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The association of COVID-19 severity and susceptibility and genetic risk factors: A systematic review of the literature

Angela Ishak^{a,*}, Meghana Mehendale^a, Mousa M AlRawashdeh^{a,b}, Cristina Sestacovschi^a, Medha Sharath^{a,c}, Krunal Pandav^a, Sima Marzban^a

^a Department of Research & Academic Affairs, Larkin Community Hospital, South Miami, Florida, USA

^b European University Cyprus - School of Medicine, Nicosia, Cyprus

^c Bangalore Medical College and Research Institute, Bangalore, Karnataka, India

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ABSTRACT

Background: COVID-19 is associated with several risk factors such as distinct ethnicities (*genetic ancestry*), races, sexes, age, pre-existing comorbidities, smoking, and genetics. The authors aim to evaluate the correlation between variability in the host genetics and the severity and susceptibility towards COVID-19 in this study.

Methods: Following the PRISMA guidelines, we retrieved all the relevant articles published until September 15, 2021, from two online databases: PubMed and Scopus.

Findings: High-risk *HLA* haplotypes, higher expression of *ACE* polymorphisms, and several genes of cellular proteases such as *TMPRSS2*, *FURIN*, *TLL-1* increase the risk of susceptibility and severity of COVID-19. In addition, upregulation of several genes encoding for both innate and acquired immune systems proteins, mainly CCR5, IFNs, TLR, DPPs, and TNF, positively correlate with COVID-19 severity. However, reduced expression or polymorphisms in genes affecting TLR and IFN λ increase COVID-19 severity.

Conclusion: Higher expression, polymorphisms, mutations, and deletions of several genes are linked with the susceptibility, severity, and clinical outcomes of COVID-19. Early treatment and vaccination of individuals with genetic predisposition could help minimize the severity and mortality associated with COVID-19.

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, mainly spreads via respiratory droplets and primarily targets the respiratory tract (Go et al., 2020; Talalaev et al., 2022). Recently, it caused a global pandemic with deleterious effects on a large scale leading to unprecedented damage and high number of deaths worldwide (Ferreira

Caceres et al., 2022; Go et al., 2020; Hathaway et al., 2020; Sarfraz et al., 2021; Sosa et al., 2021). The severity of COVID-19 seems to be affected by various risk factors (Glotov et al., 2021). Heightened risk of COVID-19 associated mortality is seen in about 27–30% of the population suffering from arterial hypertension, 16.2% of the diabetic population, and 5.8% patients with cardiovascular issues (Glotov et al., 2021). In addition, approximately 60% of the deceased patients are reportedly

Abbreviations: ACE-1, angiotensin-converting enzyme 1; ACE-2, angiotensin-converting enzyme 2; ACE, Angiotensin-converting enzyme; AR, Androgen receptor; BPIFB4, BPI fold containing family B member 4; C3, Complement component 3; CCR5, C-C Motif Chemokine Receptor 5; CCR9, CC motif chemokine receptor 9; COVID-19, Coronavirus disease 2019; CXCR6, Chemokine Receptor Type 6; CYP2R1, cytochrome P450 family 2 subfamily R member 1; DDR1, discoidin domain receptor tyrosine kinase 1; DPP, dipeptidyl peptidases; FYCO1, fyve and coiled-coil domain-containing protein 1; GOLGA3, Golgin A3; HLA, Human leukocyte antigen; HNRNPk, heterogeneous nuclear ribonucleoprotein K; IFI30, gamma-interferon-inducible lysosomal thiol reductase; IFITM3, Interferon Induced Transmembrane Protein 3; IFN, interferons; IFNAR, interferon alpha and beta receptor; IL, Interleukin; KIR3DS1, Killer cell immunoglobulin-like receptor 3DL1; LZTFL1, Leucine Zipper Transcription Factor Like; MBL2, mannose binding lectin 2; MERS, Middle East Respiratory Syndrome; MUC5B, mucin 5B; PNPLA3, patatin-like phospholipase domain-containing protein 3; RMI1, RecQ mediated genome instability 1; SLC6A20, Solute Carrier Family 6 Member 20; SNP, single nucleotide polymorphisms; TAS2R38, taste receptor 2 member 38; TLL-1, Toll-like protein 1; TLR, Toll-like receptor; TNF- α , tumor necrosis factor- α ; TNFRSF13C, TNF Receptor Superfamily Member 13C; TNFRSF1A, TNF Receptor Superfamily Member 1A; Transmembrane protease serine2, TMPRSS2; XCR1, X-C motif chemokine receptor 1; TIRAP, TIR Domain Containing Adaptor Protein; IFN λ 3, interferon lambda 3.

* Corresponding author at: Department of Research & Academic Affairs, Larkin Community Hospital, South Miami, Florida 33143, USA.

E-mail address: angela.ishak.10@gmail.com (A. Ishak).

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males (D'Amico et al., 2021). Race and ethnicity appear to have an importance in shaping the course of the COVID-19, as individuals from the black community reportedly contributed to roughly 58 percent of COVID-19 deaths in the United States in 2020 (Millett et al., 2020). Similarly, cohort studies from the United Kingdom show that certain ethnic minorities such as South Asians were more likely to acquire COVID-19 infection and suffer from complications associated with severe infection (Mathur et al., 2021).

COVID-19 has a wide clinical range- from asymptomatic individuals to full-blown illness, with symptoms ranging from moderate to severe (Booth et al., 2021; Casanova et al., 2020). Fever, cough, myalgias, fatigue, and dyspnea are the most common symptoms seen in moderate to severe cases of COVID-19 (Huang et al., 2020). Critical COVID-19 cases are depicted by acute respiratory distress syndrome (ARDS) and extrapulmonary manifestations affecting the cardiovascular, renal, gastrointestinal, hepatobiliary, and central nervous system, arising in 15% of COVID-19 cases (Casella et al., 2022; Maslove et al., 2021; Yildirim et al., 2021). It takes around seven days for the patient to develop moderate to critical illness from symptom onset, receiving treatment only in the late phase of COVID-19 during hospitalization (Giammaria and Pajewski, 2020). Early treatment of high-risk patients has shown a reduction in the disease progression to a severe form of COVID-19 (Giammaria and Pajewski, 2020). Hence, identifying the populations at risk from suffering from severe complications of COVID-19 disease is crucial to reducing hospitalizations, intensive care unit (ICU) admissions, and death (Giammaria and Pajewski, 2020).

Recent research suggests that individuals with a varied expression of several genes and their alleles such as *HLA*, Angiotensin-converting enzyme-2 (*ACE-2*), cellular proteases, and immune response proteins might have a genetic predisposition to severe COVID-19 (Yildirim et al., 2021).

After viral binding and entry, the SARS-CoV-2 virus invades the upper and the lower respiratory tract, triggering the immune response by releasing numerous cytokines and interleukins (IL-1, IL-6, IL-8, IL-120, and IL-12), tumor necrosis factor- α (TNF- α), and interferons (IFN) from the infected host cells (Casella et al., 2022; Parasher, 2021). The cytokine-induced inflammatory response in the lungs and extrapulmonary tissues leads to a severe course of COVID-19 (Parasher, 2021).

We aim to evaluate the existing pool of literature signifying the correlation between the variability of human genomic expression, the severity of COVID-19, and susceptibility to COVID-19 infection. A thorough understanding of the roleplay between different genetic factors and the progression of COVID-19 infection is crucial to develop new therapeutic options, strategies for disease prevention, and diagnostic, predictive models to anticipate severe clinical outcomes, thereby starting medical intervention during the early course of the disease, which could help in improving the clinical outcomes.

2. Methods

2.1. Search strategy

This systematic review was reported following the Preferred Reporting Item for Systematic Review and Meta-Analysis (PRISMA) statement (Page et al., 2021). PubMed and Scopus were systematically searched until 15th September 2021. A medical subject subheadings (MESH) term and keyword searches were performed using relevant combinations. The search strategy included terms related to COVID-19, disease susceptibility, disease severity, genetic predisposition, and specific genes associated with COVID-19, such as *ACE*. Citations of relevant articles and reviews were also searched for relevant articles. The exact search strategy for each electronic database is provided in the **Appendix**. Additionally, an updated database search was undertaken on May 5th, 2022, using the same search strategy.

2.2. Study selection

Two reviewers performed the abstract/title and full-text screening processes for the eligible articles. Any disagreements that arose during the screening were resolved independently by a third reviewer. The following were the inclusion criteria: (1) studies available in English, (2) studies including COVID-19 patients that discussed the link between certain genes and COVID-19 disease severity or susceptibility, and (3) articles on the adult population. On the other hand, the exclusion criteria were: (1) articles in languages other than English, (2) animal studies (3) studies with overlapping data. Reviews, editorials, letters to editors, conference abstracts, and articles with incomplete results were also excluded.

2.3. Data extraction

Data were extracted onto an Excel® 2019 sheet by two authors. The extracted information included the author, year, the gene studied, the specific genetic polymorphism, sample size, and population characteristics.

2.4. Study outcomes

The primary outcome of this review was to assess the genetic risk factors that can increase the severity of COVID-19 infections and render certain individuals more susceptible to infection. Secondary outcomes included assessing if certain genes were more prevalent in specific populations.

2.5. Definitions

Mild COVID-19 disease (controls) was defined as patients who were asymptomatic or those who were symptomatic but did not develop pneumonia, while severe/critical disease was defined as patients who developed radiographical evidence of pneumonia with confirmatory COVID-19 diagnosis and required hospitalization.

3. Results

295 articles were screened from PubMed (202 articles) and Scopus (93 articles) during the initial search. Sixteen duplicate articles were removed, leaving 279 articles for the preliminary (title and abstract) screening process, of which 63 were eligible for full-text screening. 106 more articles were identified following an updated database search. Of these, 19 were eligible for full-text screening. 20 articles were excluded for reasons explained in **Figure 1**. Therefore, 60 articles were included in the final qualitative analysis. The detailed screening process and reasons for article exclusion are summarized in **Figure 1**.

This systematic review elucidates the impact of the genetic makeup of an individual or certain populations on the severity and susceptibility towards COVID-19 infection. Based on this premise, all the genes found in association with increased risk of COVID-19 severity and susceptibility are described in detail below.

4. Discussion

4.1. Angiotensin-converting enzyme

Our systematic review identified several angiotensin-converting enzyme (ACE) polymorphisms that affect the pathogenesis of COVID-19 infection, summarized in **Table 1**. Entry of SARS-CoV-2 virus to the host cell occurs via the attachment of its S protein to ACE-2. Therefore, variations in the sequence of *ACE-2* affecting its interaction with the SARS-CoV-2 virus via conformational changes in its structure or affecting the degree of its affinity to the viral S proteins, could be a genetic risk factor for the susceptibility and severity of COVID-19

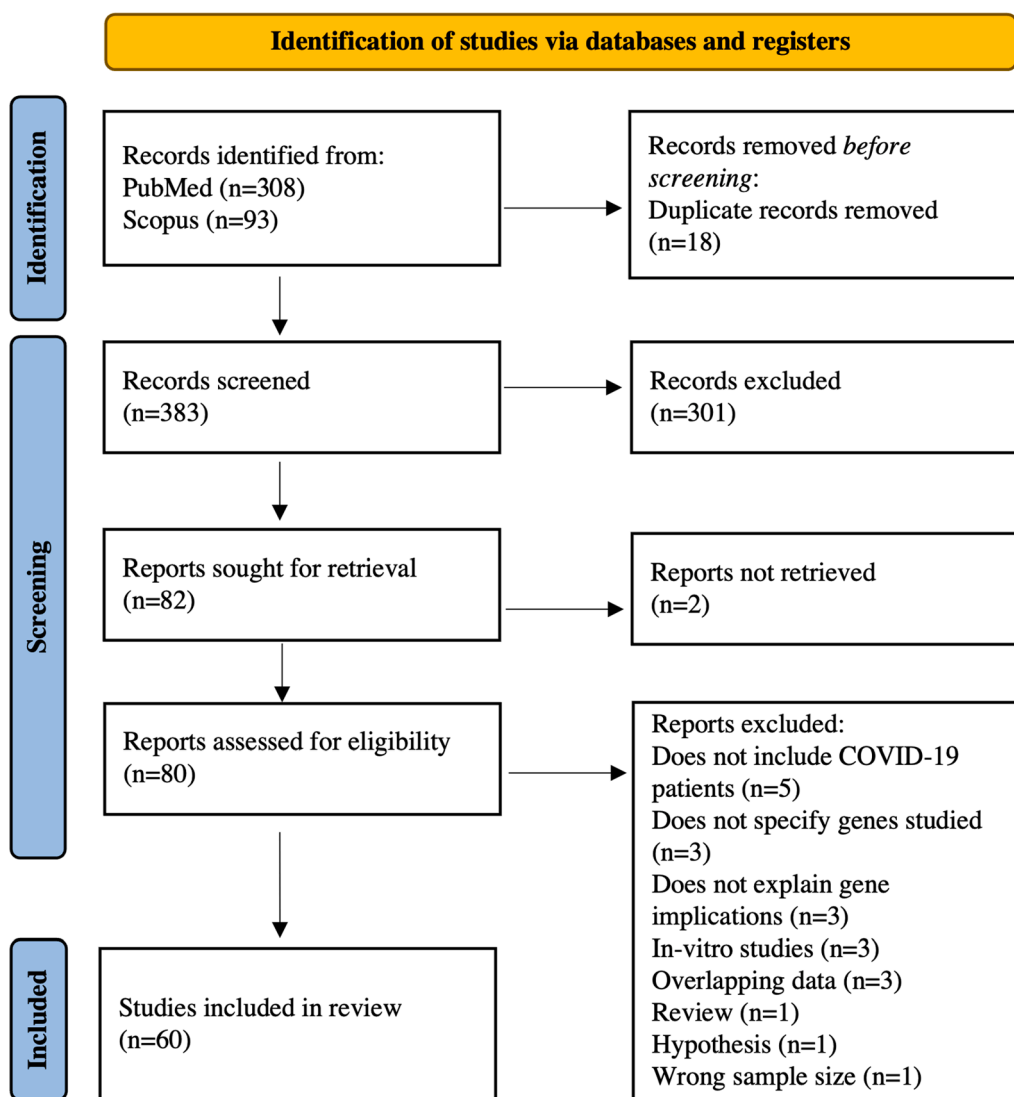


Figure 1. The 2020 PRISMA flowchart detailing study screening and selection

infection, ultimately governing its clinical outcome. It has been observed that variations located at the proteolytic cleavage site led to soluble ACE-2 acting as a decoy receptor for the virus and decreasing virus intake by cell surface ACE-2 (Darbeheshti et al., 2021).

The S protein exerts an inhibitory effect on ACE-2 expression which leads to increased levels of angiotensin II and/or angiotensin 1–7 in the affected cells, which could lead to severe acute pulmonary damage by causing increased vascular permeability, inflammation, and hypoxia, thereby increasing disease severity and patient mortality (Hashemi et al., 2021). There are varying levels of expression of ACE-2 among different individuals, depending on polymorphisms of the regulatory and non-coding regions such as promoter, in ACE-2. A higher level of ACE-2 expression has been hypothesized to provide protection against severe manifestations in pediatric COVID-19 patients (Hashemi et al., 2021).

Lower expression of ACE-2 and TMPRSS2 (transmembrane protease serine 2) in the African population could perhaps explain the fewer reported cases of COVID-19 in Africa (Khayat et al., 2020; Ortiz-Fernández and Sawalha, 2020). Individuals with ACE-2 variants K31R and E37K, S331F, and K26R (rs4646116) showed decreased susceptibility to COVID-19, while individuals with K26R and T92I variants showed increased susceptibility (Lanjanian et al., 2021; Suryamohan et al., 2021).

Our review found that ACE-1 single nucleotide polymorphisms (SNP) rs4341 and rs4343 were linked to severe infection in hypertensive, dyslipidemic, and type 2 diabetic patients. rs2074192 (ACE-2) and rs1799752 (ACE-1) variants, and rs699 (AGT) SNP were also hypothesized to predict the clinical outcome of patients infected with SARS-CoV-2 (Cafiero et al., 2021; Íñiguez et al., 2021). However, we found just one study assessing the rs1799752 polymorphism of ACE-1 receptor which showed no association with ICU admission of severe COVID-19 patients (Baştuğ et al., 2022).

The mutations in the D allele of ACE-1 lead to high levels of serum ACE-1, increasing the severity of COVID-19 and a higher risk of development of pulmonary embolism in these patients (Calabrese et al., 2021; Hashemi et al., 2021; Verma et al., 2021). ACE D/I polymorphism was associated with increased COVID-19 mortality (Saad et al., 2021; Yamamoto et al., 2020; Delanghe et al., 2021). Conversely, the presence of the ACE-2 rs2285666 in the Indian population whereas rs2074192 and rs1978124 variants in the Spanish population demonstrated a protective effect by lowering the risk of susceptibility and mortality rate (Sabater Molina et al., 2022; Srivastava et al., 2020). However, other studies revealed that ACE I/D, DD, ACE-2 receptor rs2106809, and rs2285666 polymorphisms had no associations with COVID-19 severity (Asselta et al., 2020; Aung et al., 2020; Karakaş Çelik et al., 2021; Mahmood et al., 2022).

Table 1
ACE polymorphisms and their association with COVID-19 severity and susceptibility

ACE gene	ACE Polymorphism	Population	Sample size	Implication	Reference
ACE2	rs2285666, rs35803318	Italy	7268 individuals	No correlation between ACE2 expression and disease severity based on patients' gender.	(Asselta et al., 2020)
ACE	Not mentioned	Asia, Europe, North America, Australia, Africa	COVID-19 patients*	The II genotype of the ACE (which is highly prevalent in East Asians) was strongly associated with decreased COVID-19-related deaths.	(Aung et al., 2020)
ACE2	rs2074192, rs2106809	Italy	54 symptomatic COVID-19 patients and, 50 asymptomatic	rs2074192 polymorphism of ACE2 is associated with increased severity of COVID-19 illness.	(Cafiero et al., 2021)
ACE1	rs1799752	Italy	54 symptomatic COVID-19 patients and, 50 asymptomatic	The II genotype of the ACE1 rs1799752 polymorphism is found at a higher frequency in asymptomatic patients.	(Cafiero et al., 2021)
ACE	rs1799752	Italy	68 hospitalized patients	D/D ACE polymorphism had a significant impact on the severity of disease and the development of pulmonary embolism.	(Calabrese et al., 2021)
ACE1	rs1799752	Lebanon	232 COVID-19 patients, 155 controls	ACE 1 I/D polymorphism was associated with a worse COVID-19 clinical outcome.	(Saad et al., 2021)
ACE	N/A	Turkey	90 COVID-19 patients	ACE II genotype was prominent in asymptomatic patients and ACE D/D genotype common in patients with critical disease.	(Gunal et al., 2021)
ACE	rs4341, rs4343	Spain	128 COVID-19 patients	rs4341 and rs4343 were associated with more severe SARS-CoV-2 disease in patients with hypertension and diabetes.	(Íñiguez et al., 2021)
ACE, ACE2	rs2106809, rs2285666	Turkey	155 COVID-19 patients	No association was observed with the severity of SARS-CoV-2 infection.	(Karakaş Çelik et al., 2021)
ACE1	Not mentioned	European, Mediterranean, and the Middle East	Not mentioned	ACE D/I polymorphism was associated with increased COVID-19-related death.	(Delanghe et al., 2021)
ACE2	rs4646116, rs769062069, rs776995986	Iran	15,000	S331F and K26R mutations (rs4646116) could decrease the affinity of the ACE2 receptor to the viral spike protein.	(Lanjanian et al., 2021)
ACE	rs3730025	Spain and Italy	Not mentioned	Variants decreasing ACE expression do not lead to increased risk of COVID-19 infection or disease severity.	(Monticelli et al., 2021)
ACE2	Not mentioned	Africa	Not mentioned	Genetic variants in ACE2 may alter an individual's variability in susceptibility to COVID-19 infection and severity of the disease.	(Ortiz-Fernández and Sawalha, 2020)
ACE1	Not mentioned	India	269 COVID-19 patients	ACE1 D/D genotype was markedly higher in COVID-19 patients with severe disease.	(Verma et al., 2021)
ACE1	Not mentioned	Europe and Asia	Not mentioned	ACE1 II genotype had a negative correlation with the incidence of cases and mortality rates from SARS-CoV-2 infection.	(Yamamoto et al., 2020)
ACE2	rs147311723, rs142017934, rs4646140	Africa, America, Asia, Europe	2504 individuals	rs142017934 polymorphisms, more frequently observed in Africans, can amplify the expression of the ACE2 gene.	(Khayat et al., 2020)
ACE2	rs5934250	Africa, America, Asia, Europe	2504 individuals	rs5934250 is found in higher frequencies in Europeans and few Africans and can minimize the expression of ACE2.	(Khayat et al., 2020)
ACE2	rs2285666	India	Not mentioned	Strong positive correlation for alternate allele (T/T-plus stand or A/A-minus strand) of ACE2 rs2285666 polymorphism, with the lower susceptibility to COVID-19 and lower case-fatality rate.	(Srivastava et al., 2020)
ACE2	rs2285666	Mexico	481 COVID-19 patients	T allele of rs2285666 is associated with severe outcomes in COVID-19 patients.	(Martínez-Gómez et al., 2022)
ACE2	rs2074192, rs1978124, rs2106809, rs2285666	Spain	318 COVID-19 patients	rs2074192 and rs1978124 showed a protective role in COVID-19 patients, while rs2106809 and rs2285666 were associated with severe disease.	(Sabater Molina et al., 2022)
ACE2	rs2285666	Iraq	99 COVID-19 patients, 96 controls	No association between ACE2 rs2285666 polymorphism and risk of developing COVID-19.	(Mahmood et al., 2022)
ACE1	rs1799752	Turkey	50 ICU patients, 50 non-ICU patients	This polymorphism did not predict COVID-19 patients requiring ICU.	(Baştuğ et al., 2022)

ACE: Angiotensin receptor enzyme

*Number of participants was not clear

4.2. Human leukocyte antigen (HLA)

HLA haplotypes and variants identified to play an important role in SARS-CoV-2 infection are summarized in Table 2. HLA alleles are highly polymorphic with the presence of different HLA alleles, generating varied immune responses against COVID-19, thus leading to a diverse spectrum of disease susceptibilities and severities. HLA are however accompanied by linkage disequilibrium. Hence, additional genes in the proximity of HLA could also influence for the course of the disease (Pisanti et al., 2020; Yung et al., 2021).

A study of 190 unrelated Chinese patients found a strong relation between the B22 serotype and COVID-19 (Yung et al., 2021). HLA-DRB1*08 allele was associated with the highest risk for severe COVID-19 illness in Sardinian patients (Littera et al., 2020). HLA-DPA1*02:02 was also found to be linked to higher susceptibility to COVID-19 but did not seem to affect the risk of hospitalization (Warren and Birol, 2021). The presence of HLA-A*11, HLA-C*01, HLA-A*11:01, HLA-C*04:01, HLA-C rs143334143, DQA1*01:02, HLA-DRB1*03 and HLA-DQB1*04 were associated with higher mortality (Ebrahimi et al., 2021; Hovhannisyan et al., 2022; Lorente et al., 2021; Weiner et al., 2021). In a study of 178 Japanese COVID-19 patients, the risk for severe

infection was noted to be increased in the presence of the DRB1*09:01 allele compared to pre-existing comorbid conditions like diabetes, hypertension, or cardiovascular diseases (Anzures et al., 2021).

On the contrary, certain HLA variants such as HLA-A*02:05, HLA-B*58:01, HLA-C*07:01, and HLA-DRB1*03:01 are thought to be protective against critical COVID-19 infection (Ebrahimi et al., 2021; Langton et al., 2021; Littera et al., 2020; Lorente et al., 2021; Pisanti et al., 2020; Tomita et al., 2020). Higher frequencies of activating B-telomeric *KIR3DS1* (Killer cell immunoglobulin-like receptor 3DL1) in HLA-B*15:01 were linked to less severe infection (Bernal et al., 2021). However, other studies reported no link between HLA and SARS-CoV-2 infection (Ben Shachar et al., 2021; de Sousa et al., 2020). Of importance, Ben Shachar et al., studied the association of various HLA loci and severity of COVID-19 severity and in 6,413 COVID-19 positive Israeli patients, largest patient population among included studies, and revealed that was no association between COVID-19 severity and several HLA loci (Ben Shachar et al., 2021).

A major limitation in studying the HLA loci is that various methodologies can be utilized which can affect the observed results. The studies included used a variety of different methodologies and used different sources of their DNA samples (peripheral blood or

Table 2
HLA locus and their association with COVID-19 severity and susceptibility

HLA locus	HLA allele/haplotype	Population	Sample size	Implication	Reference
HLA-A, -C, -B, and -DRB1	HLA-DRB1*09:01	Japan	178 COVID-19 patients	HLA-DRB1*09:01 was strongly associated with increased severity of COVID-19 illness.	(Anzures et al., 2021)
HLA-A, -B, -C, -DQB1, -DRB1	Not mentioned	Israel	6,413 COVID-19 patients and 66,499 controls	No association was reported with risk for infection or illness severity.	(Ben Shachar et al., 2021)
HLA-DRB1, -DQB1	HLA-DRB1*03, HLA-DRB1*15, DRB1*15 ~ DQB1*05, DRB1*15/DRB1*04, HLA-DRB1*04	Iran	144 COVID-19 patients	HLA-DRB1*03 was notably higher in severely ill patients. HLA-DRB1*04 was determined to be a protective factor against the development of severe forms of the disease. Frequencies of HLA-DRB1*15, DRB1*15 ~ DQB1*05, and DRB1*15/DRB1*04 were lower in COVID-19 patients.	(Ebrahimi et al., 2021)
HLA-DRB1 and HLA-DQB1	HLA-DRB1*04:01, HLA-DQA1*01:01-DQB1*05:01-DRB1*01:01	England	147 COVID-19 patients	Compared to the asymptomatic group, frequencies of HLA-DRB1*04:01 allele and the haplotype. HLA-DQA1*01:01-DQB1*05:01-DRB1*01:01 were drastically lower in severe COVID-19 patients.	(Langton et al., 2021)
HLA-A, HLA-B, HLA-C, HLA-DRB1	HLA-A*02:05, HLA-B*58:01, HLA-C*07:01, HLA-DRB1*03:01, HLA-DRB1*08	Italy	182 patients, 619 controls	HLA-A*02:05, B*58:01, C*07:01, DRB1*03:01 haplotype could protect against COVID-19. HLA-DRB1*08 allele was associated with the highest risk for severe COVID-19 illness.	(Littera et al., 2020)
HLA-A, HLA-B, HLA-C, HLA-DRB1 and HLA-DQB1	HLA-A*32, HLA-A*03, HLA-B*39, HLA-C*16, HLA-A*11, HLA-C*01, HLA-DQB1*04	Spain	3886 healthy controls, 72 COVID-19 patients	Lower frequency of HLA-A*32 in COVID-19 patients compared to controls, and higher frequency of HLA-A*03, HLA-B*39, and HLA-C*16 in COVID-19 patients compared to controls. The presence of HLA-A*11, HLA-C*01, and HLA-DQB1*04 was linked with an increased risk for COVID-19-related death.	(Lorente et al., 2021)
HLA-A, -B, -C and -DRB1	HLA-A*01:01 g-B*08:01 g-C*07:01 g-DRB1*03:01 g, HLA-A*02:01 g-B*18:01 g-C*07:01 g-DRB1*11:04 g	Italy	N/A	The presence of HLA-A*01:01 g-B*08:01 g-C*07:01 g-DRB1*03:01 g was positively associated with risk of COVID-19 infection and death. The haplotype HLA-A*02:01 g-B*18:01 g-C*07:01 g-DRB1*11:04 g could offer protection against COVID-19 infection.	(Pisanti et al., 2020)
HLA-A, -B, -C, -DPB1, -DQB1, -DRB1	HLA-A*2:01, HLA-A*11:01, HLA-A*24:02	Worldwide	N/A	The presence of HLA-A*2:01 may predispose an individual to an increased risk for COVID-19 infection.	(Tomita et al., 2020)
HLA class I and class II	HLA-I C*04:01, HLA-A*11:01, HLA-DPA1*02:02	USA	100 hospitalized COVID-19 patients, and 26 controls	HLA-I C*04:01 and A*11:01 were significantly associated with poor outcomes in COVID-29 infection. HLA-DPA1*02:02 was discovered to be at a higher frequency COVID-19-positive patients	(Warren and Birol, 2021)
HLA-C	rs143334143	Europe and USA	435 symptomatic COVID-19 patients	rs143334143 strongly correlated to increased COVID-19 illness severity.	(Weiner et al., 2021)
HLA-B	Not mentioned	China	190 COVID-19 patients	Strong positive correlation between the B22 serotype and risk of SARS-CoV-2 infection.	(Yung et al., 2021)
HLA-C	HLA-C*04:01	Armenia	299 COVID-19 patients	HLA-I C*04:01 was significantly associated with a more severe COVID-19 disease.	(Hovhannisyan et al., 2022)

HLA: Human leukocyte antigen

nasopharyngeal samples). Therefore, larger genome-wide association studies and whole-genome sequencing among different populations are still required to understand the association between specific *HLA* loci and COVID-19 disease course. A recent study using whole genome sequencing in 7,491 critically COVID-19 hospitalized in the UK showed that only HLA-DRB1*04:01 reached genome-wide significance (Kousathanas et al., 2022) which as previously mentioned is thought to be protective against severe COVID-19 infection (Langton et al., 2021).

These results suggest that HLA typing could play an important role in predicting the course of COVID-19 disease in certain populations and could help stratify patients infected with SARS-CoV-2. Other genes that are implicated in the progression of COVID-19 infection and disease severity are described in Table 3.

4.3. Cellular proteases

4.3.1. Transmembrane protease serine 2

TMPRSS2 is an androgen-responsive gene and a key agent in prostate cancer, driving ETS-family oncogene expression (Stopsack et al., 2020), which is why males are expected to have higher *TMPRSS2* expression; however, recent literature suggests that estrogen also can upregulate it (Asselta et al., 2020).

Recent evidence revealed that the cleavage and activation of SARS-CoV-2 S protein during membrane fusion is a function of *TMPRSS2* along with cathepsin L and furin (Hoffmann et al., 2020). A recent analysis identified several SNPs could affect the function and structural composition of *TMPRSS2*, with rs2070788, rs9974589, rs17854725, rs75603675, rs12329760, rs4303795, and rs7364083 types being associated with increased severity of the disease and rs77675406, rs713400, rs112657409, and rs11910678 polymorphisms causing upregulation of the *TMPRSS2* (Asselta et al., 2020; Irham et al., 2020; Paniri et al., 2021; Rokni et al., 2022). A study performed by Andolfo et al identified five common variants at locus 21q22.3 within *TMPRSS2* and near the *MX1* and revealed that higher frequencies of this variants were linked to more severe COVID-19 disease in the Italian population (Andolfo et al., 2021).

TMPRSS2 expression could vary among different populations. A study demonstrated that the East Asian population presented the highest expression of *TMPRSS2*, and the African population had the lowest (Ortiz-Fernández and Sawalha, 2020). In contrast, a study from Italy showed lower expression of *TMPRSS2* in Asians than Italians, explaining the higher susceptibility towards COVID-19 in Italians (Asselta et al., 2020). Exonic variant p.Val160Met (rs12329760) has the highest allele frequency in the European population (~25%), whereas p.Val197Met missense variant (rs12329760) studies showed an increased allelic frequency in the East Asian population (Hou et al., 2020; Wang et al., 2020). A recent study reported that both isoforms were associated with a reduction in *TMPRSS2* stability and binding capacity with ACE-2, thus reducing the risk of acquiring SARS-CoV-2 infection (Wang et al., 2020). Finally, the potential increased risk of infection among populations with Down syndrome is highly suggestive of a relation with the *TMPRSS2* locus (Hou et al., 2020).

4.3.2. Furin

Furin is a calcium-dependent serine endoprotease that is predominantly found in T-cells to maintain peripheral immune tolerance (Takeda, 2022). *TMPRSS2* and furin play are involved in the proteolytic activation of SARS-CoV-2 by cleaving the S protein from the S1/S2 site of SARS-CoV-2 (Bestle et al., 2020; Hoffmann et al., 2020). Furin's role is especially noteworthy concerning the delta variant, as a mutation in D614G in the delta variant enhances the cleavability of S1/S2 domains by furin (Takeda, 2022).

Furin might increase the risk of acquiring COVID-19 infection in certain populations. It has been hypothesized that diabetic patients have increased levels of plasmatic furin, explaining their vulnerability to a severe course of COVID-19 (Fernandez et al., 2018; Muniyappa and

Gubbi, 2020). Another study revealed that the conversion of the *FURIN* to allelic type GG mediated by CRISPR/Cas9 showed a decrease in the alveolar and neuronal expression of furin, reducing SARS-CoV-2 infectivity (Dobrindt et al., 2020).

Certain *FURIN* mutations could exist in different ethnicities explaining the differences in the prevalence of COVID-19 infections worldwide. A study in the Italian population showed that individuals with the c.893G > A, (p.Arg298Gln) missense mutation of *FURIN* have the highest frequency of contracting severe COVID-19 resulting in death, compared to the general European population (Latini et al., 2020).

4.3.3. Tolloid-like protein 1

Our results imply that the A allele of the Tolloid-Like Protein 1 (*TLL-1*) rs17047200 variant is linked with poor COVID-19 outcomes. *TLL-1* is a protein-encoding gene located on 4q32.3, responsible for astacin-like, zinc-dependent, metalloprotease expression (Sieron et al., 2019). An *in-silico* analysis found that *TLL-1* protease acted on several S1/S2 cleavage sites (Grimaudo et al., 2021). This leads to the idea that this protein might be involved in S protein cleavage (Grimaudo et al., 2021). In a study on the intronic variant rs17047200 (A > T) of *TLL-1*, it was determined that the homozygotes TT has a higher risk of infection and severe manifestation of SARS-CoV2 infection (Grimaudo et al., 2021). Conversely, another study stated that the AA genotype has a higher incidence of the disease, higher comorbidities risk, and ventilation necessity (Agwa et al., 2021).

4.4. Immune system genes

4.4.1. Toll-like receptors

Toll-like receptors (TLRs) recognize pathogen-associated molecular patterns and are highly active during times of infection (Lim and Staudt, 2013). Various evidence suggests that TLR could play an essential role in cytokine activation in COVID-19 (Zheng et al., 2021). *TLR3*, located on 4q35.1, encodes for the *TLR3* protein, also known as CD283, that recognizes double-stranded (ds) viral RNA, therefore being a key factor for activation and sensitization of the innate immune system (Lim and Staudt, 2013). Our review suggests that a missense mutation in *TLR3* (rs3775291) leads to a complicated course of COVID-19. Additionally, an *in silico* analysis showed that the rs73873710 polymorphism was associated with lower expression of the *TLR3*, whereas the rs3775290 and rs3775291 variants enhanced the *TLR3* expression, which led to increased recognition of the SARS-CoV-2 dsRNA genome and a more severe immune response (Teimouri et al., 2020). Another four *TLR3* variants (p.Ser339fs, p.Pro554Ser, p.Trp769* and p.Met870Val) are also associated with severe evolution and complications of COVID-19 pneumonia (Darbeheshti et al., 2021).

TLR7 is located on Xp22.2 and is a key factor in recognizing single-strand RNAs (via uridine or guanosine) and enhancing the host immune response (Zhang et al., 2016). The outcome of our study establishes a link between variable expression of *TLR7* polymorphisms (rs189681811, rs147244662, rs149314023, rs200146658, rs5743781) and severe COVID-19. In addition, we found reduced expression of the *TLR7* in COVID-19 positive males. Likewise, another study identified two mutations in males with severe COVID-19 - a missense variant (c.2383G > T; p.[Val795Phe]) and a deletion variant (c.2129_2132del; p.[Gln710Argfs*18]), attributing the decreased number of IFN production to the lower expression of *TLR7* (van der Made et al., 2020). These deficiencies significantly impact males due to hemizygoty on the X chromosome (Kotsev et al., 2021). Furthermore, *TIRAP* corresponds to the *TLR/IL-1* receptor complex. *TIRAP* promotes the induction of transduction signaling pathways, that lead to the release of IL-1, IL-6, and TNF- α through the NF- κ B pathway. The rs8177374 polymorphism of the *TIRAP* (TIR Domain Containing Adaptor Protein) has been shown to reduce the COVID-19 related mortality (Traets et al., 2022).

Table 3

Candidate genes, their polymorphisms and their association with COVID-19 severity and susceptibility in select populations

Gene	Polymorphism	Population	Sample size	Implication	Reference
<i>3p21.31 cluster</i>	rs11385942	Spain and Italy	1980	The <i>3p21.31</i> cluster was observed in patients with respiratory failure.	(The Severe Covid-19 GWAS Group, 2020)
<i>Androgen receptor</i>	Not mentioned	European males	1178	Androgen receptors with shorter polyQ alleles offered protection against severe COVID-19 in Italian males.	(Baldassarri et al., 2021)
<i>BPIFB4</i>	LAV-BPIFB4	Italy	171, 64 with COVID-19	Values of BPIFB4 were markedly lower in COVID-19-positive individuals as compared with negative patients. BPIFB4 levels in plasma are negatively correlated with SARS-CoV-2 illness severity.	(Ciaglia et al., 2021)
<i>Complement 3</i>	Complement 3 (S)	European, Mediterranean, and the Middle East	Not mentioned	C3 was associated with increased COVID-19-related death.	(Delanghe et al., 2021)
<i>CCR5</i>	rs9845542, rs12639314, rs35951367, rs34418657	Europe	6406 hospitalized COVID-19 patients and 902,088 controls	rs9845542, rs12639314, rs35951367 polymorphisms were associated with severe COVID-19 illness and low CCR5 expression	(Cantalupo et al., 2021)
<i>CCR5</i>	rs333	Czech Republic	416	Δ32 deletion in the <i>CCR5</i> , most found in Caucasians, could offer protection against COVID-19 illness.	(Hubacek et al., 2021)
<i>TLL-1</i>	rs4618569	Egypt	141 patients, 100 controls	The A allele of the <i>TLL-1</i> rs17047200 variant is associated with poor clinical outcomes.	(Agwa et al., 2021)
<i>GOLGA3, DPP7, TMPRSS2</i>	rs12329760 in <i>TMPRSS2</i>	China	332	The rs12329760 variant in <i>TMPRSS2</i> was less prevalent in severe SARS-CoV-2 patients. Loss of function mutation in <i>DPP7</i> and <i>GOLGA3</i> was observed in severe COVID-19 disease.	(Wang et al., 2020)
<i>IFI30</i>	rs11554159	Spain and Italy	N/A	<i>IFI30</i> polymorphisms may be a risk factor to acquiring severe COVID-19 disease	(Monticelli et al., 2021)
<i>MEFV</i>	rs3743930	Spain and Italy	N/A	Deleterious variants in <i>MEFV</i> could affect the severity of COVID-19.	(Monticelli et al., 2021)
<i>IFITM3</i>	rs12252, rs34481144	Germany	239 patients with COVID-19 and 253 controls.	There was no association between these polymorphisms and severity of COVID-19 illness.	(Schönfelder et al., 2021)
<i>IFITM3</i>	rs12252	China	80	Presence of the rs12252 variant of the <i>IFITM3</i> correlated with a more critical COVID-19 infection.	(Zhang et al., 2020)
<i>LZTFL1, XCR1, CCR9, FYCO1, SLC6A20, CXCR6, HNRNPK, RMI1, IFNAR2, ABO</i>	rs9976829 in <i>IFNAR2-IL10RB</i>	Italy and Spain	1,610 COVID-19 patients and 2,205 controls	All genes were strongly associated with risk of SARS-CoV-2 infection. A 16% higher chance of having SARS-CoV-2 in subjects with the G allele of rs9976829.	(Ma et al., 2021)
<i>MBL2</i>	rs1800450	N/A	284 patients, 100 control	Reduced <i>MBL2</i> levels correlated with a more severe COVID-19 clinical course.	(Medetalibeyoglu et al., 2021)
<i>MUC5B</i>	rs35705950	Europe	4124 cases and 20,465 controls	rs35705950 offered protection against COVID-19 in patients with pulmonary fibrosis.	(Fadista et al., 2021)
<i>PNPLA3, TLL-1</i>	<i>PNPLA3</i> rs738409, <i>TLL-1</i> rs17047200,	Italy	383	Polymorphisms of <i>PNPLA3</i> and <i>TLL-1</i> were markedly associated with severe COVID-19 disease and worse outcomes.	(Grimaudo et al., 2021)
<i>TAS2R38</i>	Not mentioned	USA	1935, 265 tested positive	T2Rs may protect against illness by SARS-CoV-2.	(Barham et al., 2021)
<i>DDR1</i>	rs17047200	Egypt	141 patients, 100 controls	The AG genotype of the <i>DDR1</i> rs4618569 is associated with poor outcomes in COVID-19 patients.	(Agwa et al., 2021)
<i>TLR3</i>	rs3775291	Spain and Italy	N/A	A missense mutation in <i>TLR3</i> (rs3775291) is associated with severe disease.	(Monticelli et al., 2021)
<i>TLR7</i>	rs189681811, rs147244662, rs149314023, rs200146658, rs5743781	Italy	79 cases, 77 controls	<i>TLR7</i> variants were found in 2.1% of males with severe disease, while none were found in asymptomatic males. Lower <i>TLR7</i> expression was observed in COVID-19 patients.	(Fallerini et al., 2021)
<i>TMPRSS2</i>	rs2298659, rs17854725, rs12329760, rs3787950	Italy	3984	Exonic variant (p.Val160Met) and two haplotypes in <i>TMPRSS2</i> showed substantial disparities between East Asians and Italians, showing increased levels of <i>TMPRSS2</i> in Italians, leading to increased susceptibility to infection.	(Asselta et al., 2020)
<i>TMPRSS2</i>	N/A	Africa	N/A	Genetic variants in <i>TMPRSS2</i> may alter an individual's variability in susceptibility to COVID-19 infection and disease severity.	(Ortiz-Fernández and Sawalha, 2020)
<i>TNFRSF1A</i>	rs767455	Mexico	102 patients, 25 controls	This polymorphism is associated with increased COVID-19 disease severity.	(Palacios et al., 2021)
<i>TNFRSF13C</i>	p.His159Tyr	Italy	500	p.His159Tyr variant of <i>TNFRSF13C</i> was notably increased in patients with severe illness compared to asymptomatic patients.	(Russo et al., 2021)
		Serbia	120 males		(Kotur et al., 2021)

(continued on next page)

Table 3 (continued)

Gene	Polymorphism	Population	Sample size	Implication	Reference
Vitamin D (<i>DHCR7/NADSYN1</i>), <i>CYP2R1</i>	Vitamin D (<i>DHCR7/NADSYN1</i>) rs12785878, <i>CYP2R1</i> rs10741657			The presence of <i>CYP2R1</i> and <i>DHCR7/NADSYN1</i> correlated with COVID-19 increased illness severity in adults.	
<i>IFNλ3</i>	rs12979860, rs8099917, rs12980275	Iran	750 patients with COVID-19	Frequency of these favorable variants was significantly higher in patients who survived from COVID-19 infection.	(Rahimi et al., 2021)
<i>IFNλ4</i>	rs368234815	Iran	750 COVID-19 positive patients	Higher frequency of this variant was present in patients who survived from COVID-19 infection.	(Rahimi et al., 2021)
<i>TMPRSS2</i>	rs2070788	India	393 COVID-19 patients	rs2070788 may lead to worse clinical outcomes in COVID-19 patients.	(Pandey et al., 2022)
<i>TIRAP</i>	rs8177374	Netherlands	116 COVID-19 patients	Carriers of rs8177374 could be associated with a significantly lower COVID-19 mortality.	(Traets et al., 2022)
<i>TMPRSS2</i>	rs17854725/rs75603675/rs12329760/rs4303795	Iran	288 COVID-19 patients	These polymorphisms were associated with increased risk of COVID-19 infection and severe disease.	(Rokni et al., 2022)
<i>IL-6</i>	rs1800795, rs1800796, rs1800797	Iran	175 COVID-19 patients, 171 controls	No significant differences in severity of COVID-19 disease in patients with these polymorphisms.	(Falahi et al., 2022)
<i>TMPRSS2/MX1</i> (21q22.3) locus	rs3787946, rs9983330, rs12329760, rs2298661, rs9985159	Italy	6,406 COVID-19 patients, 902,088 controls	These polymorphisms showed an association with severe COVID-19 disease.	(Andolfo et al., 2021)

BPIFB4: BPI fold containing family B member 4, *CCR5*: CC motif chemokine receptor 5, *CCR9*: CC motif chemokine receptor 9, *CXCR6*: C-X motif chemokine receptor 6, *DPP7*: dipeptidyl peptidase 7, *DDR1*: discoidin domain receptor tyrosine kinase 1, *GOLGA3*: Golgin A3, *TMPRSS2*: transmembrane protease, serine 2, *IFI30*: gamma-interferon-inducible lysosomal thiol reductase, *SLC6A20*: solute carrier family 6 member 20, *LZTFL1*: human leucine zipper transcription factor like 1, *XCRI*: X-C motif chemokine receptor 1, *FYCO1*: fyve and coiled-coil domain-containing protein 1, *TLR3*: toll like receptor 3, *TLR7*: toll like receptor 7, *IFNAR2*: interferon alpha and beta receptor subunit 2, *IFNλ3*: interferon lambda 3, *IFNλ3*: interferon lambda 3, *MUC5B*: mucin 5B, *HNRNPk*: heterogeneous nuclear ribonucleoprotein K, *IFITM3*: interferon induced transmembrane protein 3, *RMI1*: RecQ mediated genome instability 1, *MBL2*: mannose binding lectin 2, *PNPLA3*: patatin-like phospholipase domain-containing protein 3, *TLL1*: toll like 1, *TAS2R38*: taste receptor 2 member 38, *TNFRSF13C*: TNF receptor superfamily member 13C, *TNFRSF1A*: TNF receptor superfamily member 1A, *CYP2R1*: cytochrome P450 family 2 subfamily R member 1, *TIRAP*: TIR Domain Containing Adaptor Protein

4.4.2. Interferons

IFNs are specialized cytokines with essential antiviral functions that are secreted in response to various inflammatory stimuli and are classified into three distinct subgroups: type I, type II, and type III (R. R. Goel et al., 2021). Our review suggests interferons and their receptors are heavily implicated in COVID-19 disease, especially polymorphisms in genes that affect IFNλ (type III) expression.

This review's findings suggest that both IFNλ 3 and 4 are potential markers for severe COVID-19. *IFNλ3* rs12979860 CC and rs368234815 TT variants were associated with higher efficiency in clearing RNA viruses (Grimaudo et al., 2021). Similar results were noted with rs8099917, rs12980275 variants of *IFNλ3* (Rahimi et al., 2021). However, in a study on the rs12979860 variant, the CC genotype was associated with a remarkably increased susceptibility to SARS-CoV-2 infection (Agwa et al., 2021). Controversially, the TC genotype was linked with higher mortality and a more severe course of disease (Agwa et al., 2021). However, there seems to be a discrepancy in the effects of *IFNλ4* polymorphisms on the course of COVID-19. Additionally, The polymorphism at the rs368234815 TT/ΔG locus, resulted in a reduced expression of *IFNλ4*, seemingly increasing the risk of acquiring SARS-CoV-2 and was linked to a higher viral load due to a reduction in viral clearing (Amodio et al., 2020). However, rs368234815 was discovered to have a protective function against COVID-19, as the patients' survival rate was reported to be higher (Rahimi et al., 2021).

Interferon-α/β receptors (IFNAR), formed by *IFNAR1* and *IFNAR2*, bind to type I IFNs to induce the production of large amounts of protective IFNα (Hashemi et al., 2021). *IFNAR2* variant rs2236757, which results in lower expression of type I IFNs, was found in patients with critical COVID-19 infection (The GenOMICC Investigators et al., 2021). In another study, the p.Trp73Cys, p.Ser422Arg and p.Pro335del variants of *IFNAR1*, and p.Glu140fs variant of *IFNAR2* were also present in patients with critical COVID-19 infections, further corroborating the link between serious COVID-19 disease and dysregulations of type I IFNs (Zhang et al., 2020).

Another IFN inducible gene associated with the abysmal aftermath of COVID-19 is gamma-interferon-inducible lysosomal thiol reductase

(*IFI30*). *IFI30* plays an important protective role against SARS-CoV-2 viruses (Monticelli et al., 2021). The *IFI30* rs11554159 polymorphism is linked with increased susceptibility and severe outcome of COVID-19 due to high viral charge (Monticelli et al., 2021). Moreover, Interferon Induced Transmembrane Protein 3 (*IFITM3*) polymorphisms were also associated with a higher disease burden and a greater risk of acquiring SARS-CoV-2 infection (Gómez et al., 2021; Iyer et al., 2020; Kotsev et al., 2021; Zhang et al., 2020). However, a study showed that there was no association between the rs12252 and rs34481144 variants of *IFITM3* and SARS-CoV-2 severity German patients with COVID-19 (Schönfelder et al., 2021).

4.4.3. Complement component (C3)

The findings of this review suggest a correlation between age, C3 levels and the course of COVID-19 infection could exist. In a univariate analysis, C3 levels were elevated in young patients with severe COVID-19 infection. However, in the general population, it showed no statistically significant difference. The same results were observed in a multivariable analysis. However, critically low levels were associated with higher mortality overall (Cheng et al., 2021). This might explain the risk of severe COVID-19 and associated mortality in the elderly due to immunosenescence lowering the activity of C3 (Cheng et al., 2021).

4.4.4. Tumor necrosis factor (TNF) receptors

TNF Receptor Superfamily Member 1A (TNFRSF1A) binds to TNF-α, playing a vital role in the inflammatory cascade (Iyer et al., 2020). This review indicates that polymorphism rs767455 of *TNFRSF1A* is associated with a severe progression of COVID-19 (Palacios et al., 2021). Another receptor implicated with severe COVID-19 is TNF Receptor Superfamily Member 13C (TNFRSF13C) which contributes to B-cell survival (Smulski and Eibel, 2018). A rare variant, p.His159Tyr variant of *TNFRSF13C*, was drastically more frequent in severe cases (n = 38) compared to asymptomatic patients (n = 375) (Russo et al., 2021). This mutation was associated with a gain of function and significantly increased NF-κb1 and NF-κb2 activation (Russo et al., 2021).

4.5. Chromosome 3p21.31

C-C Motif Chemokine Receptor 5 (*CCR5*) located on *3p21.31* is highly expressed in macrophages and T cells, serving as a co-receptor for macrophage-tropic viruses and plays an important role in COVID-19 infection (Ray et al., 2020). The rs9845542, rs12639314, rs34418657, and rs35951367 variants of *CCR5* were associated with severe COVID-19 illness (Cantalupo et al., 2021). Our results pointed out that the Δ 32 deletion within *CCR5* leads to reduced expression of *CCR5*, playing a protective role against COVID-19 infection (Hippisley-Cox et al., 2020; Hubacek et al., 2021). Our results showed that the *CCR5* Δ 32 allele is present in 11.4 % of the Czech population (Hubacek et al., 2021). This allele has a predilection for Northern-European Caucasians (16%), whereas approximately 5% of Southern Europeans were carriers and Asian and African populations were devoid of this deletion (Hippisley-Cox et al., 2020).

The findings of this review suggest that the younger population carrying a GA allele of the rs11385942 variant were prone to severe COVID-19 infection. The GA allele of the rs11385942 variant is associated with enhanced expression of *SLC6A20* (Solute Carrier Family 6 Member 20), and *LZTFL1* (Leucine Zipper Transcription Factor Like 1) and reduced expression of *CXCR6* (Chemokine Receptor Type 6) (The Severe Covid-19 GWAS Group, 2020). These three proteins are part of the genes that form the association signal at locus *3p21.31*, collectively aggravating the likelihood of contracting COVID-19 infection (Kasela et al., 2021; Ma et al., 2021). This cluster is also linked with an increased risk of respiratory failure and necessity for mechanical ventilation (Anastassopoulou et al., 2020). Fine mapping of this structure identified over 20 variants; therefore, it is impossible to infer which individual variant is responsible for this association (Yao et al., 2021). Using CRISPR/Cas genome editing various genes were found to be targets of locus *3p21.31* including *CXCR6*, *SLC6A20*, *CCR9* (Kasela et al., 2021; Yao et al., 2021). It is important to note that the functional mechanisms between the proteins associated with locus *3p21.31* and COVID-19 severity remain ambiguous, requiring more further studies to understand the mechanism of this strong association (Kasela et al., 2021).

4.6. ABO locus

The correlation between the ABO system and COVID-19 evolution has been widely investigated. Studies have shown that Group O was allied with a lower risk of infection, while group A attributed to a higher risk owing to SNP rs657152 (The Severe Covid-19 GWAS Group, 2020; Wu et al., 2020; Zhao et al., 2021). Other SNPs located on the *ABO* locus were also found to protect the risk of critical illness from COVID-19 infection. These include rs199969472, rs34266669, rs76700116, rs7849280, rs34039247, rs10901251, rs9411475, and rs13291798 (Jelinek et al., 2022).

The lower susceptibility associated with blood group O was supported by a recent meta-analysis of 30 studies (Gutiérrez-Valencia et al., 2022). Additionally, a recent cross-sectional study showed that blood group O offered a protective effect against developing critical COVID-19 (Jelinek et al., 2022). This could arise since human anti-A antibodies, found in patients with blood group O, are hypothesized to bind to the S protein of SARS-CoV-2, thereby hindering its attachment to the ACE2 receptor and preventing its invasion of lung tissue (R. Goel et al., 2021). However, another study showed that group A was associated with a statistically significantly lower incidence of intubation compared to O group, but, the susceptibility to infection remained lower in patients with group O (Zietz et al., 2020). It is poorly understood how specific blood groups affect COVID-19 infection course. It is hypothesized that specific ABO blood groups could alter the glycotransferase activity which results in an increased risk of venous thromboembolism which is a common complication of severe COVID-19 infection, thus, explaining the critical outcomes in some patients (Yildirim et al., 2021).

A meta-analysis, consisting of up to 49,562 patients from 19

countries, by Niemi et al revealed that ABO locus was a susceptibility rather a severity locus, as there was a significantly higher association with infections than with hospitalization (COVID-19 Host Genetics Initiative et al., 2021). Another meta-analysis revealed there was no significant differences in hospitalization, ICU admission and mechanical ventilation among the different blood groups but mortality was higher in blood O compared to blood group B (Gutiérrez-Valencia et al., 2022). Both meta-analyses, however, showed high heterogeneity and pooled various ethnicities together, therefore, their results should be interpreted with caution.

4.7. Androgen receptor gene

It is suggested that there is a substantial relationship between higher free androgen levels and SARS-CoV-2 susceptibility and evolution. It was thought to be mediated by ACE-2 and TMPRSS2 activity. However, the protein interaction map suggested a crosstalk between androgen receptor (AR) signaling pathways, inflammatory markers, and peptidases pertinent to the viral receptor and co-receptors (Samuel et al., 2020). Furthermore, new research shows no link between androgen deprivation and TMPRSS2 levels as previously thought (Rastrelli et al., 2021; Schroeder et al., 2021).

The polymorphic CAG nucleotide repeat segment near the N-terminal transactivation domain of AR is responsible for different variations in the course of COVID-19 infection, and the mortality rate among African Americans compared to other ethnic groups (Mohamed et al., 2021). The AR polyQ length is also associated with the function of the AR receptor. Shorter polymorphic glutamine repeats are linked with mild COVID-19 infection. Less than 22 glutamine repeats were associated with a protective effect, whereas longer polyQ was associated with a severe outcome of infection (Baldassarri et al., 2021).

4.8. Dipeptidyl Peptidases

The results of this review indicated that numerous dipeptidyl peptidases (DPP) were implicated with the risk of acquiring severe COVID-19 infection. DPP4 was previously associated with nasopharyngitis and Middle East Respiratory Syndrome (MERS), serving as a receptor for MERS-CoV (Kleine-Weber et al., 2018). It is hypothesized that DPP4 could play a similar role for SARS-CoV-2. The rs13015258 variant was found to affect the key genes implicated in invasion of SARS-CoV-2 into cells. However, some studies suggested that DPP4 does not have a receptor role for SARS-CoV-2 (Hashemi et al., 2021; Wang et al., 2020).

Other DPPs were also associated with COVID-19, namely DPP7 and DPP9. A 1 base pair insertion in *DPP7* was found in asymptomatic COVID-19 patients (Wang et al., 2020). It represents the rs11391519 variant, which is associated with decreased peptidase expression, therefore interfering with the immune response (Wang et al., 2020). The rs2109069 polymorphism of the *DPP9* is associated with more severe manifestations and outcomes of SARS-CoV-2 infection due to increased risk of lung fibrosis (Hashemi et al., 2021).

5. Conclusion

Higher expression, polymorphisms, mutation, and deletion of several genes and their alleles could play a crucial role in determining the severity and clinical fate of COVID-19 patients. HLA polymorphisms appear to influence the course of COVID-19, however, further genome-wide association studies with larger patient populations are required to fully assess the role of several *HLA* loci in the course of COVID-19 infections. ACE-2, TMPRSS2, furin, and TLL-1 are associated with viral entry and binding to the host cells. Specific proteins such as TLR, IFN λ , and *CCR5* govern the immune response to COVID-19. Further experimental studies are also needed to understand the functional significance of many of these associations with COVID-17 disease severity and susceptibility. This could prove important as genotyping can help identify

the population at high risk and anticipate the severity of the disease. Additionally, vaccination can be prioritized in individuals with genetic susceptibility to severe COVID-19. Furthermore, early treatment aimed at some of the pathophysiological mechanisms altered by these genetic associations could minimize the severity and mortality risk.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix

Search strategy for PubMed

((“COVID-19”[All Fields] OR “COVID-19”[MeSH Terms] OR “SARS-CoV-2”[All Fields] OR “sars-cov-2”[MeSH Terms] OR “Severe Acute Respiratory Syndrome Coronavirus 2”[All Fields] OR “NCOV”[All Fields] OR “2019 NCOV”[All Fields]) AND (“Genetic Susceptibility” [Title/Abstract] OR “Genetic Predisposition” [Title/Abstract] OR “allelic variation” [Title/Abstract] OR “ACE” [All Fields] OR “TLR7” [All Fields] OR “HLA” [All Fields] OR “Polymorphism” [All Fields])) AND (“disease severity” [All Fields] OR “clinical outcome” [All Fields] OR “Disease Susceptibility” [All Fields] OR “clinical course”[All Fields])

Search strategy for Scopus

(ALL (covid-19 OR sars-cov-2) AND TITLE-ABS-KEY (genetic AND susceptibility OR genetic AND predisposition OR allelic AND variation OR ace OR tlr7 OR hla OR polymorphism) AND ALL (disease AND severity OR clinical AND outcome OR disease AND susceptibility OR clinical AND course))

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members, Pasanici, B., Julienne, H., Aschard, H., Shi, H., Yengo, L., Polimanti, R., Ghoussaini, M., Schwartztruber, J., Dunham, I., Project management group, Project management leader, Project management support, Chwialkowska, K., Francescatti, M., Trankiem, A., Balacanis, M.K., Phenotype steering group, Davis, L., Lee, Sulggi, Priest, J., Renieri, A., Sankaran, V.G., van Heel, D., Deelen, P., Richards, J.B., Nakanishi, T., Biesecker, L., Kerchberger, V.E., Baillie, J.K., Data dictionary, Mari, F., Bernasconi, A., Baillie, S.C., Canakoglu, A., Scientific communication group, Scientific communication leaders, Wolford, B., Scientific communication members, Faucon, A., Dutta, A.K., Schurmann, C., Harry, E., Birney, E., Nguyen, H., Nasir, J., Kaunisto, M., Solomons, M., Dueker, N., Vadgama, N., Limou, S., Translators, Rahmouni, S., Mbarek, H., Darwish, D., Uddin, M.M., Albertos, R., Pérez-Tur, J., Li, Ruolin, Folkersen, L., Moltke, I., Koelling, N., Teumer, A., Kousathanas, A., Utrilla, 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Team, ACCOunT, Analysis team leader, Perera, M., Data collection leaders, O'Leary, K., Tuck, M., O'Brien, T., Meltzer, D., O'Donnell, P., Nutescu, E., Analysis team members, Yang, G., Data collection members, Alarcon, C., Herrmann, S., Mazurek, S., Banagan, J., Hamidi, Z., Barbour, A., Raffat, N., Moreno, D., Admin team member, Friedmann, P., Amsterdam UMC COVID Study Group, Analysis team leader, Ferwerda, B., Data collection leaders, van de Beek, D., Brouwer, M.C., Vlaar, A.P.J., Wiersinga, W.J., Analysis team members, Posthuma, D., Tissink, E., Koos Zwinderman, A.H., Uffelmann, E., Data collection members, van Agtmael, M., Algeria, A.G., van Baarle, F., Bax, D., Beudel, M., Jan Bogaard, H., Bomers, M., Bonta, P.I., Bos, L., Botta, M., de Brabander, J., de Bree, G., de Bruin, S., Bugiani, M., Bulle, E., Chouchane, O., Cloherty, A., Dongelmans, D., Elbers, P., Fleuren, L., Geerlings, S., Geerts, B., Geijtenbeek, T., Girbes, A., Goorhuis, B., Grobusch, M.P., Hafkamp, F., Hagens, L., 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B., Woolley, A.E., Admin team leader, Green, R.C., Data collection member, Perez, E. F., Michigan Genomics Initiative (MGI), Analysis team leader, Wolford, B., Admin team leader, Zöllner, S., Analysis team members, Wang, J., Beck, A., Mount Sinai Health System COVID-19 Genomics Initiative, Analysis team leader, Sloopman, L.G., Data collection leaders, Ascolillo, S., Sebra, R.P., Collins, B.L., Levy, T., Admin team leaders, Sealfon, S.C., Analysis team members, Jordan, D.M., Thompson, R.C., Gattler, K., Chaudhary, K., Belbin, G.M., Preuss, M., Hoggart, C., Choi, S., Underwood, S.J., Data collection members, Salib, I., Britvan, B., Keller, K., Tang, L., Peruggia, M., Hiester, L.L., Niblo, K., Aksentijevich, A., Labkowsky, A., Karp, A., Zlatopolsky, M., Zyndorf, M., Admin team members, Charney, A.W., Beckmann, N. D., Schadt, E.E., Abul-Husn, N.S., Cho, J.H., Itan, Y., Kenny, E.E., Loos, R.J.F.M., Nadkarni, G.N., Do, R., O'Reilly, P., Huckins, L.M., MyCode Health Initiative, Analysis team leaders, Ferreira, M.A.R., Abecasis, G.R., Data collection leaders, Leader, J.B., Cantor, M.N., Admin team leaders, Justice, A.E., Carey, D.J., Analysis team members, Chittoor, G., Josyula, N.S., Kosmicki, J.A., Horowitz, J.E., Baras, A., Data collection members, Gass, M.C., Yadav, A., Admin team member, Mirshahi, T., Netherlands Twin Register, Analysis team leader, Jan Hottenga, J., Data collection leader, Bartels, M., Admin team leader, de Geus, E.J.C., Analysis team member, Nivard, M.G., Penn Medicine Biobank, Analysis team leaders, Verma, A., Ritchie, M. D., Admin team leader, Rader, D., Analysis team members, Li, B., Verma, S.S., Lucas, A., Bradford, Y., Population controls, Analysis team leader, Zara, F., Analysis team members, Salpietro, V., Scala, M., Iacomini, M., Scudieri, P., Boccardi, R., Data collection members, Minetti, C., Riva, Antonella, Vari, M.S., Rahier, J.-F., Giorgio, E., Carli, D., Data collection leaders, Louis, E., Bulik, C.M., Landén, M., Brusco, A., Ferrero, G.B., Admin team leaders, Madia, F., Fundin, B., Qatar Genome Program,

Analysis team leader, Data collection leader, Ismail, S.I., Analysis team members, Saad, C., Al-Sarraj, Y., Data collection members, Badji, R.M., Al-Muftah, W., Al Thani, A., Afifi, N., Study of the COVID-19 host genetics in the population of Latvia, Analysis team leader, Klovinis, J., Data collection leader, Rovite, V., Analysis team members, Rescenko, R., Peculis, R., Data collection member, Ustinova, M., The genetic predisposition to severe COVID-19, Analysis team leader, Data collection leader, Zeberg, H., Analysis team members, Data collection members, Frithiof, R., Hultström, M., Lipcsey, M., UCLA Precision Health COVID-19 Host Genomics Biobank, Analysis team leader, Johnson, Ruth, Data collection leader, UCLA Health ATLAS & Data Mart Working Group*, UCLA Health ATLAS & Data Mart Working Group, Geschwind, D.H., Admin team leaders, Freimer, N., Butte, M.J., Geschwind, D.H., Pasaniuc, B., Analysis team members, Ding, Y., Chiu, A., Chang, T.S., Boutros, P., UK 100,000 Genomes Project (Genomics England), Analysis team leader, Moutsianas, L., Data collection leaders, Caulfield, M.J., Scott, R.H., Analysis team members, Walker, Susan, Stuckey, A., Odhams, C.A., Rhodes, D., Data collection members, Fowler, T., Rendon, A., Chan, G., Arumugam, P., UK Biobank, Analysis team leaders, Karczewski, K.J., Wilson, D.J., Spencer, C.A., Data collection leaders, Crook, D.W., Wyllie, D.H., O'Connell, A.M., Admin team leader, Analysis team members, Atkinson, E.G., Kanai, M., Tsuo, K., Baya, N., Turley, P., Gupta, R., Walters, R.K., Palmer, D.S., Sarma, G., Solomonson, M., Cheng, N., Lu, W., Churchhouse, C., Goldstein, J.I., King, D., Seed, C., Daly, M.J., Neale, B.M., Bryant, S., Satterstrom, F.K., Band, G., Earle, S.G., Lin, S.-K., Arming, N., Data collection members, Armstrong, J., Rudkin, J.K., Admin team members, Callier, S., Bryant, S., Cusick, C., UK Blood Donors Cohort, Analysis team leaders, Soranzo, N., Zhao, J.H., Data collection leaders, Danesh, J., Di Angelantonio, E., Analysis team member, Butterworth, A.S., VA Million Veteran Program (MVP), Analysis team leaders, Sun, Y.V., Huffman, J.E., Data collection leader, Cho, K., Admin team leaders, O'Donnell, C.J., Tsao, P., Gaziano, J.M., Analysis team member, Peloso, G., Data collection member, Ho, Y.-L., Val Gardena, Analysis team leader, Data collection leader, Mian, M., Data collection member, Scaggiante, F., Admin team members, CHOP_CAG, Chang, X., Glessner, J.R., Hakonarson, H., GenOMICC/ISARIC4C, Data collection leaders, McGuigan, P.J., Prockter Moore, L.S., Vizcaychipi, M.P., Hall, K., Campbell, A., Nichol, Ailstair, Ward, G., Page, V.J., Semple, M.G., Adeniji, K., Agranoff, D., Agwuh, K., Ail, D., Aldera, E.L., Alegria, A., Angus, B., Ashish, A., Atkinson, D., Bari, S., Barlow, G., Barnass, S., Barrett, N., Bassford, C., Basude, S., Baxter, D., Beadsworth, M., Bernatoniene, J., Berridge, J., Best, N., Bothma, P., Chadwick, D., Brittain-Long, R., Bulteel, N., Burden, T., Burtenshaw, A., Caruth, V., Chamberler, D., Chee, N., Child, J., Chukkambotla, S., Clark, T., Collini, P., Cosgrove, C., Cupitt, J., Coutino-Moguel, M.-T., Dark, P., Dawson, C., Dervisevic, S., Donnison, P., Douthwaite, S., Drummond, A., DuRand, I., Dushianthan, A., Dyer, T., Evans, C., Eziefula, C., Fegan, C., Finn, A., Fullerton, D., Garg, S., Garg, A., Gkrania-Klotsas, E., Goffen, J., Goldsmith, A., Graham, C., Hardy, E., Hartshorn, S., Harvey, D., Havalda, P., Hawcutt, D.B., Hobrok, M., Hodgson, L., Hormis, A., Jacobs, M., Jain, S., Jennings, P., Kaliappan, A., Kasipandian, V., Kegg, S., Kelsey, M., Kendall, J., Kerrison, C., Kerslake, I., Koch, O., Koduri, G., Koshy, G., Laha, S., Laird, S., Larkin, S., Leiner, T., Lillie, P., Limb, J., Linnett, V., Little, J., Lytle, M., MacMahon, M., MacNaughton, E., Mankregod, R., Masson, H., Matovu, E., McCullough, K., McEwen, R., Meda, M., Mills, G.H., Minton, J., Ward, K., Mirfenderesky, M., Mohandas, K., Mok, Q., Moon, J., Moore, E., Morgan, P., Morris, C., Mortimore, K., Moses, S., Mpege, M., Mulla, R., Murphy, M., Nagel, M., Nagarajan, T., Nelson, M., O'Shea, M. K., Otahal, I., Ostermann, M., Pais, M., Panchatsharam, S., Papakonstantinou, D., Paraiso, H., Patel, Brij, Pattison, N., Pepperell, J., Peters, M., Phull, M., Pintus, S., Pooni, J.S., Post, F., Price, D., Prout, R., Rae, N., Reschreiter, H., Reynolds, T., Richardson, N., Roberts, M., Roberts, D., Rose, Alistair, Rousseau, G., Ryan, B., Saluja, T., Shah, A., Shanmuga, P., Sharma, A., Shawcross, A., Sizer, J., Shankar-Hari, M., Smith, R., Snelson, C., Spittle, N., Staines, N., Stambach, T., Stewart, R., Subudhi, P., Szakmany, T., Tatham, K., Thomas, J., Thompson, Chris, Thompson, Robert, Tridente, A., Tupper-Carey, D., Twagira, M., Ustianowski, A., Vallotton, N., Vincent-Smith, L., Visuvanathan, S., Vuylsteke, Alan, Waddy, S., Wake, R., Walden, A., Welters, I., Whitehouse, T., Whittaker, P., Whittington, A., Papineni, P., Wijesinghe, M., Williams, Martin, Wilson, L., Cole, Sarah, Winchester, S., Wiselka, M., Wolverson, A., Wooton, D.G., Workman, A., Yates, B., Young, P., Analysis team members, Beale, R., Bretherick, A.D., Chloisey, S., Fourman, M.H., Furniss, J., Gountouna, E., Grimes, G., Haley, C., Harrison, D., Hayward, C., Keating, Sean, Klaric, L., Klenerman, P., Law, Andy, Meynert, A.M., Millar, J., Pairo-Castineira, E., Parkinson, N., Ponting, C.P., Porteous, D.J., Rawlik, K., Richmond, A., Rowan, K., Russell, C.D., Scott, R.H., Shen, X., Shih, B., Tenesa, A., Vitart, V., Wang, B., Wilson, J.F., Wu, Y., Yang, J., Yang, Z., Zechner, M., Zhai, R., Zheng, C., Norman, L., Pius, R., Drake, T.M., Fairfield, C.J., Knight, S.R., McLean, K.A., Murphy, D., Shaw, C.A., Dalton, J., Girvan, M., Saviciute, E., Roberts, S., Harrison, J., Marsh, L., Connor, M., Halpin, S., Jackson, C., Gamble, C., Leeming, G., Law, Andrew, Wham, M., Hendry, R., Scott-Brown, J., Data collection members, Begg, C., Hinds, C., Wai Ho, A.Y., Horby, P.W., Knight, J., Ling, L., Maslove, D., McAuley, D., Montgomery, H., Nichol, Ailistair, Openshaw, P.J.M., Semple, M.G., Shankar-Hari, M., Summers, C., Walsh, T., Armstrong, L., Bates, H., Dooks, E., Farquhar, F., Hairsine, B., McParland, C., Packham, S., Aildis, Z., Astin-Chamberlain, R., Bibi, F., Biddle, J., Blow, S., Bolton, M., Borra, C., Bowles, R., Burton, M., Choudhury, Y., Collier, David, Cox, A., Easthope, A., Ebano, P., Fotiadis, S., Gurasashvili, J., Halls, R., Hartridge, P., Kallon, D., Kassam, J., Lancoma-Malcolm, I., Matharu, M., May, P., Mitchelmore, O., Newman, T., Patel, M., Pheby, J., Pinzuti, I., Prime, Z., Prsyazhna, O., Shiel, J., Taylor, Melanie, Tierney, C., Wood, S., Zak, A., Zongo, O., Forshey, M., Kaliappan, A., Nicholson, Anne, Riches, J., Vertue, M., Wasson, C., Finn, S., Green, J., Collins, Erin, King, B., Grauslyte, L., Hussain, M., Phull, M., Pogreban, T., Rosaroso, L., Saliute, E., Franke, G., Wong, J., George, A., Akheroyd, L., Bano, S., Bromley, M., Gurr, L., Lawton, T., Morgan, J., Sellick, K., Warren, D., Wilkinson, B., McGowan, J., Ledgard, C., Stacey, A., Pye, K., Bellwood, R., Bentley, M., Hobrok, M., Loosley, R., McGuinness, H., Tench, H., Wolf-Roberts, R., Gibson, S., Lyle, A., McNeela, F., Radhakrishnan, J., Hughes, A., Ali, A., Brady, M., Dale, S., Dance, A., Gledhill, L., Greig, J., Hanson, K., Holdroyd, K., Home, M., Kelly, D., Kitson, R., Matapuru, L., Melia, D., Mellor, S., Nortcliffe, T., Pinnell, J., Robinson, M., Shaw, L., Shaw, R., Thomis, L., Wilson, A., Wood, T., Bayo, L.-A., Merwaha, E., Ishaq, T., Hanley, S., Antcliffe, D., Banach, D., Brett, S., Coghlan, P., Fernandez, Z., Gordon, A., Rojo, R., Arias, S.S., Templeton, M., Jha, R., Krishnamurthy, V., Lim, Lai, Bi, R., Scholefield, B., Ashton, L., Williams, Alison, Cheyne, C., Saunderson, A., Allan, A., Anderson, F., Kaye, C., Liew, J., Medhora, J., Scott, T., Trumper, E., Botello, A., Polgarova, P., Stroud, K., Meaney, E., Jones, M., Ng, A., Agrawal, S., Pathan, N., White, D., Daubney, E., Elston, K., Parker, R., Reddy, A., Turner-Bone, I., Wilding, L., Harding, P., Jacob, R., Jones, C., Denmark, C., Croft, M., White, I., Lim, Li, Griffin, D., Muchenje, N., Mupudzi, M., Partridge, R., Conyngham, J.-A., Thomas, R., Wright, M., Corral, M.A., Bastion, V., Clarke, D., David, B., Kent, H., Lorusso, R., Lubimbi, G., Murdoch, S., Penacerrada, M., Thomas, Alastair, Valentine, J., Vochin, A., Wulandari, R., Djeguiog, B., Dawson, J., Garricho, S., Tolson, M., Aldridge, J., de Almeida Martins, L.G., Carungcong, J., Beavis, S., Dale, K., Gascoyne, R., Hawes, J., Pritchard, K., Stevenson, L., Whileman, A., Cowley, A., Highgate, J., Crowley, R., Crew, A., Cunningham, M., Daniels, A., Harrison, L., Hope, S., Inweregbu, K., Jones, S., Lancaster, N., Matthews, J., Nicholson, Alice, Wray, G., Benham, L., Bradshaw, Z., Brown, J., Caswell, M., Cupitt, J., Melling, S., Preston, S., Slawson, N., Stoddard, E., Warden, S., Combes, E., Joefield, T., Monnery, S., Beech, V., Trotman, S., Hopkins, B., Scriven, J., Thrasyloulou, L., Willis, H., Anderson, Susan, Birch, Janine, Collins, Emma, Hammerton, K., O'Leary, R., Abernathy, C., Foster, L., Gratrix, A., Martinson, V., Parkinson, P., Stones, E., Carbal-Ortega, L., Kapoor, R., Loader, D., Castle, K., Brandwood, C., Smith, L., Clark, R., Birchall, Katie, Kolakaluri, L., Baines, D., Sukumaran, A., Mafunde, I., Meredith, M., Morris, L., Ryan, L., Clark, A., Sampson, J., Peters, C., Dent, M., Langley, M., Ashraf, Saima, Wei, S., Andrew, A., Chablani, M., Kirkby, A., Netherton, K., Bates, M., Dasgin, J., Gill, J., Nilsson, A., Scriven, J., Apetri, E., Basikolo, C., Blackledge, B., Catlow, L., Charles, B., Dark, P., Doonan, R., Harris, J., Harvey, A., Horner, D., Knowles, K., Lee, Stephanie, Lomas, D., Lyons, C., Marsden, T., McLaughlan, D., McMorrow, L., Pendlebury, J., Perez, J., Poulaka, M., Proudfoot, N., Slaughter, M., Slevin, K., Taylor, Melanie, Thomas, V., Walker, D., Michael, A., Collis, M., Clark, Martyn, Couilding, M., Jude, E., McCormick, J., Mercer, O., Potla, D., Rehman, H., Savill, H., Turner, V., Davey, M., Golden, D., Seaman, R., Hunt, Jodie, Dearden, J., Dobson, E., Mulcahy, M., Munt, S., O'Connor, G., Philbin, J., Rishoton, C., Tully, R., Winnard, S., Cagova, L., Fofano, A., Garner, L., Holcombe, H., Mephams, S., Mitchell, A.M., Mwaura, L., Praman, K., Vuylsteke, Alain, Zamikula, J., Bercades, G., Brealey, D., Hass, I., MacCallum, N., Martir, G., Raith, E., Reyes, A., Smyth, D., Taylor, A., Hughes, R.A., Thomas, H., Rees, A., Duskova, M., Phipps, J., Brooks, S., Edwards, M., Alexander, P., Allen, S., Bradley-Potts, J., Brantwood, C., Egan, J., Felton, T., Padden, G., Ward, L., Moss, S., Glasgow, S., Beesley, K., Board, S., Kubisz-Pudelko, A., Lewis, A., Perry, J., Pippard, L., Wood, D., Buckley, C., Brown, Alison, Gregory, J., O'Connell, S., Smith, T., Belagodu, Z., Fuller, B., Gherman, A., Olufuwa, O., Paramsothy, R., Stuart, C., Oakley, N., Kamundi, C., Tyl, D., Collins, K., Silva, P., Taylor, J., King, L., Coates, C., Crowley, M., Wakefield, P., Beadle, J., Johnson, L., Sargeant, J., Anderson, M., Jardine, C., Williams, D., Parris, V., Quaid, S., Watson, E., Melville, J., Naisbitt, J., Joseph, R., Lazo, M., Walton, O., Neal, A., Hill, M., Kannan, T., Wild, L., Allan, E., Darlington, K., Davies, F., Easton, J., Kumar, S., Lean, R., Menzies, D., Pugh, R., Qiu, X., Davies, L., Williams, H., Scanlon, J., Davies, G., Mackay, C., Lewis, J., Rees, S., Coetzee, S., Gales, A., Otahal, I., Raj, M., Sell, C., Langton, H., Prout, R., Watters, M., Novis, C., Arbane, G., Bociek, A., Campos, S., Grau, N., Jones, T.O., Lim, R., Marotti, M., Ostermann, M., Shankar-Hari, M., Whitton, C., Barron, A., Collins, C., Kaul, S., Passmore, H., Prendergast, C., Reed, A., Rogers, P., Shokkar, R., Woodruff, M., Middleton, H., Polgar, O., Nolan, C., Thwaites, V., Mahay, K., Sri-Chandana, C., Scherewode, J., Stephenson, L., Marsh, S., Bancroft, H., Bellamy, M., Carmody, M., Daghli, J., Moore, F., Rhodes, J., Sangombe, M., Kadiri, S., Scriven, J., Ayers, A., Harrison, W., North, J., Cavazza, A., Cockrell, M., Corcoran, E., Depante, M., Finney, C., Jerome, E., McPhail, M., Nayak, M., Noble, H., O'Reilly, K., Pappa, E., Saha, Rohit, Saha, S., Smith, John, Knighton, A., Gill, M., Paul, P., Ratnam, V., Shelton, S., Wynter, I., Baptista, D., Crowe, R., Fernandes, R., Herdman-Grant, R., Joseph, A., Loveridge, A., McKenley, I., Morino, E., Naranjo, A., Simms, R., Sollesta, K., Swain, A., Venkatesh, H., Khera, J., Fox, J., Barber, R., Hewitt, C., Hilldrith, A., Jackson-Lawrence, K., Shephardson, S., Wills, M., Butler, S., Tavares, S., Cunningham, A., Hindale, J., Arif, S., George, L., Twiss, S., Wright, D., Holland, M., Keenan, N., Lyons, M., Wassall, H., Marsh, C., Mahenthiran, M., Carter, E., Kong, T., Adanini, O., Bhatia, N., Msiska, M., Mew, L., Mwaura, E., Stewart, R., Williams, F., Wren, L., Sutherland, S.-B., Battle, C., Brinkworth, E., Harford, R., Murphy, C., Newey, L., Rees, T., Williams, Marie, Arnold, S., Brealey, D., Hardy, J., Houlden, H., Moncur, E., Raith, E., Tariq, A., Tucci, A., Convery, K., Fottrell-Gould, D., Hudig, L., Keshet-Price, J., Randell, G., Stammers, K., Abdelrazik, M., Bakthavatsalam, D., Elhassan, M., Ganesan, A., Haldeos, A., Moreno-Cuesta, J., Purohit, D., Vincent, R., Xavier, K., Rohit, K., Alasdair, F., Saleem, M., David, C., Jenkins, Samuel, Lamond, Z., Wall, A., Yates, B., Reynolds, J., Campbell, H., Thompson, M., Dadds, S., Duffy, S., Butcher, D., O'Sullivan, S., Butterworth-Cowin, N., Deacon, B., Hibbert, M., Potheary, C., Tetla, D., Woodford, C., Durga, L., Kennard-Holden, G., de Gordo, L.O.-R., Peasgood, E., Phillips, C., Skinner, D., Gaylard, J., Mullan, D., Newman, J., Davies, E., Roche, L., Sathe, S., Brimfield, L., Daly, Z., Pogson, D., Rose, S., Collins, A., Khaliq, W., Gude, E.T., Allen, L., Beranova, E., Crisp, N., Deery, J., Hazelton, T., Knight, A., Price, C., Tilbey, S., Turki, S., Turney, S., Giles, J., Booth, S., Bell, G., English, K., Katary, A., Wilcox, L., Campbell, R., Clarke, N., Whiteside, J., Mascarenhas, M., Donaldson, A., Matheson, J., Barrett, F., O'Hara, M., O'Keefe, L., Bradley, C., Collier, Dawn, Hormis, A., Walker, R., Maynard, V., Patel, T., Smith, M., Chukkambotla, S., Kazi, A., Hartley, J., Dykes, J., Hijazi, M., Keith, S., Khan, M., Ryan-Smith, J., Springle, P., Thomas, Jacqueline, Truman, N., Saad, S., Coleman, D., Fine, C., Matt, R., Gay, B., Dalziel, J., Ali, S.,

- Goodchild, D., Harling, R., Bhatteerjee, R., Goddard, W., Davison, C., Duberly, S., Hargreaves, J., Bolton, R., Laha, S., Verlander, M., Williams, Alexandra, Blackman, H., Creagh-Brown, B., Donlon, S., Michalak-Glinska, N., Mtuwa, S., Pristopan, V., Salberg, A., Smith, E., Stone, S., Piercy, C., Verula, J., Burda, D., Montaser, R., Harden, L., Mayangao, I., Marriott, C., Bradley, P., Harris, C., Cooper, J., Finch, C., Litherth, S., Quinn, A., Waddington, N., Fidler, K., Tagliavini, E., Donnelly, K., Abel, L., Brett, M., Digby, B., Gemmell, L., Hornsby, J., MacGoey, P., O'Neil, P., Price, R., Rodden, N., Rooney, K., Sundaram, R., Thomson, N., Flanagan, R., Hughes, G., Latham, S., McKenna, E., Anderson, J., Hull, R., Rhead, K., Branney, D., Frankham, J., Pitts, S., White, N., Cristiano, D., Dormand, N., Farzad, Z., Gummadi, M., Liyanage, K., Patel, B.V., Salmi, S., Sloane, G., Thwaites, V., Varghese, M., Zborowski, A.C., Bean, S., Burt, K., Spivey, M., Eastgate-Jackson, C., Filipe, H., Martin, D., Maharajh, A., Garcia, S.M., De Neef, M., Deacon, B., Lynch, C., Potchecary, C., Roche, L., Howe, G.S., Singh, J., Turner, K., Ellis, H., Stroud, N., Cherian, S., Cutler, S., Heron, A.E., Roynon-Reed, A., Szakmany, T., Williams, G., Richards, O., Cheema, Y., Ahmad, N., Barker, J., Baumhuller, K., Bird, S., Cawthron, K., Harrington, K., Jackson, Y., Kibutu, F., Lenagh, B., Masuko, S., Mills, G.H., Raithatha, A., Wiles, M., Willson, J., Newell, H., Lye, A., Nwafor, L., Jarman, C., Rowland-Jones, S., Foote, D., Cole, Joby, Thompson, Roger, Watson, J., Hesselton, L., Macharia, I., Chetam, L., Smith, Jacqui, Ford, A., Anderson, Samantha, Birchall, Kathryn, Housley, K., Walker, Sara, Milner, L., Hanratty, H., Trower, H., Phillips, P., Oxspring, S., Donne, B., Bevan, E., Martin, J., Trodd, D., Watson, G., Brown, C.W., Bunni, L., Jennings, C., Latif, M., Marshall, R., Subramanian, G., Bandla, N., Gellamuch, M., Davies, M., Thompson, Christopher, Trim, F., Eapen, B., Ahmed, C., 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