations (90–92) and other SNPs of TLR8 were associated with asthma, SLE, and chikungunya virus infection (84, 87, 88). With regard to the fourth TLR sensing intracellular viral antigens, TLR9 has 4 SNPs which were found to be associated with several infectious, autoimmune, and neoplastic diseases. Confirmed associations with infectious diseases include malaria, cytomegalovirus (CMV), and tuberculosis (90, 93–97), while individuals with certain TLR9 polymorphisms are more susceptible to post-infectious irritable bowel syndrome, SLE and lupus nephritis, Graves’ disease-related ophthalmopathy, and RA (98–104). With respect to neoplastic diseases, acute myeloid leukemia (AML), and cervical cancer were also associated with TLR9 genetic variants (105–107), while rs187084 is proposed to be a prognostic factor in patients with prostate cancer (108).

TLR2 and TLR4 SNPs are probably the most widely investigated genetic variants in the scope of our review. Similarly to studies conducted in other TLR genes, TLR2 polymorphisms were also found to be associated with tuberculosis and CMV infection (90, 109–111), and additional pathogenic role concerning bacterial vaginosis in HIV-infected patients, recurrent vulvovaginal candidiasis, aggressive periodontitis, neonatal sepsis, Lyme disease, pneumonia, and reactive arthritis were also proposed (112–119). SNP rs3804100 has been linked to measles-specific antibody levels following immunization, while rs5743708 associated with nasal Staphylococcus aureus carriage (120, 121). Autoimmune disorders linked to TLR2 SNPs incorporate psoriasis and T1DM (122, 123), while hepatocellular carcinoma (HCC), marginal zone lymphoma, oral, and laryngeal squamous cell carcinoma and prognosis of women with breast cancer have also been linked to certain genetic variants of TLR2 (124–127).

TLR4 polymorphisms have been associated with various infectious diseases. Manifest tuberculosis is associated with rs11536889, rs12377632, rs1927911, and rs7873784 (109, 110, 128), while additional associated infection-related diseases include sepsis and sepsis-related organ failure for rs11536889 and Chlamydia trachomatis infection in women with pelvic inflammatory disease for rs1927911 (129–131). The most intensively investigated TLR4 SNP, rs4986790 is associated with a wide range of infections including Gram-negative and Mycobacterium bacteria in high-risk populations, severe respiratory syncytial virus disease, clinical malaria, recurrent cystitis, chronic cavitary pulmonary aspergillosis, HCV infection, and prognosis of HBV-infected individuals (132–141). It also has a probable effect on IL-4 secretion after measles vaccination (142). Another SNP of TLR4, rs5030717 is associated with childhood otitis media (143).

With respect to autoimmune-related diseases, TLR4 SNPs associate with ankylosing spondylitis, RA, giant cell arteritis, and preeclampsia (144–147). In addition, rs10759932 and rs4986790 are linked to acute rejection following kidney and lung transplantation, respectively (148, 149). Several TLR4 polymorphisms (rs10759932, rs10983755, rs11536889, rs1927911, rs2149356, and rs4986790) are associated with gastric cancer susceptibility, where the risk-elevating Helicobacter pylori infection might have an important role (150–154). Other tumors linked to TLR4 genetic variants include HCC, prostate cancer, CRC, and non-Hodgkin lymphoma (NHL) (79, 155–160).

Genetic variants of adapter molecule MYD88 are associated with tuberculosus susceptibility, Buerger disease and treatment response in patients with RA (90, 161–163). SNPs of the other key adapter agent, TRIF are associated with pneumonia susceptibility and thyroid cancer (164, 165).
FIGURE 1 | Polygenic risk scores might detect high-risk individuals regarding COVID-19 susceptibility and severity. The actual susceptibility and severity of COVID-19 varies widely within the population (left panel, redder individuals are more, greener individuals are less prone for severe COVID-19 disease). Genome-wide association studies might distinguish a group of SNPs from which a clinically relevant polygenic risk score can be built (right panel). Color-coded squares represent the presence of the risk allele (red) or the alternative allele (green) in each individual. The intensity of red corresponds to the odds ratio of the risk allele compared to the alternative allele. Resultant values of the odds ratios of each SNPs are color-coded as the polygenic risk score (orange background). Personalized risk scores correlate well with actual COVID-19 risk, however additional environmental, anthropometric factors and comorbidities also modify the phenotype.

In addition to type I IFN response viral recognition in the innate immune system leads to NF-kB activation. NF-kB is a multiprotein complex consisting of NFKB1, NFKB2, RELA, RELB, and REL (166). Type I IFN response and NF-kB activation result in IL-6 and IL-8 production (35). The activation of these mediators contributes to inflammation and complex antiviral immune response (35).

As a key player in inflammatory response, NFKB1 genetic variants has also been associated with atherosclerotic manifestations including coronary artery disease, acute coronary syndrome, dilated cardiomyopathy, and ischaemic stroke (167–173). Promoter polymorphism rs28362491 is linked to HCV infection and autoimmune diseases including Behcet’s disease and SLE (174–176), while rs3774937 is associated with acute rejection after renal transplantation (177). Neoplastic diseases associated with NFKB1 SNPs include CRC, Hodgkin lymphoma, NHL, cervical squamous cell carcinoma, liver, thyroid, breast, and lung cancer (178–186). rs11574851 of NFKB2 was found to be linked to RA susceptibility among anti-citrullinated protein antibodies-positive patients (187), while in healthy women rs1049728 of RELA associated with the concentration of soluble ICAM-1, which is an endothelium-derived inflammatory marker (188). Genetic variants of REL have been shown to be linked to various autoimmune diseases including RA, psoriasis, and celiac disease (189–193).

Polymorphisms of IL6 have been shown to pre-dispose to pulmonary tuberculosis, acute lung injury in patients with systemic inflammatory response syndrome and post-infectious irritable bowel syndrome (98, 194, 195). An association with RA has also been proposed (196). rs1800795 has been shown to have a role in the prognosis of patients following renal and lung transplantation (197–199). IL6 SNPs were also confirmed to have a role in the susceptibility of various cardiovascular disorders including hypertension and stroke (200–202).

IL-8 is coded by CXCL8 gene, SNPs of which have been shown to be linked to infectious, autoimmune, and neoplastic diseases. Acne vulgaris, chronic periodontitis, and invasive aspergillosis among immunocompromised patients have been shown to be associated with various variants (203–205). Autoimmune diseases including idiopathic pulmonary fibrosis, childhood IgA nephropathy, erosive oral lichen planus, childhood asthma, and Graves’ disease have also been linked to genetic variants of CXCL8 (206–210). Concerning neoplastic diseases, non-small cell lung cancer, and gastric cancer have been proposed to be associated with CXCL8 SNPs (154, 211, 212).

In conclusion, large majority of the discussed SNPs present pleiotropic effects, among which the frequent presence of various autoimmune and infection-related traits highlights their putative involvement in the susceptibility and severity of COVID-19.

TOWARD PRECISION RISK ASSESSMENT: PREDICTING COVID-19 SUSCEPTIBILITY AND SEVERITY BASED ON A POLYGENIC RISK SCORE

As genetic susceptibility regarding COVID-19 is an ongoing topic of several large international collaborations we anticipate
to acquire a large amount of evidence regarding susceptibility loci in the near future. Indeed, recent studies identified germline variants of TLR3- and IRF7-dependent type I IFN immunity to associate with more severe COVID-19 infection (213). In particular, disease-causing germline variants have been detected in TLR3, UNCG9381, TICAM1, TBK1, IRF3, IRF7, IFNAR1, and IFNAR2 in patients with life-threatening COVID-19 (213). Another recent study analyzing 1,610 COVID-19 patients and 2,205 control subjects from the first wave in heavily affected Italy and Spain found 2 chromosomal loci on chromosome three and nine with significant association with COVID-19 patients (214). On chromosome three the affected area includes several actors which might alter COVID-19 susceptibility including chemokine receptors, while on chromosome nine the association signal coincided with the AB0 blood group locus (214). AB0 blood group has independently been linked to COVID-19 susceptibility (214–216). Further studies are needed to confirm these associations in independent populations.

Applying this knowledge to detect individuals with elevated risk for severe disease might help to prioritize them for vaccination and stricter protection measures. As COVID-19 susceptibility and severity seem to have a polygenic background, we propose that a curated polygenic risk score (PGRS) might facilitate the detection of individuals with high risk for infection (Figure 1). Based on genome-wide analyses, polygenic risk scores are able to detect high-risk individuals in various diseases, fine-tuning the more widely used risk stratification dependent on baseline anthropometric and physiological characteristics (217, 218). A most recent GWAS on a cohort of COVID-19 patients from the U.K. found eight lead variants from independent genome-wide significant regions including rs2236757 in IFNAR2 coding for interferon α and β receptor subunit 2 (219). Though the individual odds ratio for each of the relatively frequent variants varies between 1.3 and 2.1, the combined odds ratio in the case of harboring all these susceptibility variants rises to 29.5, underlining the applicability of a polygenic risk score (219).

In addition to COVID-19 susceptibility, inclusion of genetic predictors of disease severity and treatment response might also be included. In particular, based on the effectiveness of glucocorticoid administration confirmed by the randomized, controlled RECOVERY clinical trial (220), it would be interesting to see if pharmacogenetic modifiers of glucocorticoid action, sensitivity and metabolism contribute to the severity of COVID-19 infection and treatment response (221).

It is important to note that the majority of the observed associations in Table 1 and Supplementary Table 1 were only validated in specific populations. By analyzing the population-specific allelic frequencies of the reviewed viral entry and innate immunity-related SNPs reviewed (Supplementary Table 2) we can conclude that the large variations in SNP frequencies might heavily influence their association with various traits in select populations. Additionally, pronounced differences in risk allele frequencies of the 8 proposed lead COVID-19-related SNPs (219) are present in different populations (Supplementary Table 3).

Moreover, these differences most probably alter epistatic interactions between genes, adding an additional layer of complexity (222).

Therefore, the observed population dependency of genotype-phenotype associations would probably result in population-specific PGRSs rather than a universal PGRS optimal for all populations. Dedicated efforts to perform population-specific GWASs regarding COVID-19 susceptibility and severity to build population-specific PGRSs are needed to address these differences.

DISCUSSION

The disruption caused by the COVID-19 pandemic has yet unknown consequences on the whole human society and on each affected patient’s health as well. Understanding the susceptibility toward this disease is important to detect high-risk individuals and also to decipher molecular mechanisms needed for the development of the clinical phenotype. Viral entry and innate immunity are key mechanisms in the initiation of SARS-CoV-2 infection. We performed a thorough literature review concerning genotype-phenotype association studies regarding agents of these mechanisms. Our results indicated that SNPs in the genes of these processes are frequently associated with susceptibility to various bacterial and viral infections. Additionally, several autoimmune diseases are also linked to these genes, underlining the versatile immune consequences of these genetic variants. Based on the confirmed associations it is highly plausible that the abovementioned SNPs might confer altered susceptibility to SARS-CoV-2 infection and its complex clinical consequences.

In addition to viral entry and innate immunity, other mechanisms including adaptive immunity are also of paramount importance regarding the susceptibility to COVID-19 (35). To better characterize putative genomic susceptibility loci, well-designed, international genome-wide association studies (GWAS) are needed.

As multiple GWASs on host genetic susceptibility are ongoing, several genomic susceptibility loci are proposed to be detected. Translating these individual susceptibility variants into clinically relevant polygenic risk scores would fully leverage this acquired knowledge to easily detect high-risk individuals prioritized for vaccination and stricter protective measures.

All things considered, genetic variants of genes of viral entry and innate immunity might alter susceptibility, and prognosis of COVID-19. Further GWASs are needed to better characterize susceptibility loci and to develop clinically relevant risk stratification strategies.

AUTHOR CONTRIBUTIONS

VG contributed to the design, performed literature search, and drafted the manuscript. AB contributed to the literature search. JP contributed to the design and the literature search.
AP conceived the review, contributed to the design, and literature search. All authors read and have agreed to the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2021.653489/full#supplementary-material

REFERENCES

1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis. (2020) 20:533–4. doi: 10.1016/S1473-3099(20)30120-1

2. Allison AC. Polymorphism and natural selection in human populations. Cold Spring Harb Symp Quant Biol. (1964) 29:137–49. doi: 10.1101/SQB.1964.029.01.018

3. Hill AV, Allsop CE, Kwiatkowski D, Anstey NM, Twumasi P, Rowe PA, et al. Common West African HLA antigens are associated with protection from severe malaria. Nature. (1991) 352:595–600. doi: 10.1038/352595a0

4. Liu R, Paxton WA, Choe S, Ceradini D, Martin SR, Horuk R, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. (2020) 181:271–80.e8. doi: 10.1016/j.cell.2020.02.052

5. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. (2020) 579:270–6. doi: 10.1038/s41586-020-2012-7

6. Fromer M, Roussos P, Sieberts SK, Johnson JS, Kavanagh DH, Perumal TM, et al. A genome-wide expression quantitative trait loci analysis of proprotein convertase subtilisin/kexin enzymes identifies a novel regulatory gene variant for FURIN expression and blood pressure. Hum Genet. (2015) 134:627–36. doi: 10.1007/s00439-015-1546-5

7. Zhang Q, Gu D, Kelly TN, Hisaxon JE, Rao DC, Jaquish CE, et al. Association of genetic variants in the apelin-APJ system and ACE2 with blood pressure responses to potassium supplementation: the GenSalt study. Am J Hypertens. (2010) 23:606–13. doi: 10.1038/ajh.2010.36

8. Bhanushali A, Rao P, Raman V, Kokate P, Ambekar A, Mandva S, et al. Status of TMPRSS2-ERG fusion in prostate cancer patients from India: correlation with clinicopathological details and TMPRSS2 Met160Val polymorphism. Prostate Int. (2018) 6:145–50. doi: 10.1016/j.proint.2018.03.004

9. FitzGerald LM, Agullu I, Johnson K, Miller MA, Kwon EM, Hurtado-Coll A, et al. Association of TMPRSS2-ERG gene fusion with clinical characteristics and outcomes: results from a population-based study of prostate cancer. BMC Cancer. (2008) 8:230. doi: 10.1186/1471-2405-8-230

10. Cheng Z, Zhou J, To KK, Chu H, Li C, Wang D, et al. Identification of SNRPR as a susceptibility gene for severe 2009 pandemic (H1N1) influenza and A(H7N9) influenza. J Infect Dis. (2015) 212:1214–21. doi: 10.1093/infdis/jiv246

11. Turpeinen H, Seppala I, Lytikainen LP, Raitoharju E, Nutri-Kahonen N, Levula M, et al. A genome-wide expression quantitative trait loci analysis of proprotein convertase subtilisin/kexin enzymes identifies a novel regulatory gene variant for FURIN expression and blood pressure. Hum Genet. (2015) 134:627–36. doi: 10.1007/s00439-015-1546-5

12. Fromer M, Roussos P, Sieberts SK, Johnson JS, Kavanah DH, Perumal TM, et al. Gene expression elucidates functional impact of polygenic risk for schizophrenia. Nat Neurosci. (2016) 19:1442–53. doi: 10.1038/nn.4399

13. Consortium CAD, Deloukas P, Kanoni S, Willenborg C, Farrall M, Assimes TL, et al. Large-scale association analysis identifies new risk loci for coronary artery disease. Nat Genet. (2015) 47:25–33. doi: 10.1038/ng.2480

14. Ueyama C, Horibe H, Yamase Y, Fujimaki T, Oguri M, Kato K, et al. Association of FURIN and ZP3 polymorphisms with metabolic syndrome. Biomed Rep. (2015) 3:641–7. doi: 10.3892/br.2015.684

15. Pilling LC, Kuo CL, Scininski K, Tamosauskaite J, Kuchel GA, Harries I.W., et al. Human longevity: 25 genetic loci associated in 389,166 UK biobank participants. Aging. (2017) 9:2504–20. doi: 10.18632/aging.101334

16. Fan Y, Li X, Zhang Y, Fan X, Zhang N, Zheng H, et al. Genetic variants of TPCN2 associated with type 2 diabetes risk in the Chinese population. PLoS ONE. (2016) 11:e0149614. doi: 10.1371/journal.pone.0149614

17. Fan Y, Li X, Zhang Y, Fan X, Zhang N, Zheng H, et al. Genetic variants of TPCN2 associated with type 2 diabetes risk in the Chinese population. PLoS ONE. (2016) 11:e0149614. doi: 10.1371/journal.pone.0149614

18. Sulem P, Gudbjartsson DF, Stacey SN, Helgason A, Rafnar T, Jacobsdottir M, et al. Two newly identified genetic determinants of pigmentation in Europeans. Nat Genet. (2008) 40:835–7. doi: 10.1038/ng.160
32. Chen S, Wang Z, Zhang L, Lu G, Zhou C, Wang DW, et al. Association between polymorphism in the human cathespin L (CTSL1) promoter with hypertension in the uruy, kazak and han populations in China. J Coll Phys Surg Pak. (2013) 23:5640–3.

33. Mbewe-Campbell N, Wei Z, Zhang K, Friese RS, Mahata M, Schork AI, et al. Genes and environment: novel, functional polymorphism in the human cathespin L (CTSL1) promoter disrupts a xenobiotic response element (XRE) to alter transcription and blood pressure. J Hypertens. (2012) 30:1961–9. doi: 10.1097/HJH.0b013e328356b88a

34. Vickers C, Hales P, Kaushik V, Dick L, Gavin J, Tang J, et al. Hydrolysis of biologically peptides by human angiotensin-converting enzyme-related carboxypeptidase. J Biol Chem. (2002) 277:14838–43. doi: 10.1074/jbc.M205081200

35. Li K, Hao Z, Zhao X, Du J, Zhou Y. SARS-CoV-2 infection-induced immune responses: friends or foes? Scand J Immunol. (2020) 92:e12895. doi: 10.1111/sj.12895

36. Nikonov A, Molder T, Sikut R, Kiiver K, Mannik A, Toots U, et al. Nuclear receptors in lung function. J Appl Physiol. (2012) 113:24–30. doi: 10.1152/japplphysiol.00549.2011

37. Lee NR, Ban J, Lee NJ, Yi CM, Choi JY, Kim H, et al. Activation of TLR1-mediated antiviral signaling triggers autophagy through the MAVS-TRAF6-beclin-1 signaling axis. Front Immunol. (2018) 9:2096. doi: 10.3389/fimmu.2018.02096

38. Xie T, Chen T, Li C, Wang W, Cao L, Rao H, et al. RACK1 attenuates RLR antiviral signaling by targeting VISA-TRAF complexes. Biochem Biophys Res Commun. (2019) 508:667–74. doi: 10.1016/j.bbrc.2018.11.203

39. Ovsyannikova IG, Haralambieva IH, Dhiman N, O’Byrne MM, Pankratz VS, Jacobson RM, et al. Polymorphisms in the vitamin A receptor and innate immune genes influence the antibody response to rubella vaccination. Vaccine. (2019) 37:9899–907. doi: 10.1016/j.vaccine.2019.09.043

40. Moumad K, Lascorz J, Bevier M, Khyatti M, Ennaji MM, Benider A, et al. Analysis of predicted loss-of-function variants in UK Biobank identifies variants protecting for disease. Nat Commun. (2018) 9:1613. doi: 10.1038/s41467-018-03911-8

41. Nejentsev S, Walker N, Riches D, Egholm M, Todd JA. Rare variants of IFIH1, a gene implicated in antiviral responses, protect against type 1 diabetes. Science. (2009) 324:387–9. doi: 10.1126/science.1167728

42. Chistjakov DA, Voronova NV, Savost'Anov KV, Turakulov RL. Loss-of-function mutations E67X and R923V of IFIH1 are associated with lower poly(I:C)-induced interferon-beta production in peripheral blood mononuclear cells of type 1 diabetes patients. Hum Immunol. (2010) 71:1128–34. doi: 10.1016/j.humimm.2010.08.005

43. Enevold C, Oturai AB, Sorensen PS, Ryder LP, Koch-Henriksen N, Bendtz K. Multiple sclerosis and polymorphisms of innate pattern recognition receptors TLR1-10, NOD1-2, DDX58, and IFIH1. J Neuroimmunol. (2019) 321:212–31. doi: 10.1016/j.jneuroim.2019.04.008

44. Yang H, Wang Z, Xu K, Gu R, Chen H, Yu D, et al. IFIH1 gene polymorphisms in type 1 diabetes: genetic association analysis and genotype-phenotype correlation in Chinese Han population. Autoimmun. (2012) 45:226–32. doi: 10.3109/08916934.2011.633134

45. Wang C, Ahlford A, Laxman N, Nordmark G, Eloranta ML, Gunnarsson I, et al. Contribution of IKBKE and IFIH1 gene variants to SLE susceptibility. Genes Immun. (2013) 14:217–22. doi: 10.1038/gene.2013.9

46. Liu J, Tang LY, Wang YG, Lu SY, Zhang EN, Wang ZG, et al. Identification of MAVS as a novel risk factor for the development of osteoarthritis. Aging Dis. (2018) 9:40–50. doi: 10.14336/AD.2017.0308

47. Lin LH, Ling P, Liu MF. The potential role of interferon-regulatory factor 7 among Taiwanese patients with systemic lupus erythematosus. J Rheumatol. (2011) 38:1914–9. doi: 10.3899/jrheum.101004

48. Fu Q, Zhao J, Qian X, Wong YL, Kaufman KM, Yu CY, et al. Association of a functional IRF7 variant with systemic lupus erythematosus. Arthritis Rheum. (2011) 63:749–54. doi: 10.1002/art.30193

49. Carmona FD, Gutala R, Simeon CP, Carreira P, Ortego-Centeno N, Vicente-Babanea E, et al. Novel identification of the IRF7 region as an antecedent the anti-thrombin propensity locus in systemic sclerosis. Ann Rheum Dis. (2012) 71:114–9. doi: 10.1136/annrheumdis-2011-200275

50. Bartoszewska-Gorycka A, Wajda A, Stypinska B, Walczyk E, Walczyk A, Ciereszko M, Giel-Giemsza A, et al. Interferons (IFN-A/B-G) genetic variants in patients with mixed connective tissue disease (MCTD). J Clin Med. (2019) 8:2046. doi: 10.3390/jcm8122046

51. Fujita M, Scheurer ME, Decker SA, McDonald HA, Kohanbash G, Kastenhuber ER, et al. Role of type 1 IFNs in antiangiogenic treatment for cancer. Cancer Immunol Immunother. (2010) 63:765–74. doi: 10.1007/s00262-009-0782-0

52. Spiegel M, Pichlmair A, Martinez-Sobrero L, Cros J, Garcia-Sastre A, Al-Qahtani A, et al. Toll-like receptor 3 polymorphism and its association with hepatitis B virus infection. J Invest Dermatol. (2010) 130:278–82. doi: 10.1038/jid.2010.214

53. Molineros JE, Maiti AK, Sun C, Looper LL, Han S, Kim-Howard X, et al. Admixutre mapping in lupus identifies multiple functional variants within IFIH1 associated with apoptosis, inflammation, and autoantibody production. PLoS Genet. (2013) 9:e1003222. doi: 10.1371/journal.pgen.1003222

54. Jermendy A, Szatmari I, Laine AP, Lukacs K, Horvath KH, Korner A, et al. The interferon-induced helicase IFIH1 Ala946Thr polymorphism is associated with type 1 diabetes in both the high-incidence finnish and the medium-incidence Hungarian populations. Diabetologia. (2010) 53:98–102. doi: 10.1007/s00125-009-1561-y

55. Smyth DJ, Cooper JD, Bailey R, Field S, Burren O, Smink LJ, et al. A genome-wide association study of nonsynonymous SNPs identifies a type 1 diabetes locus in the interferon-induced helicase (IFIH1) region. Nat Genet. (2006) 38:617–9. doi: 10.1038/ng1800

56. Emdin CA, Khera AV, Chaffin M, Klarin D, Natarajan P, Aragam K, et al. Analysis of predicted loss-of-function variants in UK Biobank identifies variants protecting for disease. Nat Commun. (2018) 9:1613. doi: 10.1038/s41467-018-03911-8
virus infection in Saudi Arabian patients. *J Med Virol.* (2012) 84:1353–9. doi: 10.1002/jmv.22371

67. Huang X, Li H, Wang J, Huang C, Lu Y, Qin X, et al. Genetic polymorphisms in Toll-like receptor 3 gene are associated with the risk of hepatitis B virus-related liver diseases in a Chinese population. *Gene.* (2015) 569:218–24. doi: 10.1016/j.gene.2015.05.054

68. Qian F, Bolen CR, Jing C, Wang X, Zheng W, Zhao H, et al. Impaired toll-like receptor 3-mediated immune responses from macrophages of patients chronically infected with hepatitis C virus. *Clin Vaccine Immunol.* (2013) 20:146–55. doi: 10.1128/CVI.00530-12

69. Al-Anzai MR, Matou-Nasri S, Abdo AA, Sanii FM, Alkahtani S, Alarifi S, et al. Association of toll-like receptor 3 single-nucleotide polymorphisms and hepatitis C virus infection. *J Immunol Res.* (2017) 2017:1590653. doi: 10.1155/2017/1590653

70. Svensson A, Tunback P, Nordstrom I, Padyukov L, Eriksson K. Polymorphisms in Toll-like receptor 3 confer natural resistance to human herpes simplex virus type 2 infection. *J Gen Virol.* (2012) 93:1717–24. doi: 10.1099/vir.0.042572-0

71. Sironi M, Biasin M, Cagliani R, Forni D, De Luca M, Saulle I, et al. A common polymorphism in TLR3 confers natural resistance to melanoma progression. *Cancer Epidemiol Biomarkers Prev.* 2019;28:2444–51. doi: 10.1158/1055-9965.EPI-19-0402

72. Huik K, Avi R, Pauskar M, Kallas E, Jogeda EL, Karki T, et al. Genetic variation in TLR pathway and the risk of asthma in a Han population. *Thorax.* (2015) 70:1196–6. doi: 10.1136/thoraxjnl-2015-207399

73. Castro FA, Forsti A, Buch S, Kalthoff H, Krauss C, Bauer M, et al. TLR-3.

74. Kawasaki A, Furukawa H, Kondo Y, Ito S, Hayashi T, Kusaoi M, et al. TLR-7.

75. Ikezoe K, Handa T, Tanizawa K, Kubo T, Ito I, Sokai A, et al. A toll-like receptor polymorphism is associated with the risk of hepatitis C virus infection in Saudi Arabian patients. *Infect Genet Evol.* (2014) 27:264–70. doi: 10.1016/j.meegid.2014.07.034

76. Dutta SK, Tripathi A. Association of toll-like receptor polymorphisms with susceptibility to chikungunya virus infection. *Virology.* (2011) 413:207–13. doi: 10.1016/j.virome.2011.07.013

77. Moller-Larsen S, Nyeegaard M, Haagerup A, Vestbo J, Kruse TA, et al. Association of toll-like receptor 9 gene polymorphism in Chinese patients with tuberculosis in a Moldavian population. *Infect Genet Evol.* (2019) 68:84–90. doi: 10.1016/j.meegid.2018.12.005

78. Davila S, Hiberd ML, Hari Dass R, Wong HE, Sahiratmadja E, Bonnard C, et al. Genetic association and expression studies indicate a role of toll-like receptor 8 in pulmonary tuberculosis. *PLoS Genet.* (2008) 4:e1000218. doi: 10.1371/journal.pgen.1000218

79. Edwards AO, Chen D, Fridley BL, James KM, Wu Y, Abecasis G, et al. Toll-like receptor polymorphisms and age-related macular degeneration. *Invest Ophthalmol Vis Sci.* (2008) 49:1652–9. doi: 10.1167/iovs.07-3737

80. Varzari A, Deyneko IV, Vladei I, Grallert H, Schieck M, Tudor E, et al. Genetic variation in TLR pathway and the risk of pulmonary tuberculosis in a Moldavian population. *Infect Genet Evol.* (2019) 68:84–90. doi: 10.1016/j.meegid.2018.12.005

81. Edwards AO, Chen D, Fridley BL, James KM, Wu Y, Abecasis G, et al. Toll-like receptor polymorphisms and age-related macular degeneration. *Invest Ophthalmol Vis Sci.* (2008) 49:1652–9. doi: 10.1167/iovs.07-3737

82. Varzari A, Deyneko IV, Vladei I, Grallert H, Schieck M, Tudor E, et al. Genetic variation in TLR pathway and the risk of pulmonary tuberculosis in a Moldavian population. *Infect Genet Evol.* (2019) 68:84–90. doi: 10.1016/j.meegid.2018.12.005

83. Davila S, Hiberd ML, Hari Dass R, Wong HE, Sahiratmadja E, Bonnard C, et al. Genetic association and expression studies indicate a role of toll-like receptor 8 in pulmonary tuberculosis. *PLoS Genet.* (2008) 4:e1000218. doi: 10.1371/journal.pgen.1000218

84. Wang MG, Zhang MM, Wang Y, Wu SQ, Zhang M, He QJ. Association of TLR8 and TLR9 polymorphisms with tuberculosis in a Chinese Han population: a case-control study. *BMC Infect Dis.* (2018) 18:561. doi: 10.1186/s12879-018-3485-3

85. Esposito S, Molteni CG, Zampiero A, Baggi E, Lavizzari A, Semino M, et al. Role of polymorphisms of toll-like receptor (TLR) 4, TLR9, toll-interleukin 1 receptor domain containing adaptor protein (TIRAP) and FCGR2A genes in malaria susceptibility and severity in Burundian children. *Malar J.* (2012) 11:196. doi: 10.1186/1475-2875-11-196

86. Omar AH, Yasunami M, Yamazaki A, Shibata H, Ofori MF, Akamnori BD, et al. Toll-like receptor 9 (TLR9) polymorphism associated with symptomatic malaria: a cohort study. *Malar J.* (2012) 11:166. doi: 10.1186/1475-2875-11-168

87. Paradowska E, Jablonska A, Studzinska M, Skowronska K, Suzuki P, Wniesiwskaja-Liger M, et al. TLR9-1486T/C and 2848C/T SNPs are associated with human cytomegalovirus infection in infants. *PLoS ONE.* (2016) 11:e0154100. doi: 10.1371/journal.pone.0154100

88. Kobayashi K, Yuliwulandari R, Yanai H, Naka I, Lien LT, Hang NT, et al. Association of TLR polymorphisms with development of tuberculosis in Indonesian females. *Tissue Antigens.* (2012) 79:199–207. doi: 10.1111/j.1399-0039.2011.01821.x

89. Torres-Garcia D, Cruz-Lagunas A, Garcia-Sancho Figueroa MC, Fernandez-Plata R, Baez-Saldana R, Mendoza-Milla C, et al. Variants in toll-like receptor 9 gene influence susceptibility to tuberculosis in a Mexican population. *J Transl Med.* (2013) 11:220. doi: 10.1186/1475-2875-11-220

90. Villani AC, Lemire M, Thabane M, Belisle A, Geneau G, Garg AX, et al. Genetic risk factors for post-infectious irritable bowel syndrome following a waterborne outbreak of gastroenteritis. *Gastroenterology.* (2010) 138:1502–13. doi: 10.1053/j.gastro.2009.12.049

91. Santos BP, Verlende JV, Rohr P, Monticello OA, Brenol JC, Xavier RM, et al. TLR7/8/9 polymorphisms and their associations in systemic lupus erythematosus patients from southern Brazil. *Lupus.* (2012) 21:302–9. doi: 10.1177/0961203311425522

92. Zhang J, Zhu Q, Meng F, Lei H, Zhao Y. Association study of TLR-9 gene polymorphisms and systemic lupus erythematosus in northern Chinese Han population. *Gene.* (2014) 533:385–8. doi: 10.1016/j.gene.2013.08.051

93. Huang CM, Huang PH, Chen CL, Lin YJ, Tsai CH, Huang WL, et al. Association of toll-like receptor 9 gene polymorphism in Chinese patients...
Schroder NW, Diterich I, Zinke A, Eckert J, Draing C, von Baehr V, et al. (2012) 32:2105–9. doi: 10.1007/s00296-011-1925-8

Zhou XJ, Lv JC, Cheng WR, Yu L, Zhao MH, Zhang H. Association of TLR9 gene polymorphisms with lupus nephritis in a Chinese Han population. Clin Exp Rheumatol. (2010) 28(3):397–400.

Liao WL, Chen RH, Lin HJ, Liu YH, Chen WC, Tsai Y, et al. Toll-like receptor gene polymorphisms are associated with susceptibility to Graves' ophthalmopathy in Taiwanese males. BMC Med Genet. (2010) 11:154. doi: 10.1186/1471-2353-11-154

Etem EO, Elyas H, Ozgoçmen S, Yıldırım A, Gökdemerdan A. The investigation of toll-like receptor 3, 9 and 10 gene polymorphisms in Turkish rheumatoid arthritis patients. Rheumatol Intl. (2011) 31:1369–74. doi: 10.1007/s00296-010-1472-8

Ryba J, Gebura K, Wrobel T, Wysoczanska B, Stefanko E, Kucilczkowski K, et al. Variations in genes involved in regulation of the nuclear factor – kappaB pathway and the risk of acute myeloid leukaemia. Int J Immunogenet. (2016) 43:101–6. doi: 10.1111/iji.12255

Roszak A, Lianeri M, Sowinska A, Jagodzinski PP. Involvement of Toll-like Receptor 9 polymorphism in cervical cancer development. Mol Biop Rep. (2012) 39:8425–30. doi: 10.1186/1471-2180-11-1985

Lai ZZ, Ni Z, Pan XL, Song L. Toll-like receptor 9 (TLR9) gene association investigation of toll-like receptor 3, 9 and 10 gene polymorphisms in Turkish rheumatoid arthritis patients. Rheumatol Intl. (2011) 31:1369–74. doi: 10.1007/s00296-010-1472-8

Stark JR, Wiklund F, Gronberg H, Schumacher F, Sinnott JA, Stampfer MJ, et al. Toll-like receptor signaling pathway variants and prostate cancer mortality. Cancer Epidemiol Biomark Prev. (2009) 18:1859–63. doi: 10.1158/1055-9966.EPI-08-0981

Xue X, Qiu Y, Jiang D, Jin T, Yan M, Zhu X, et al. The association analysis of TLR2 and TLR4 gene with tuberculosis in the Tibetan Chinese population. Oncotarget. (2017) 8:113082–9. doi: 10.18632/oncotarget.22996

Wu L, Hu Y, Li D, Jiang W, Xu B. Screening toll-like receptor markers to predict latent tuberculosis infection and subsequent tuberculosis disease in a Chinese population. BMC Med Genet. (2015) 16:19. doi: 10.1186/s12881-015-0166-1

Taniguchi R, Koyano S, Suzutani T, Goishi K, Ito Y, Morioka I, et al. Polymorphisms in TLR2 and TLR4 are associated with congenital cytomegalovirus (CMV) infection but not with congenital CMV disease. Int J Infect Dis. (2013) 17:e1092–7. doi: 10.1016/j.ijid.2013.06.004

Royse KE, Kempf MC, McGwin G, Wilson CM, Tang J, Shrestha S. Toll-like receptor gene variants associated with bacterial vaginosis among HIV-1 infected adolescents. J Reprod Immunol. (2012) 96:84–8. doi: 10.1016/j.jregim.2012.08.002

Mackelprang RD, Scoville CW, Cohen CR, Orondo RO, Bingham AW, Celum C, et al. Toll-like receptor gene variants and bacterial vaginosis among HIV-1 infected and uninfected African women. Genes Immun. (2015) 16:362–5. doi: 10.1038/genes.2015.13

Rosentul DC, Delsing CE, Jaeger M, Plantinga TS, Oosting M, Costantini I, et al. Gene polymorphisms in pattern recognition receptors and cytomegalovirus (CMV) infection but not with congenital CMV disease. Front Microbiol. (2014) 5:483. doi: 10.3389/fmicb.2014.00483

Takahashi M, Chen Z, Watanabe K, Kobayashi H, Nakajima T. The association between Toll-like receptor 2 single-nucleotide polymorphisms and hepatocellular carcinoma susceptibility. BMC Cancer. (2012) 12:57. doi: 10.1186/1471-2407-12-57

Kimura A, et al. Toll-like receptor 2 gene polymorphisms associated with increased susceptibility of human tuberculosis disease in a Chinese population. Exp Rheumatol Clin Rheum. (2017) 49:110–5. doi: 10.5603/AIT.a2017.0027

Mackelprang RD, Scoville CW, Cohen CR, Orondo RO, Bingham AW, Celum C, et al. Toll-like receptor gene variants and bacterial vaginosis among HIV-1 infected and uninfected African women. Genes Immun. (2015) 16:362–5. doi: 10.1038/genes.2015.13

Rosentul DC, Delsing CE, Jaeger M, Plantinga TS, Oosting M, Costantini I, et al. Gene polymorphisms in pattern recognition receptors and susceptibility to idiopathic recurrent vulvovaginal candidiasis. Front Microbiol. (2014) 5:483. doi: 10.3389/fmicb.2014.00483

Abah-Osain S, Gurel G. The polymorphism rs4969480 in the TLR2 gene is associated with psoriasis patients in the Turkish population. Immunol Lett. (2019) 211:28–32. doi: 10.1016/j.imlet.2019.05.008

Junjie X, Songyao J, Minmin S, Yanyan S, Baiyong S, Xiaixiang D, et al. The association between Toll-like receptor 2 single-nucleotide polymorphisms and hepatocellular carcinoma susceptibility. BMC Cancer. (2012) 12:57. doi: 10.1186/1471-2407-12-57

Mansur A, von Gruben L, Popov AF, Steinau M, Bergmann I, Ross D, et al. Investigation of Toll-like receptor gene variants and risk of non-Hodgkin lymphoma. Cancergenesis. (2009) 30:275–81. doi: 10.1016/j.cancergen.2009.09.015

Taylor BD, Darville T, Ferrell RE, Krammer CM, Ness RB, Haggerty CL. Variants in toll-like receptor 1 and 4 genes are associated with Chlamydia trachomatis among women with pelvic inflammatory disease. J Infect Dis. (2012) 205:603–9. doi: 10.1093/infectdis/jir822

Agneze DM, Calvano JE, Hahn SJ, Coyle SM, Corbett SA, Calvano SE, et al. Human toll-like receptor 4 mutations but not CD14 polymorphisms are associated with an increased risk of gram-negative infections. J Infect Dis. (2002) 186:15125–2. doi: 10.1086/348493

Sampath V, Mulrooney NP, Garland JS, He J, Patel AL, Cohen JD, et al. Toll-like receptor genetic variants are associated with Gram-negative infections in VLBW infants. J Perinatol. (2013) 33:772–7. doi: 10.1038/jp.2013.80

Wagner J, Skinner NA, Catto-Smith AG, Cameron DJ, Michalski WP, Visvanathan K, et al. TLR4, IL10RA, and NOD2 mutation in paediatric Crohn’s disease patients: an association with Mycobacterium avium subspecies paratuberculosis and TLR4 and IL10RA expression. Med Microbiol Immunol. (2013) 202:267–76. doi: 10.1007/s00430-013-0290-5

Tal G, Mandelberg A, Dalal I, Cesar K, Somekh E, Tal A, et al. Association between common Toll-like receptor 4 mutations and severe respiratory infection due to mycobacterial avium subspecies paratuberculosis. J Infect Dis. (2004) 189:257–63. doi: 10.1086/420830

da Silva Santos S, Clark TG, Campino S, Suarez-Mutis MC, Rockett KA, Kwiatkowski DP, et al. Investigation of host candidate malaria-associated risk/protective SNPs in a Brazilian amazonian population. PLoS ONE. (2012) 7:e36692. doi: 10.1371/journal.pone.0036692

Tsui FW, Xi N, Rohekar S, Riahi R, Bilotta R, Tsui HW, et al. Toll-like receptor 2 variants are associated with acute reactive arthritis. Arthritis Rheum. (2008) 58:3456–8. doi: 10.1002/art.23967

Ovsyannikova IG, Haralambieva IH, Vierkant RA, Pankratz VS, Jacobson RM, Poland GA. The role of polymorphisms in Toll-like receptors and their associated intracellular signaling genes in measles vaccine immunity. Hum Genet. (2011) 130:547–61. doi: 10.1007/s00439-011-1077-x

Zukowski M, Taryma-Lesniak O, Kaczmarczyk M, Kofis S, Szydlowski L, Ciechanowicz A, et al. Relationship between toll-like receptor 2 R753Q and T16934A polymorphisms and Staphylococcus aureus nasal carriage. Anaesthesia Intensive Ther. (2017) 49:110–5. doi: 10.5603/AIT.a2017.0027
137. Hawn TR, Scholes D, Li SS, Wang H, Yang Y, Roberts PL, et al. Toll-like receptor polymorphisms and susceptibility to urinary tract infections in adult women. PLoS ONE. (2009) e95590. doi: 10.1371/journal.pone.0095590
138. Carvalho A, Pasqualotto AC, Pitzurra L, Romani L, Denning DW, Rodrigues F. Polymorphisms in toll-like receptor genes and susceptibility to pulmonary aspergillosis. J Infect Dis. (2014) 209:576–82. doi: 10.1093/infdis/jit129
139. Al-Qahtani AA, Al-Anazi MR, Al-Zoghaihi E, Abdo AA, Sanai FM, Khan MQ, et al. The association of toll-like receptor 4 polymorphism with hepatitis C virus infection in Saudi Arabian patients. Biomed Res Int. (2014) 2014:357062. doi: 10.1155/2014/357062
140. Cussigh A, Fabris C, Fattovich G, Falletti E, Cmet S, Bitteto D, et al. Toll-like receptor 4 D299G associates with disease progression in caucasian patients with chronic HBV infection: relationship with gender. J Clin Immunol. (2013) 33:313–6. doi: 10.1007/s10875-012-9822-9
141. Wu JF, Chen CH, Ni YH, Lin YT, Chen HL, Hsu HY, et al. Toll-like receptor and hepatitis B virus clearance in chronically infected patients: a long-term prospective cohort study in Taiwan. J Infect Dis. (2012) 206:662–8. doi: 10.1093/infdis/jis420
142. Dhiman N, Ovsyannikova IG, Vierkant RA, Ryan JE, Pankratz VS, Jacobson RM, et al. Associations between SNPs in toll-like receptors and related intracellular signaling molecules and immune responses to measles vaccine: preliminary results. Vaccine. (2008) 26:1731–6. doi: 10.1016/j.vaccine.2008.01.017
143. Hafren L, Einarsdottir E, Kentala E, Hammaren-Malmi S, Bhutta MF, et al. Polymorphism of the TLR4 gene and its interaction with infected patients. J Infect Dis. (2008) 197:618–21. doi: 10.1086/526500
144. Carvalho A, Pasqualotto AC, Pitzurra L, Romani L, Denning DW, Rodrigues F. Associations between SNPs in toll-like receptor 4 (TLR4) polymorphisms and the risk of prostate cancer in Korean men. Cancer Genet Cytogenet. (2009) 199:88–92. doi: 10.1016/j.cancergen.2008.12.011
145. Tullids KK, Helzlouer KJ, Smith MW, Grinberg V, Hoffman-Bolton J, Clipp SL, et al. Association of common polymorphisms in IL10, and in other genes related to inflammatory response and obesity with colorectal cancer. Cancer Causes Control. (2009) 20:1739–51. doi: 10.1007/s10555-009-9427-7
146. Gu X, Shen Y, Fu L, Zuo HY, Yasen H, He P, et al. Polymorphic variation of inflammation-related genes and risk of non-hodgkin lymphoma for Uygur and Han Chinese in Xinjiang. Asian Pac J Cancer Prev. (2014) 15:9177–83. doi: 10.7314/APJCP.2014.15.21.9177
147. Van Rijn BB, Franx A, Steegers EA, de Groot CJ, Bertina RM, Pausterkamp G, et al. Polymorphic variation of the TLR4 gene and its interaction with susceptibility to urinary tract infections in children. J Infect Dis. (2013) 207:1020–6. doi: 10.1093/infdis/jit870
148. Hwang YH, Ro H, Choi I, Kim H, Oh KH, Hwang JI, et al. Polymorphic variation of the TLR4 gene and its interaction with susceptibility to urinary tract infections in children. J Infect Dis. (2013) 208:675–80. doi: 10.1093/infdis/jit677
149. Palmer SM, Burch LH, Davis RD, Herczyk WF, Howell DN, Reinsmoen NL, et al. Association of common polymorphisms in cytokines and Toll-like receptor 4 polymorphisms with Buerger disease but not with takayasu arteritis in Japanese. J Hum Genet. (2011) 56:545–7. doi: 10.1038/jhg.2011.44
150. Potter C, Cordell HJ, Barton A, Daly AK, Hyrich KL, Mann DA, et al. Association between anti-tumour necrosis factor treatment response and genetic variants within the TLR and NF-kB signalling pathways. Ann Rheum Dis. (2010) 69:1315–20. doi: 10.1136/ard.2009.117309
151. Yang Y, Yang S, Chen Z, Liu L. Correlation between TICAM1 gene polymorphisms and community-acquired pneumonia in children. J Biochem Mol Toxicol. (2020) 34:e22503. doi: 10.1002/jbt.22503
152. Sigurdson AJ, Brenner AV, Roach JA, Goudeva L, Muller JA, Neri R, et al. Selected single-nucleotide polymorphisms in FOXE1, SERPINA5, FTO, EVPL, TICAM1 and SCARB1 are associated with type 2 diabetes and obesity. Genet Test Mol Biomarkers. (2014) 18:905–12. doi: 10.1089/gtmb.2013.0431
153. Yang YN, Zhang JY, Ma YT, Xie X, Li XM, Liu F, et al. Functional polymorphism in NFKB1 and NFKBIA and coronary artery disease in a Chinese Uygur population. PLoS ONE. (2015) 10:e0129144. doi: 10.1371/journal.pone.0129144
154. Lai HM, Li XM, Yang YN, Ma YT, Xu R, Pan S, et al. Genetic Variation in NFKB1 and NFKBIA and susceptibility to coronary artery disease in a Chinese Uygur population. PLoS ONE. (2015) 10:e0129144. doi: 10.1371/journal.pone.0129144
155. Jin SY, Luo JY, Li XM, Liu F, Ma YT, Gao XM, et al. NFKB1 gene rs2836249 polymorphisms with coronary artery disease in a Han Chinese population. Int J Clin Exp Med. (2015) 8:21487–96. doi: 10.7150/ijtem.2015.8.14.21487
156. Lai HM, Li XM, Yang YN, Ma YT, Xu R, Pan S, et al. Genetic Variation in NFKB1 and NFKBIA and susceptibility to coronary artery disease in a Chinese Uygur population. PLoS ONE. (2015) 10:e0129144. doi: 10.1371/journal.pone.0129144
157. Lai HM, Li XM, Yang YN, Ma YT, Xu R, Zhai H, et al. The association of toll-like receptor 4 (TLR4) polymorphism with susceptibility to urinary tract infections in adult women. PLoS ONE. (2009) e95590. doi: 10.1371/journal.pone.0095590
158. Grolmusz et al. Genetic Variants in COVID-19 Susceptibility
207. Suh JS, Hahn WH, Cho BS. Polymorphisms of CXCL8 and its receptor CXCR2 contribute to the development and progression of childhood IgA nephropathy. *J Interferon Cytokine Res.* (2011) 31:309–15. doi: 10.1089/jir.2010.0031

208. Dan H, Liu W, Zhou Y, Wang J, Chen Q, Zeng X. Association of interleukin-8 gene polymorphisms and haplotypes with oral lichen planus in a Chinese population. *Inflammation.* (2010) 33:76–81. doi: 10.1007/s10753-009-9160-0

209. Charrad R, Kaabachi W, Rafrafi A, Berraies A, Hamzaoui K, Hamzaoui A. IL-8 gene variants and expression in childhood Asthma. *Lung.* (2017) 195:749–57. doi: 10.1007/s00408-017-0058-6

210. Gu LQ, Jia HY, Zhao YJ, Liu N, Wang S, Cui B, et al. Association studies of interleukin-8 gene in Graves’ disease and Graves’ ophthalmopathy. *Endocrine.* (2009) 36:452–6. doi: 10.1007/s12020-009-9240-9

211. Rafrafi A, Chahed B, Kaabachi S, Kaabachi W, Maalmi H, Hamzaoui K, et al. Association of IL-8 gene polymorphisms with non small cell lung cancer in Tunisia: a case control study. *Hum Immunol.* (2013) 74:1368–74. doi: 10.1016/j.humimm.2013.06.033

212. Gonzalez-Hormazabal P, Romero S, Musleh M, Bustamante M, Stambuk J, Pisano R, et al. IL-8 -251T>A (rs4073) Polymorphism is associated with prognosis in gastric cancer patients. *Anticancer Res.* (2018) 38:5703–8. doi: 10.21873/anticancerres.12907

213. Zhang Q, Bastard P, Liu Z, Le Pen J, Moncada-Velez M, Chen J, et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science.* (2020) 370. doi: 10.1126/science.aba4570

214. Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Invernizzi P, et al. Genomewide association study of severe Covid-19 with respiratory failure. *N Engl J Med.* (2020) 383:1522–34. doi: 10.1056/NEJMoa2020283

215. Zhao J, Yang Y, Huang H, Li D, Gu D, Lu X, et al. Relationship between the ABO blood group and the COVID-19 susceptibility. *Clin Infect Dis.* (2020) ciaa1150. doi: 10.1093/cid/ciaa1150

216. Zietz M, Tatonetti NP. Testing the association between blood type and COVID-19 infection, intubation, and death. *medRxiv.* (2020). doi: 10.1101/2020.04.08.20058073

217. Torkamani A, Wineinger NE, Topol EJ. The personal and clinical utility of polygenic risk scores. *Nat Rev Genet.* (2018) 19:581–90. doi: 10.1038/s41576-018-0018-x

218. Lambert SA, Abraham G, Inouye M. Towards clinical utility of polygenic risk scores. *Hum Mol Genet.* (2019) 28:R133–R42. doi: 10.1093/hmg/ddz187

219. Pairo-Castineira E, Clohisey S, Klaric L, Bretherick AD, Rawlik K, Pasko D, et al. Genetic mechanisms of critical illness in Covid-19. *Nature.* (2020). doi: 10.1038/s41586-020-03065-y. [Epub ahead of print].

220. Group RC, Horby P, Lim WS, Emberson JR, Matham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19 - preliminary report. *N Engl J Med.* (2020). doi: 10.1056/NEJMoa2021436

221. Young MJ, Clyne CD, Chapman KE. Endocrine aspects of ACE2 regulation: RAAS, steroid hormones and SARS-CoV-2. *J Endocrinol.* (2020) 247:R45–62. doi: 10.1530/JOE-20-0260

222. Phillips PC. Epistasis—the essential role of gene interactions in the structure and evolution of genetic systems. *Nat Rev Genet.* (2008) 9:855–67. doi: 10.1038/nrg2452

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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