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Impact on Genetic Risk on SARS-CoV-2 Susceptibility and Severity among ASEAN Countries' Population: A Narrative Review.

Noor Nabilah Talik Sisin[1], Nasihah Mohd Zahid[1], and Nor Fazila Che Mat[1]*

[1] Biomedicine Programme, School of Health Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia

Corresponding author: fazilacm@usm.my

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Abstract

The coronavirus disease 2019 (COVID-19) outbreak, prompted by SARS-CoV-2, has had far-reaching global consequences, needing a multidimensional response including public health, economic, and scientific endeavours. Although vaccinations have been produced, new mutations pose difficulties. Genetics of the host has been identified as a crucial determinant of COVID-19 illness severity, with studies finding particular genetic variants associated with disease manifestations. However, there is a lack of studies on genetic risks in the Association of Southeast Asian Nations (ASEAN) region. This review seeks to fill this void by investigating the genetic risks of COVID-19 across ASEAN countries, considering the region's different populations, demographics, and social factors. We review recent research on genetic variations linked to COVID-19 susceptibility, severity, and viral burden from Thailand, Indonesia, and Vietnam. These findings are consistent with global reports emphasising the significance of TMPRSS2, ACE2, IFNAR2, and TYK2 genes. According to these findings, these genes have been reported to be involved in the SARS-CoV-2 entry pathway (ACE2 and TMPRSS2) and host immune response (IFNAR2, TYK2). The involvement of TMPRSS2, ACE2, IFNAR2, and TYK2 genes in coronavirus pathogenesis varies across populations and geographic regions. Consequently, analyzing genetic variants of these genes can elucidate their relationship with the severity of COVID-19. However, additional study is required to clarify genetic variables across all ASEAN nations. It is critical to address problems such as limited sample numbers, study design, and replication of findings to confirm these correlations. Furthermore, considering demographic, socioeconomic, and cultural characteristics influencing COVID-19 outcomes among ASEAN countries is critical for effective public health interventions. To better combat the pandemic, the ASEAN area must address these obstacles and increase its research efforts to gain a more in-depth understanding of the genetic risks associated with COVID-19 within the region's various ASEAN populations.

Keywords

COVID-19, ASEAN, Genetic risks, Susceptibility, Severity

Introduction

COVID-19 is a highly contagious viral illness caused by the SARS-CoV-2 virus. It first appeared in Wuhan, China, in December 2019 and quickly spread globally, culminating in a pandemic [1]. Infected people may have a wide range of symptoms, from no symptoms to life-threatening respiratory distress [1]. The most common COVID-19 symptoms are cough, fever, and difficulty in breathing [1]. COVID-19 poses a substantial threat to public health due to its high transmission rates and potential for severe results, particularly in vulnerable groups such as the elderly and those with pre-existing health issues. The outbreak of COVID-19 has had extraordinary worldwide repercussions, triggering a complex global crisis that includes public health, social, economic, and political elements.

To combat the virus's spread, governments worldwide have established various measures, including lockdowns, travel restrictions, and social distancing protocols [2]. These efforts attempted to lessen the burden on healthcare systems and flatten the infection rate curve. Despite these efforts, the virus has killed millions of people and infected millions more, putting a strain on the world's healthcare systems [3,4]. The scientific community has contributed to the solution, working relentlessly to study the virus and produce efficient diagnoses, treatments, and vaccines. The rapid development and approval of numerous vaccinations for emergency use proved the strength of global collaboration and scientific progress. Nonetheless, new mutations have caused difficulties in vaccination effectiveness and public health interventions[5].

SARS-CoV-2 utilizes specific molecules to enter cells [6]. Transmembrane protease serine 2 (TMPRSS2) cleaves the spike (S) protein of SARS-CoV-2, facilitating viral entry into host cells and contributing to immune evasion, crucial for evading host immune surveillance. Angiotensin-converting enzyme 2 (ACE2) serves as a receptor for SARS-CoV-2 attachment, enabling viral entry into cells [7,8]. The interaction between ACE2 and the virus enhances immune evasion by concealing the receptor-binding domain, weakening immune surveillance mechanisms [9]. Besides, reduced expression of IFN-α and -β receptor subunit 2 (IFNAR2) has been linked to an increased risk of severe COVID-19, indicating its role in modulating the immune response to the virus and potentially influencing disease severity [9–11]. Tyrosine kinase 2 (TYK2), identified in genome-wide association studies (GWAS), is involved in antiviral functions, highlighting its significance in the host response to viral infections and suggesting its potential role in mitigating viral spread and disease progression[6,11]. In short, SARS-CoV-2 utilizes TMPRSS2 and ACE2 for cell entry while modulating host immune responses through IFNAR2 and TYK2, highlighting key mechanisms in viral spread and disease severity.

A more comprehensive understanding of the risk variables associated with severe consequences was developed as the pandemic progressed. Variation in host genetics has been discovered as a critical driver of COVID-19 severity [10,12–14]. Investigating genetic risks in COVID-19 patients has yielded important insights into the mechanisms driving disease susceptibility and severity. The discovery of particular genetic variations linked to important COVID-19 can help with risk assessment, early intervention, and the development of targeted therapeutics. Furthermore, this knowledge can guide public health strategies and budget allocation to manage vulnerable groups successfully.

Like many other regions, the pandemic has significantly impacted the ASEAN countries. While existing studies on COVID-19 genetic risks have primarily focused on global data, a notable scarcity of research is dedicated to understanding the genetic determinants of COVID-19 severity and susceptibility within the ASEAN region (Brunei Darussalam, Cambodia, Indonesia, Lao People's Democratic Republic (Laos), Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam) [15]. ASEAN countries have diverse populations with distinct genetic histories, demographics, socioeconomics, sociocultures, and healthcare systems. Investigating genetic hazards linked with COVID-19 in ASEAN countries is a critical research field that must be addressed thoroughly.

A comprehensive analysis of the genetic risks of COVID-19 in ASEAN countries can close crucial knowledge gaps, support region-specific public health initiatives, and offer essential data to global efforts to combat the pandemic effectively. A targeted study on the genetic risks within the ASEAN community can lead to a more thorough understanding of the virus's impact on this diverse region, ultimately enhancing our global knowledge of COVID-19.

This review seeks to shed light on the latest ASEAN countries' genetic risk and COVID-19 outcomes, providing valuable insights that can inform public health and intervention researchers.

Methods

A search of PubMed from Dec 2019 to July 2023 using (Genetic[Title/Abstract]) AND (Covid[Title/Abstract]) found 1054 review papers. Nevertheless, a further advance with ((Genetic[Title/Abstract]) AND (Covid[Title/Abstract])) AND (ASEAN[Title/Abstract]) produced 60 results, in which 5 of the journals are the related reviews. Three reviews compared the genetic susceptibility of the Asian population with African, European, and American nations [14,16,17]. On the other hand, two other studies identified genetic variations associated with the clinical outcomes of SARS-CoV infections in ASEAN countries [13,18]. However, these two reviews were published in 2020 and are outdated. Furthermore, a similar Google Scholar search found 18 other reviews, but none specifically related to the genetic risks of COVID-19 patients in ASEAN countries.

The decision to focus on Vietnam, Thailand, and Indonesia was based on several factors. Firstly, these countries represent diverse populations within Southeast Asia, encompassing various ethnicities, genetic backgrounds, and environmental influences that may contribute to differences in COVID-19 susceptibility and severity. Additionally, during the specified timeframe, a significant body of literature was available on COVID-19 genetics in these countries, providing a robust basis for our analysis. While other ASEAN countries, such as Malaysia, are undoubtedly important, our literature search did not yield sufficient recent studies specifically addressing the genetic risks of COVID-19 within Malaysia. Therefore, to ensure the relevance and robustness of our analysis, we focused on Vietnam, Thailand, and Indonesia, where we could gather the most comprehensive and up-to-date data on the genetic aspects of COVID-19.

Epidemiology of COVID-19 in ASEAN Countries

Approximately 12 million confirmed COVID-19 cases were in the ASEAN region between January 2020 and October 2021 [19]. From January 2020 to July 2023, the World Health Organization (WHO) retrieved COVID-19 data on cases from each ASEAN country [20]. Vietnam has recorded the highest number of cumulative cases of COVID-19, with 11.6 million cases, while Indonesia has the second most confirmed cases, with 6.8 million cases [20]. There have been 5.1 million and 4.7 million confirmed cases in Malaysia and Thailand, respectively [20]. The Philippines and Singapore recorded about 4.1 million and 2.5 million cases, respectively [20]. Other ASEAN countries, including Myanmar, Laos, Cambodia, and Brunei, have reported less than a million confirmed cases [20]. Myanmar reported around 640000 confirmed cases, more than Brunei, which reported about 310000 confirmed cases [20]. Laos and Cambodia reported the lowest number of cases in the ASEAN region, approximating 218,000 and 138000 confirmed cases, respectively [20], as illustrated in Figure 1.

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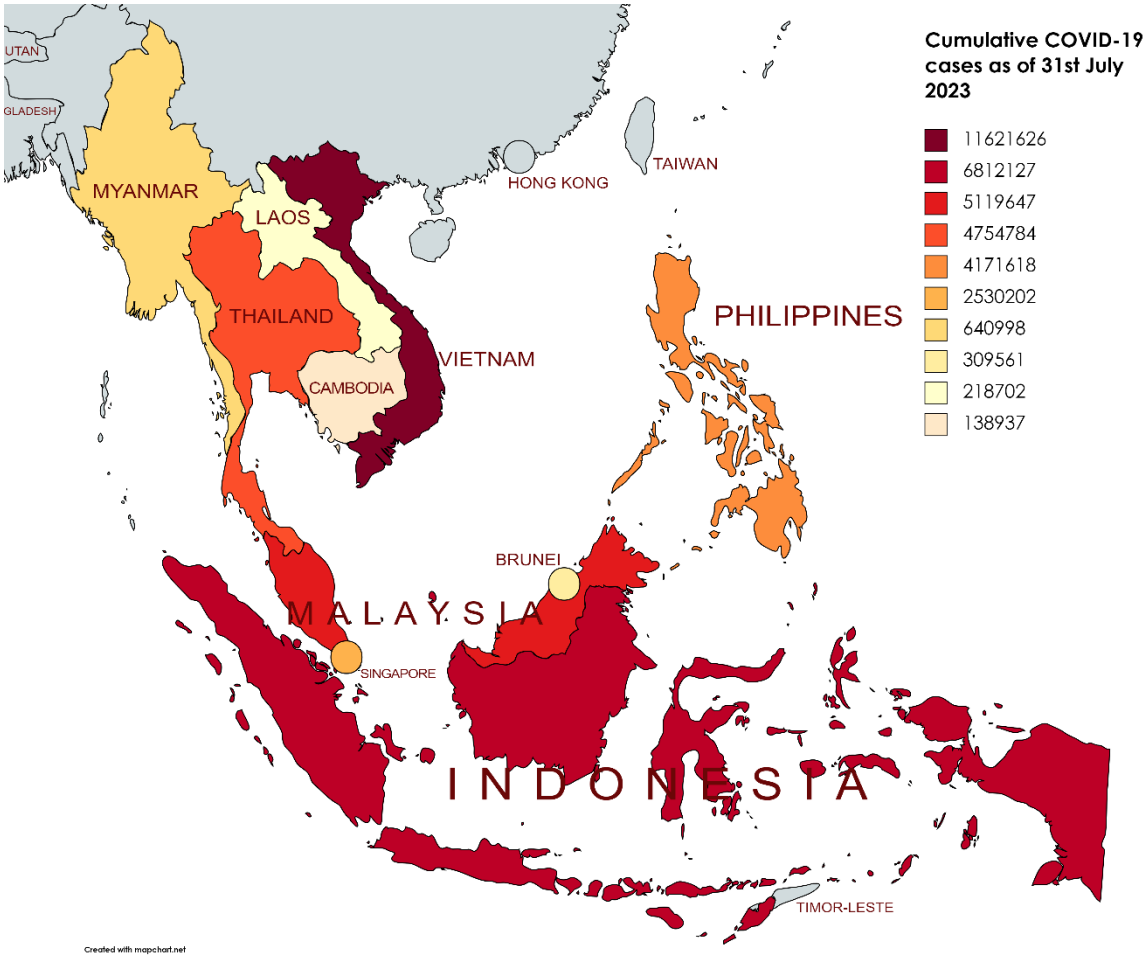

Figure 1: The map of the ASEAN countries with respective cumulative cases in the legends as of 31st July 2023.

Several studies performed across the ASEAN region showed that age, sex, population density, job types, village poverty, and sociocultural diversity are the typical demographic characteristics of COVID-19 patients in the ASEAN region [21–23]. In Thailand, research findings revealed a significant difference between male and female patients, with male patients outnumbering female patients across the age ranges of 31 to 45 years, 40 to 60 years, and more than 60 years [21]. Furthermore, population density was significantly associated with the number of COVID-19 cases [21]. This statement was supported by a study in Vietnam, demonstrating that densely populated countries in low- and middle-income countries like Vietnam are the core of the COVID-19 pandemic [24]. Because of the crowded living conditions, the virus spread quickly, with a significant risk of community transmission [24]. In addition, job types and village poverty also can be associated with COVID-19. It was stated that health workers have the highest risk for COVID-19 infection and death compared to civil servants' non-health workers, laborers, professional workers, homemakers, students, and retired persons [25]. During the early outbreak, retired persons and students were less likely to contract COVID-19 than health workers due to less social contact [25]. This situation is because school was conducted online, there were no physical classes, and like retirees, they tend to socialize less than other people [25].

Besides, based on the World Bank's data, ASEAN countries comprise a few lower-middle-income countries like Indonesia, Cambodia, Laos, Myanmar, the Philippines, and Vietnam [26]. A previous study showed that poverty is a crucial feature of Indonesia's rural population and partially influences people's health status [25]. Next, ASEAN countries are enriched with sociocultural diversity. Each culture includes native communal activities such as Javanese wedding ceremonies and religious gatherings [25]. These are part of traditional cultures that obligate the people to gather, meet each other, and gather in large numbers. As most villagers are traditionally bound to participate in such events, COVID-19 transmission may be directly mediated between and across communities [25].

Furthermore, the case fatality rate (CFR) varies by country, ranging from 0% to more than 20% [27]. Based on a previous study, from January to October 2020, the total number of patients infected with COVID-19 in Malaysia, Singapore, Thailand, Indonesia, Philippines, and Myanmar was approximately 940,000, with a mortality rate of 2.42% [28]. Over the 10 months, Indonesia had 410,088 cases with a 3.38% mortality rate; the Philippines had 380,729 cases with a 1.90% mortality rate; Singapore had 58,015 cases and 0.05% mortality rate; Myanmar had 52,706 cases with a 2.34% mortality rate; Malaysia had 31,548 with 0.79% mortality rate; and Thailand had 3,780 cases with a 1.56% mortality rate [28]. Nevertheless, from September 2020 until July 2023, the highest CFR in ASEAN countries was observed in the Philippines, with a CFR of 9.94% in January 2022 [24]. In July 2023, Brunei, Singapore, Laos, Vietnam, Thailand, and Malaysia recorded less than 1% CFR, within the range of 0.05% to 0.73% [29]. Meanwhile, countries such as the Philippines, Cambodia, Indonesia, and Myanmar recorded more than 1% CFR, ranging from 1.59% to 3.04% [29].

Challenges in Reporting Cases During the COVID-19 Pandemic

During the ongoing COVID-19 pandemic, accurate and timely reporting of cases is paramount for understanding the virus's transmission dynamics and devising effective public health strategies. However, challenges in reporting have emerged and evolved throughout the pandemic, presenting a multifaceted landscape [30,31].

Initially, limited testing capacity and resources posed significant hurdles in accurately identifying and documenting COVID-19 cases. Many countries faced shortages of testing kits, laboratory facilities, and trained healthcare professionals [32,33]. Consequently, only symptomatic or severe cases were prioritized for testing, leaving a substantial portion of infected individuals, particularly those with mild or asymptomatic symptoms, undetected and unreported, leading to a significant underestimation of the true extent of the outbreak in many regions [33].

Moreover, the evolving understanding of the virus and its varied clinical presentations contributed to misdiagnosis and under recognition of COVID-19 symptoms in the early stages [34,35]. Cases were sometimes missed or misclassified, further complicating accurate reporting. Additionally, overwhelmed healthcare systems during peak transmission periods struggled to cope with the influx of patients, diverting resources away from data collection and reporting efforts [33]. In such scenarios, the immediate priority shifted towards providing critical care and managing the healthcare response, often at the expense of comprehensive reporting [36].

Political and social factors also played a significant role in shaping reporting practices [37,38]. Some governments, concerned about the potential economic and political repercussions of high case numbers, may have been inclined to downplay or manipulate data to maintain public confidence or mitigate panic [38]. Conversely, political motivations could have led to exaggerated reporting in an attempt to showcase effective governance and crisis management.

Furthermore, disparities in reporting standards and transparency between countries introduce further complexities [30]. Variations in testing criteria, data collection methodologies, and reporting mechanisms make cross-country comparisons challenging and contribute to inconsistencies in reported case numbers [32]. These limitations of case reporting have significant implications for interpreting the epidemiological distribution of COVID-19 cases [39,40]. Disparities in reporting rates between regions and demographic groups can skew our understanding of disease transmission patterns and hinder the identification of high-risk populations [40,41]. Additionally, reliance solely on reported case counts may obscure the true magnitude of outbreaks and delay the implementation of targeted interventions.

As the pandemic wore on, pandemic fatigue and complacency set in among populations, leading to decreased adherence to preventive measures and contributing to increased transmission. In some instances, this led to a sense of resignation or apathy towards reporting, as the public's attention shifted away from the crisis [42–44].

The decision of some countries, notably China, to halt the daily release of COVID-19 case and death figures marked a significant shift in reporting practices established since early 2020. This cessation, along with disparities in reporting rates between regions and demographic groups, poses challenges to global data analysis and transparency. It underscores the critical importance of transparent and consistent data sharing to facilitate informed and effective public health responses on a global scale. Ultimately, transparent and accountable governance, alongside reliable data sharing, remains crucial for navigating the ongoing pandemic effectively [31].

Genetic Polymorphisms Associated with COVID-19 Risks Globally

Recent studies have investigated the role of genetics and host factors in determining the severity and susceptibility of COVID-19 [10,12,45,46]. The findings highlight the complex interplay between genetic variations, host immune responses, and disease outcomes in individuals infected with SARS-CoV-2.

A few reviews highlight the COVID-19 Human Genetic Effort (HGE) international consortium [45,47,48]. They studied the human genetic basis of life-threatening COVID-19 in previously healthy and relatively young patients, particularly those under 50 years old [45,47,48]. This initiative recognizes the importance of studying large populations to learn more about the genetic factors influencing susceptibility to infectious diseases and how people respond to them [47]. The focus has primarily been on single-gene predisposition forms, but looking for single-gene inborn errors of immunity (IEI) is critical [48]. Later, a few reviews accentuate the IEI factors, which involve autoantibodies against type 1 interferons (IFNs) and Toll-like receptor (TLR) deficiencies [49–51].

COVID-19 severity has been linked to changes in critical genes that control how viruses enter the body and how the immune system responds to them. Variants in the ACE2 gene, which makes the SARS-CoV-2 receptor, and genes in the innate and adaptive immune systems, like IFNAR2, oligoadenylate synthetases (OAS), TYK2, and human leukocyte antigens (HLA) proteins, have been linked to the severity of disease [12]. Moreover, specific high-risk HLA haplotypes have been related to being more likely to get COVID-19 [12,52]. The susceptibility and severity of COVID-19 have also been demonstrated to be affected by host genetic variables associated with cellular proteases such as TMPRSS2 and furin [52]. There is also a complex correlation between COVID-19 severity and genes that regulate immunological responses, such as cysteine-cysteine chemokine receptor 5 (CCR5), IFNs, TLRs, and tumor necrosis factor (TNF) [52].

Recent COVID-19 Host Genetics Initiative (HGI) reports have identified several significant loci and variants associated with SARS-CoV-2 infection and COVID-19 severity. Among the notable loci are 3p21.31, ABO, DPP9, FOXP4, TYK2, CXCR6, LZTFL1, IFNAR2, OAS1/OAS2/OAS3, HLA, and two loci on chromosomes 7 and 19. The KANSL1 locus has also been linked to COVID-19 severity [53]. More recently, updates to the list include the identification of 11 additional loci or variants associated with COVID-19 severity and SARS-CoV-2 infection. Some of these variants include rs721917 in SFTPD, rs117169628 in SLC22A31,

rs35705950 in the promoter of MUC5B, and rs190509934, located upstream of ACE2. Notably, the rs190509934 variant reduces ACE2 expression, protecting against SARS-CoV-2 infection. Conversely, variants like rs721917 in SFTPD and rs73062389 in SLC6A20 are associated with increased susceptibility to infection and hospitalization [54].

The newly discovered loci and variants provide valuable insights into the genetic basis of COVID-19 severity and susceptibility. One notable Genetics of Mortality in Critical Care (GenOMICC) study found that some previously identified genetic variants could impact genes involved in crucial biological processes such as interferon signaling, leukocyte differentiation, and blood-type antigen secretion [55]. They observed reduced expression of a membrane flippase called ATP11A and increased expression of a mucin protein called MUC1 in critically ill patients [55]. The study also supported the causal roles of specific genes, including myeloid cell adhesion molecules (SELE, ICAM5, and CD209) and the coagulation factor F8, which represent the potential targets for therapeutic interventions [55]. The study's findings suggest that critical COVID-19 can arise from at least two distinct mechanisms: failure to control viral replication and an enhanced tendency towards lung inflammation and intravascular coagulation [55].

Furthermore, significant demographic parameters impacting COVID-19 severity include age and sex. Men and people of advanced age are more likely to have life-threatening health complications [46,56]. The presence of androgens in males has also been linked to a more severe SARS-CoV-2 infection [26]. The severity of COVID-19 has also been observed to depend on the blood group. The danger of developing a life-threatening illness is higher in people with blood group A, while those with blood group O seem protected [56]. These studies highlight the importance of host genetics in determining individual susceptibility and severity of COVID-19. Understanding the genetic factors that contribute to disease outcomes can aid in identifying high-risk individuals and developing targeted interventions to mitigate the impact of the disease.

Host Genetic Risks in ASEAN Countries

Despite available data on host genetic risks from various sources, comprehensive data from ASEAN countries is scarce. A PubMed search from 2019 to July 2023 using (Genetic Research on COVID-19 in ASEAN Countries [Title/Abstract]) yielded no results. However, further advancements employing each ASEAN country revealed that three research were conducted in Indonesia, Thailand, and Vietnam to study the relationship between host genetic factors and COVID-19 disease susceptibility and severity [10,57,58].

A study performed by Nhung and colleagues in Vietnam mainly focused on the SARS-CoV-2 infection of ACE2, ADAM17, TMPRSS2, IFNAR2, TYK2, DPP9, LZTFL1, and SLC6A20 [10]. The study found that only 3 of the 19 single nucleotide polymorphisms (SNPs) tested indicated a significant difference between infected individuals and healthy controls in genetic variants associated with the SARS-CoV-2 susceptibility, including IFNAR2 (rs17860118: rs2229207) and SLC6A20 (rs139940581) [10]. For IFNAR2, both variants rs17860118 and rs2229207 were substantially different between patients and controls [10]. In the case of rs2229207, the heterozygous genotype TC frequency was considerably greater in infected people than in healthy patients [10]. There was also a markedly greater prevalence of infected patients possessing CT genotype and allele T for SLC6A20 rs139940581 than in the control group [10]. The example of an SNP with C and T alleles is illustrated in Figure 2.

For the study about genetic variants linked with the COVID-19 severity among the Vietnamese, the finding showed that there was no statistically significant difference between the groups in terms of variant frequencies of the IFNAR2, LZTFL1, and SLC6A20 genes, both at the genotype and allele levels [10]. For the ADAM17 gene, the frequency of heterozygous genotypes TG (rs4622692) and TC (rs1048610) in the moderate cases was higher than in severe or fatal cases [10]. In addition, the allele T of variant rs2304255 (p.Val362Phe) belonging to TYK2 was more common in severe or fatal patients than in asymptomatic or mild patients in Vietnam [10]. The difference in the percentage of heterozygous CT genotypes between these two groups reached statistical significance, with CT in severe or fatal cases being more prevalent than in

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asymptomatic or mild cases [10]. Additionally, for the DPP9 variant rs2277735, the percentage of heterozygous genotype AG in asymptomatic or mild infections was significantly lower than in moderate, severe, or fatal illnesses [10].

Meanwhile, for the TMPRSS2 gene, the difference in GA genotypes rs12329760 between asymptomatic or mild and severe or fatal cases was statistically significant [10]. The prevalence of the homozygous mutation AA genotype was higher in the asymptomatic or mild group than in the severe or fatal group [10].

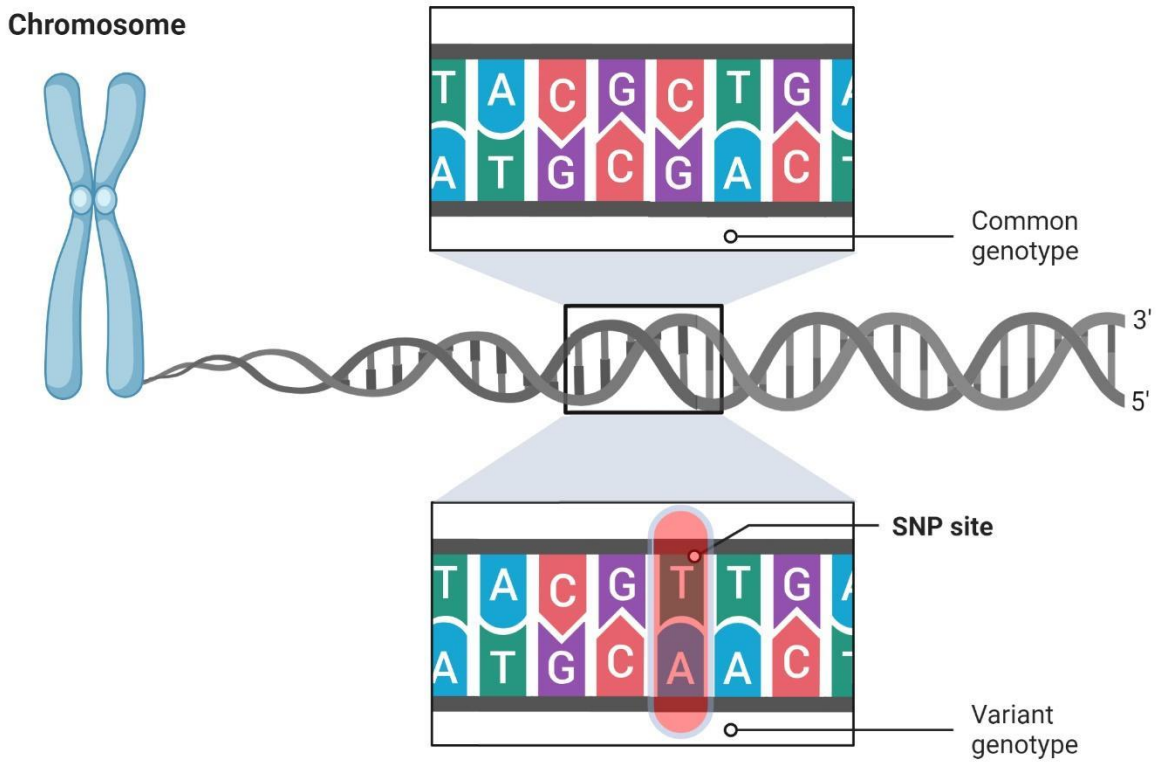

Figure 2: The example of alleles C and T in an SNP. SNP results from a change in a single DNA building block in a specific location. For example, the sequence of TACGCTGA mutated to TACGTTGA. The 'C' changed to a 'T.' This simple change leads to two versions of this genetic site. The C and T are called "alleles," meaning there are two common possibilities for that particular spot in the DNA code.

However, the finding about the genetic variants in TMPRSS2 linked with the COVID-19 severity in Vietnam did not correspond to a study conducted in Indonesia, where the results showed that there was no correlation between the presence of the TMPRSS22 genetic variant and the severity of COVID-19 disease [57]. Nevertheless, it was discovered that there was a significant association between the p.Val160Met polymorphism and SARS-CoV-2 viral load, measured by the cycle threshold (Ct) value of the diagnostic nucleic acid amplification test, where Ct value is known as a semi-quantitative predictor of the viral load [57]. Furthermore, there was a trend of association between the presence of the C allele and a higher death rate in individuals with severe COVID-19 [57].

In addition, the relationship between ABO blood group type distribution and infection in Vietnam was analyzed, and the analysis showed no difference in blood group frequencies across the three clinical groups ($p=0.389$) [10]. However, when the clinical groups were studied in pairs, there was a link between ABO blood type and disease severity. Asymptomatic or mild patients had considerably higher frequencies of blood O

type than moderate infection patients and severe infection or fatal patients [10]. As a result, it was observed that the O blood type was a protective factor that reduced the worst outcomes of the infected people [10].

Considering the genetic landscape varies by ethnicity, one study was also performed to investigate the host genetic factors associated with COVID-19 disease susceptibility and severity among the Thailand population [58]. According to Chamnanphon and colleagues, two indicative loci on chromosomes 5q32 and 9q21.13, as well as two suggestive loci on chromosomes 12q22 and 3p24.3, were linked to COVID-19 disease susceptibility and severity, respectively [58].

These studies have provided insights into the genetic landscape of COVID-19 susceptibility, severity, and outcomes, particularly within the countries in the ASEAN region [10,57,58] . However, it is essential to note that the current understanding of host genetic risks associated with COVID-19 in ASEAN nations appears limited to these three investigations. The absence of genetic risk information for countries like Brunei, Cambodia, Laos, Malaysia, Myanmar, the Philippines, and Singapore highlights the ongoing nature of research endeavors in the region. Comprehensive investigations encompassing the full spectrum of host genetic factors across all ASEAN countries are underway. The current findings emphasize the need for further research to comprehensively elucidate the genetic determinants of COVID-19 susceptibility and severity across diverse populations within the ASEAN region, contributing to a more comprehensive understanding of the disease's impact on a global scale.

Additionally, the strengths and weaknesses of existing studies are assessed. The study by Wulandari and colleagues was the first study on a possible association between TMPRSS2 p.Val160Met polymorphism and higher viral load in COVID-19 patients in Indonesia [57]. The study's strengths come from its narrowly focused hypothesis, finding the TMPRSS2 polymorphism and statistical test associations using Ct values [57]. However, the analysis's confinement to a single genetic variant disregards potential interactions between multiple genes, impeding a comprehensive understanding of the genetic landscape. Its biggest weakness is that its sample size (95 hospitalized COVID-19 patients) may limit the generalizability of the findings, and it needed more large-scale research to confirm its findings [57].

In Nhung and the team's investigation, a more holistic approach was undertaken to explore host genes and their interplay with COVID-19 outcomes in Vietnam [10]. This study encompassed a comprehensive examination of genetic variants across a cohort of 200 COVID-19 patients and 100 controls [10]. The strengths of this study encompass its multidimensional approach, considering both genetic and immunological factors, and the meticulous identification of potential mechanisms underlying genetic associations with COVID-19 outcomes. Although genetic relationships are found, the study's inability to prove causation highlights how difficult it is to separate genetic influences from the outcomes of complex diseases.

The third study, undertaken by Chamnanphon and colleagues [58], embraced a genome-wide exploration of SNPs related to COVID-19 pathogenesis, encompassing 212 COVID-19 patients and 36 controls in Thailand. Nonetheless, they must be interpreted carefully and tested in larger groups because the associations found are insignificant for the whole genome. Finally, the small sample size of controls may reduce the possibility that the association found is real, but it could still be valid.

Table 1 summarises the genetic polymorphisms associated with COVID-19 risks globally and in three ASEAN countries. Eight genes were detected in Indonesia and Vietnam, similarly registered in HGE and HGI reports. On the other hand, the Vietnam study also found that the ADAM17 gene is included in the host genetic risks of COVID-19 [10]. Although the global reports did not describe this gene, some reviews supported ADAM17 as the leading risk factor for COVID-19 [59,60]. The study from Thailand also found novel and potential links to COVID-19 susceptibility on chromosome 5q32, which houses thIL17B, and chromosome 12q22, which harbours the EEA1 gene and a non-coding RNA LOC643339 [58]. The finding on the EEA1 gene is supported by an *in silico* analysis that discovered EEA1 as a shared antigen in severe COVID-19 cases [61].

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In summary, our exploration of host genetic factors in the context of COVID-19 has yielded valuable insights, especially within ASEAN countries. While our search initially yielded limited data, subsequent studies conducted in Indonesia, Thailand, and Vietnam have shed light on the genetic landscape of COVID-19 susceptibility and severity. The research in Vietnam examined various genes related to SARS-CoV-2 infection and immune response and highlighted specific genetic variants that differ significantly between infected individuals and healthy controls. Notably, the O blood type was a protective factor against severe outcomes. Meanwhile, investigations in Indonesia and Thailand have provided additional clues, uncovering associations between specific genetic variants and COVID-19 viral load or disease susceptibility. Identifying genetic polymorphisms associated with COVID-19 risks in these ASEAN countries, while contributing to our understanding, also emphasizes the need for continued research and collaboration.

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Table 1: Summary of findings regarding genetic polymorphisms and their association with COVID-19 susceptibility or severity.

Genes/ Variants	Clinical Association	Country	Findings	Reference	Our Perspective
ABO gene	Impacted blood group, disease susceptibility, and severity	Vietnam	Specifically, blood type O frequency was significantly higher in asymptomatic/mild patients compared to moderate infection patients (p = 0.037, OR = 2.072) and severe infection/fatal patients (p = 0.041, OR = 2.061).	[10]	In contrast to the findings, the global study indicates that genetic differences in the ABO gene might affect how likely someone is to get severe COVID-19 worldwide [12]. Although. the Vietnam study focused on a specific population, the global study suggests this connection applies more broadly. Overall, they both highlight the role of genetics in COVID-19 outcomes. [10]
ACE2 gene	Linked to SARS-CoV-2 receptor and disease severity	Vietnam	The ACE2 gene produces a protein that helps the COVID-19 virus to enter cells. Variations in this gene and the amount of ACE2 in different tissues can affect how severe the illness becomes.	[10]	In short, variations in the ACE2 gene affect how severe COVID-19 is within certain populations, such as Vietnam. On a global scale, genes like ACE1, which affect the balance between ACE1 and ACE2, are linked to COVID-19 severity. These discoveries highlight the genetic complexity influencing COVID-19 outcomes.[10,62]
DPP9 gene (rs2277735, rs2109069 variants)	Linked to COVID-19 severity	Vietnam	The AG genotype of the DPP9 variant rs2277735:A>G is less common in asymptomatic/mild COVID-19 cases (23.2%) compared to moderate (43.3%) and severe/fatal cases (43.8%). This suggests a higher risk of experiencing moderate or severe/fatal COVID-19 with the AG genotype.	[10]	The global study also associates another DPP9 variant, rs2109069, with severe COVID-19 worldwide[12]. This indicates that DPP9 gene variations may affect COVID-19 severity across populations. Both studies highlight the significance of DPP9 gene variants in COVID-19 severity [10,12].
IFNAR2 gene	Associated with disease	Vietnam	The study identified two variants of the IFNAR2 gene, rs2229207	[10]	In Vietnam, two variants of the IFNAR2 gene were linked to a higher risk of getting COVID-19. They were

Genes/ Variants	Clinical Association	Country	Findings	Reference	Our Perspective
(rs2229207 and rs17860118 variants)	severity, immune response, and increased risk of infection		(TC genotype, allele C) and rs17860118 (allele T), associated with a higher risk of SARS-CoV-2 infection. These variants were more prevalent in infected individuals compared to healthy controls. Specifically, mutated alleles (allele T for rs17860118 and allele C for rs2229207) were more common in infected individuals. Moreover, the TC genotype for rs2229207 was more prevalent in infected individuals, while the wild-type genotype (TT) was less common among them compared to healthy controls.		more common in infected people than in those who stayed healthy. Similarly, a study in the UK found that IFNAR2 genes were linked to severe COVID-19. This suggests that differences in these genes could affect how severe the illness becomes [10,63].
LZTFL1 gene rs1129183	Implicated in COVID-19 severity	Vietnam	The variant of LZTFL1 rs1129183:C>T (p.D246N) presented no correlation with COVID-19 infection or the severity of the disease.	[10]	While the Vietnamese study found no link between LZTFL1 variant rs1129183:C>T and COVID-19 outcomes, previous research in other populations like Spanish and Italians suggests LZTFL1's potential role, highlighting the need to explore population-specific variants and mechanisms for a clearer understanding [10,12,53].
SLC6A20 (rs73062389 , rs139940581 variant)	Associated with increased susceptibility and reduced	Vietnam	The study detected the clinical significance of SLC6A20 (rs139940581) to COVID-19 susceptibility.	[10]	Another study by Pathak et al. (2022) also identified a significant association between another variation (rs73062389:G>A) in the SLC6A20 gene and susceptibility to COVID-19. This means that both studies found genetic variations in the SLC6A20 gene to

Genes/ Variants	Clinical Association	Country	Findings	Reference	Our Perspective
	virus sensitivity				be linked to the likelihood of getting infected with COVID-19 [10,54].
TMPRSS2 gene (rs12329760 polymorphism or p.Val160Met variant)	Affected cellular protease involved in viral entry and load and associated with asymptomatic or mild symptoms.	Vietnam, Indonesia	The variant rs12329760 (AA genotype) of TMPRSS2 was significantly associated with asymptomatic/mild symptoms as in the Vietnam population [10]. A study in Indonesia found a significant connection between the p.Val160Met polymorphism and the viral load of SARS-CoV-2. [57].	[10,57]	Both findings from Vietnam and Indonesia emphasize the importance of TMPRSS genes in protease/cell entry, which plays a crucial role in SARS-CoV-2 infection, as indicated by studies by other researchers in Europe [10,12,57,64].
TYK2 gene (rs2304255 or p.Val362Phe)	Linked to immune response and disease severity.	Vietnam	In severe/fatal COVID-19 patients, the allele T of the rs2304255:C>T variant in the TYK2 gene was more prevalent (5.5%) compared to asymptomatic/ mild patients (0.7%), suggesting a potential association with a higher risk of severe illness.	[10]	The findings align with research conducted in other countries, linking this gene to critical and severe illness. These findings suggest that genetic variations in the TYK2 gene may contribute to the severity of COVID-19 illness [10,12].
OAS genes (OAS1,OAS2,OAS3)	Involved in antiviral response and disease severity.	Multiple (Europe and Africa)	The chr12q24.13 locus, encoding OAS1–OAS3 antiviral proteins, is linked to COVID-19 susceptibility. A common haplotype linked to reduced OAS1 expression also contributes to COVID-19 severity.	[65]	This indicates that differences in these antiviral proteins could influence susceptibility to the virus and the severity of COVID-19 illness.[65] However, no studies have been conducted in any ASEAN countries regarding this gene.

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Genes/ Variants	Clinical Association	Country	Findings	Reference	Our Perspective
CCR5 gene	Correlated with COVID-19 severity and immunological responses.	Asturias, Northern Spain	The CCR5 gene is correlated with COVID-19 severity, with increased expression in severe cases. A deletion in this gene was found to protect against severe COVID-19, particularly in individuals with two copies of the deletion.	[66]	This suggests that variations in the CCR5 gene may influence the severity of COVID-19 symptoms in affected individuals. However, it's important to note that no studies in ASEAN countries have investigated this gene.
CXCR6 gene	Associated with COVID-19 severity.	Multiple European countries	The study discovered that genetic variations in CXCR6 on chromosome 3p21.31 may influence COVID-19 severity by altering its expression in lung cells.	[68]	The genetic differences in the CXCR6 gene, located on chromosome 3p21.31, might influence the severity of COVID-19 by altering its expression in lung cells. This suggests that variations in CXCR6 could potentially play a role in determining the severity of COVID-19 symptoms experienced by individuals.
FOXP4 gene (rs1886814 variant)	Correlated with COVID-19 severity	Global (HGI data)	The study revealed that the variant rs1886814 of the FOXP4 gene is associated with COVID-19 severity. It impacts FOXP4 expression in the lungs, resulting in elevated levels.	[70]	The link between FOXP4 and lung function is becoming increasingly clear. This study suggests a variant in FOXP4 (rs1886814) might contribute to COVID-19 severity by affecting its expression in the lungs. Notably, prior research has implicated FOXP4 overexpression in non-small cell lung cancer progression [69]. Understanding the mechanisms by which FOXP4 influences lung health and disease is crucial. Further research is needed to determine if the FOXP4 variant associated with COVID-19 severity also plays a role in lung cancer susceptibility or progression. Additionally, investigating FOXP4's regulatory pathways and its potential as a therapeutic target for both COVID-19 and lung cancer warrants further exploration.

Genes/ Variants	Clinical Association	Country	Findings	Reference	Our Perspective
FURIN gene (rs6224 and rs4702)	Associated with susceptibility and severity to COVID-19	Spain	Alleles rs6224 T and rs4702 A, linked to increased FURIN gene expression, were associated with higher COVID-19 mortality risk.	[72]	This study adds to the growing evidence implicating FURIN in viral entry and disease progression in COVID-19. Understanding how FURIN expression influences this process could be crucial for developing novel therapeutic strategies. Interestingly, FURIN has also been linked to the pathogenesis of various other diseases, including cancer and neurodegenerative disorders [71]. Further research is necessary to confirm the role of FURIN in COVID-19 and explore its potential as a therapeutic target. Additionally, investigating the commonalities between FURIN's function in COVID-19 and other diseases could provide valuable insights for broader therapeutic applications.
HLA haplotypes proteins	Associated with susceptibility to COVID-19	Allele Frequency Net Database (805 distinct populations across 101 different countries).	The study discovered that variations in HLA haplotypes may affect an individual's immune response, potentially increasing susceptibility to COVID-19.	[73]	This study highlights the potential role of HLA haplotypes, which influence immune response, in a person's vulnerability to the virus. Further investigation is needed to confirm these findings and explore how HLA variations might be incorporated into personalized risk assessment or therapeutic strategies.
IFNs (Interferon) genes	Related to immune response and disease severity.	United States (USA)	Severe COVID-19 cases are associated with weakened interferon signalling in the upper respiratory tract (URT) at illness onset and strong pro-inflammatory responses in the	[74]	The severity of COVID-19 may be associated with specific patterns of immune response in different regions of the respiratory tract. The findings suggest that understanding and targeting these immune responses may be crucial for managing and treating severe cases of COVID-19.

Genes/ Variants	Clinical Association	Country	Findings	Reference	Our Perspective
			lower respiratory tract (LRT) at illness peak.		
KANSL1 locus	Associated with COVID-19 severity.	Global (HGI data)	The severity of COVID-19 has also been linked to the KANSL1 gene, indicates a potential genetic link to disease outcomes	[68]	The scarcity of information suggests that further research is needed to fully elucidate the role of the KANSL1 gene in COVID-19. Investigating this gene's involvement could provide valuable insights into the genetic factors underlying disease severity and aid in the development of targeted treatments or interventions.
MUC5B promoter (rs35705950 variant)	Linked to disease severity.	Several European countries (Netherlands, United Kingdom, Italy, and Spain)	This study showed that individuals with the T-allele of MUC5B rs35705950 are protected from severe COVID-19.	[75]	It highlights the potential role of genetic variations in influencing disease severity. However, further research is needed to fully understand the mechanisms underlying this protective effect and its broader implications for COVID-19 management and treatment strategies.
SFTPD (rs721917 variant)	Impacted susceptibility and infection.	Global (HGI data)	The genetic variation rs721917:A>G in the SFTPD gene is linked to an increased likelihood of COVID-19 hospitalization, with a statistically significant p-value and odds ratio of 1.06.	[68]	The study emphasizes genetic factors in COVID-19 outcomes, particularly hospitalization risk. Further exploration of this link could reveal insights into individual susceptibility to severe COVID-19, guiding personalized healthcare approaches.
SLC22A31 (rs117169628 variant)	Associated with disease severity.	Global (HGI data)	The genetic variant rs117169628:G>A in the SLC22A31 gene is associated with an increased likelihood of COVID-19 hospitalization, with a	[68]	This particular genetic variant might contribute to the severity of COVID-19 outcomes. However, it's crucial to account for other factors and conduct more research, particularly in ASEAN countries, to comprehensively

Genes/ Variants	Clinical Association	Country	Findings	Reference	Our Perspective
			statistically significant p-value and odds ratio of 1.09.		grasp the implications of this genetic association in the context of COVID-19.
TLRs (Toll-like receptors)	Involved in immune response and disease severity.	Global (1000 Genomes Project and gnomAD data)	A missense mutation in the TLR3 gene (rs3775291) is linked to severe disease.	[76]	This suggests that TLR genes may play a role in determining the severity of the illness, highlighting their potential importance in the immune response to COVID-19.
TNF gene rs767455 variant	Regulated immunological responses and disease severity.	Mexico	The polymorphism rs767455 of TNFRSF1A is linked to a severe progression of COVID-19.	[77]	This finding from Palacios et al. (2021) suggests a link between the TNFRSF1A polymorphism rs767455 and severe COVID-19 progression. However, studies in ASEAN countries on this topic are still lacking, highlighting the need for further research in the region.
3p21.31 locus	Associated with COVID-19 severity.	Global (HGI data)	The study discovered the genetic association between variants in 3p21.31 and an increased risk of hospitalization following SARS-CoV-2 infection. While genome-wide association studies have pinpointed 3p21.31 as a key locus for severe COVID-19.	[78]	The findings linked genetic variants in 3p21.31 with an increased risk of hospitalization following SARS-CoV-2 infection, consistent with previous findings. However, research on this topic in ASEAN countries is still lacking, highlighting the need for further investigation in the region.
Loci on chromosomes 7 and 19	Linked to COVID-19 severity.	Global (HGI data)	High number of studies did not provide summary statistics for loci on chromosome 7, while for loci on chromosome 19 shows potential genetic variants linked to COVID-19 susceptibility or severity.	[53]	While chromosome 19 loci show promise in identifying genetic variants linked to COVID-19 susceptibility or severity, the lack of summary statistics for chromosome 7 limits our understanding of its potential role linked with COVID-19. Further research with complete datasets is necessary to draw more definitive conclusions about both chromosomes.

Genes/ Variants	Clinical Association	Country	Findings	Reference	Our Perspective
Rs190509934 variant	Reduced ACE2 expression, protecting against infection	United States of America (USA)	The findings indicate that the variant rs190509934 near ACE2 provides protection against SARS-CoV-2 infection and may also influence the severity of the disease in individuals who are infected with the virus. The study suggests a potential protective effect of the variant rs190509934 near ACE2.	[79]	The absence of similar studies in ASEAN countries highlights a gap in our understanding of how genetic variations impact COVID-19 in this region. Addressing this gap through dedicated research efforts in ASEAN countries could provide valuable insights into the role of genetic factors in COVID-19 susceptibility and severity, tailored to the unique genetic makeup of populations in this region.
ADAM17 (rs4622692 and rs1048610 variants)	Associated with moderate disease progression.	Vietnam	The frequencies of the TG genotype for rs4622692 and the TC genotype for rs1048610 of ADAM17 were notably higher in the moderate group compared to the severe/fatal group.	[10]	Dysregulated expression and/or activation of ADAM17 has been linked to a wide range of autoimmune and inflammatory diseases, cancer, and cardiovascular disease [80]. This Vietnamese study adds to this growing body of evidence by suggesting that specific ADAM17 genotypes (rs4622692 TG and rs1048610 TC) might be associated with a moderate disease course of COVID-19 compared to severe/fatal outcomes. Further research is crucial to validate these findings in more diverse populations and elucidate the underlying mechanisms by which ADAM17 variations influence COVID-19 severity. Additionally, investigating the potential of ADAM17 genotyping as a risk stratification tool in Vietnamese patients and exploring potential links between ADAM17 variations in COVID-19 and other diseases warrant further exploration.

Genes/ Variants	Clinical Association	Country	Findings	Reference	Our Perspective
Locus on chromosome 5q32- -IL17B gene	Associated with COVID-19 disease susceptibility.	Thailand	A region on chromosome 5q32 displayed a potential association with COVID-19 susceptibility (p-value 6.9×10^6; Q–Q plot $\lambda = 0.805$, odds ratio 0.02), meeting a significance threshold of p-value $<1 \times 10^5$.	[58]	This study highlights the importance of further investigation into the genetic factors influencing susceptibility to COVID-19, particularly in this region of chromosome 5q32. Interestingly, this region has also been linked to a susceptibility locus for psoriasis, specifically the arthritic phenotype of the disease [81]. Exploring the biological mechanisms underlying these potential associations in COVID-19 susceptibility and psoriasis pathogenesis could provide valuable insights into shared pathways and potentially inform preventive and therapeutic strategies for both diseases.
Locus on chromosome 12q22- -EEA1 gene and LOC643339, a long non-coding RNA	Involved in viral entry into cells.	Thailand	A genetic region on chromosome 12q22, housing EEA1 and LOC643339 genes, is associated with COVID-19 severity, with p-values ranging from 1.3×10^6 to 4.4×10^6 and odds ratios of 0.28–0.31. EEA1 aids viral cell entry, while LOC643339 is a long non-coding RNA. The study suggests that genetic loci on chromosomes 5q32 and 12q22 may impact COVID-19 susceptibility and severity, respectively.	[58]	Given that EEA1 facilitates viral cell entry and LOC643339 is a long non-coding RNA, these genes may contribute to the pathogenesis of COVID-19. This underscores the importance of further research into the genetic factors underlying COVID-19, particularly in understanding how specific genes and regions influence disease susceptibility and severity.
Suggestive locus 3p24.3	Associated with COVID-19 disease severity.	Thailand	At a significance threshold of p-value $<5 \times 10^5$, a locus on chromosome 3p24.3 (position 21141028–21235640) was linked	[58]	This study sheds light on chromosome 3p24.3 as a potential player in COVID-19 severity. Unraveling how genetic variations at this location influence disease progression could offer valuable insights into COVID-

Genes/ Variants	Clinical Association	Country	Findings	Reference	Our Perspective
			to COVID-19 severity, with p-values ranging from 5.0649×10^{7} to 2.5343×10^{6}.		19's underlying mechanisms. Interestingly, this same region has been implicated as a risk factor for colorectal cancer (CRC) in Swedish populations[82]. Further investigation is crucial to determine if the genetic variants linked to COVID-19 severity on chromosome 3p24.3 overlap with those associated with CRC susceptibility. Exploring the shared biological pathways potentially affected by this locus in both diseases could lead to a deeper understanding of their mechanisms and pave the way for novel therapeutic strategies.

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Conclusion, Future Directions and Challenges

As we continue to explore the genetic risks and COVID-19 outcomes in ASEAN countries, there are several crucial areas for future research. Comprehensive investigations should encompass various host genetic factors across all ASEAN nations, including countries lacking genetic risk information, such as Brunei, Cambodia, Laos, Malaysia, Myanmar, the Philippines, and Singapore. This broader approach will provide a more complete understanding of the genetic determinants of COVID-19 susceptibility and severity across diverse populations within the region.

Furthermore, we need to focus on large-scale research endeavors that can confirm the associations and identify subtle genetic influences. Moving beyond single genetic variant analyses and exploring potential interactions between multiple genes is essential, allowing for a more comprehensive understanding of the complex genetic landscape.

Additionally, considering the significant differences in COVID-19 outcomes across ASEAN countries, research should aim to uncover the underlying factors contributing to these variations, including socioeconomic disparities, cultural practices, and healthcare infrastructure. Understanding these factors will enable us to develop targeted interventions to mitigate the impact of COVID-19 in specific populations, as mentioned in Table 2.

Table 2. Comparison of Existing Knowledge and Key Contributions in this Manuscript to Understand the Genetic Factors in COVID-19.

Aspect	Existing Knowledge	Key Contribution
Genes Associated with COVID-19	ACE2, TMPRSS2	Identification of IFNAR2 and TYK2 as additional genes influencing COVID-19 outcomes in ASEAN countries.
Genetic Variants	Limited data on ASEAN populations	Highlighting specific genetic variants in Vietnam, Indonesia, and Thailand linked to COVID-19 susceptibility and severity.
Clinical Relevance	O blood type as a protective factor	Emphasizing the importance of understanding genetic polymorphisms for personalized risk assessment and therapeutic interventions.
Global Comparison	Genetic landscape in diverse populations	Providing insights into how genetic factors in ASEAN countries compare to worldwide trends in COVID-19 susceptibility and severity.

While progress has been made in understanding genetic risks in some ASEAN countries, comprehensive data remains scarce, and the existing studies have limitations. Small sample sizes and the absence of certain genetic information for specific countries highlight the ongoing nature of research efforts in the region. The challenge of proving causation in genetic studies is significant, as genetics interact with complex disease outcomes. Careful consideration of study design, rigorous statistical analysis, and replication of findings across diverse populations is essential to confirm the identified associations.

In conclusion, the ongoing research into genetic risks and COVID-19 outcomes in ASEAN countries is essential for informing public health strategies and interventions. While the current understanding is based on limited investigations, the insights gained from Vietnam, Indonesia, and Thailand studies provide valuable starting points. However, a more comprehensive approach is needed to fully elucidate the genetic factors contributing to COVID-19 susceptibility and severity in the diverse populations of the ASEAN region.

By addressing the challenges, expanding the scope of research, and leveraging the knowledge gained from existing studies, we can shed light on the complex interplay between genetics, epidemiology, and COVID-19 outcomes. Ultimately, this effort will contribute to a more comprehensive understanding of the disease's impact and empower public health initiatives to protect the populations of ASEAN countries better and beyond.

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Conflict of Interest
No conflict of interest among authors.

References

1. Singhal T. A Review of Coronavirus Disease-2019 (COVID-19). Indian J Pediatr. 2020 Apr 13;87(4):281–6.
2. Girum T, Lentiro K, Geremew M, Migora B, Shewamare S, Shimbre MS. Optimal strategies for COVID-19 prevention from global evidence achieved through social distancing, stay at home, travel restriction and lockdown: a systematic review. Arch Public Heal. 2021 Dec 21;79(1):150.
3. Han E, Tan MMJ, Turk E, Sridhar D, Leung GM, Shibuya K, et al. Lessons learnt from easing COVID-19 restrictions: an analysis of countries and regions in Asia Pacific and Europe. Lancet. 2020 Nov;396(10261):1525–34.
4. Uwishema O, Adanur I, Babatunde AO, Hasan MM, Elmahi OKO, Olajumoke KB, et al. Viral infections amidst COVID-19 in Africa: Implications and recommendations. J Med Virol. 2021 Dec 22;93(12):6798–802.
5. Haque A, Pant AB. Mitigating Covid-19 in the face of emerging virus variants, breakthrough infections and vaccine hesitancy. J Autoimmun. 2022 Feb;127:102792.
6. SeyedAlinaghi S, Mehrtak M, MohsseniPour M, Mirzapour P, Barzegary A, Habibi P, et al. Genetic susceptibility of COVID-19: a systematic review of current evidence. Eur J Med Res [Internet]. 2021 May 20;26(1):46. Available from: https://doi.org/10.1186/s40001-021-00516-8
7. Khade SM, Yabaji SM, Srivastava J. An update on COVID-19: SARS-CoV-2 life cycle, immunopathology, and BCG vaccination. Prep Biochem Biotechnol [Internet]. 2021 Aug 2;51(7):650–8. Available from: https://doi.org/10.1080/10826068.2020.1848869
8. Trougakos IP, Stamatelopoulos K, Terpos E, Tsitsilonis OE, Aivalioti E, Paraskevis D, et al. Insights to SARS-CoV-2 life cycle, pathophysiology, and rationalized treatments that target COVID-19 clinical complications. J Biomed Sci [Internet]. 2021 Dec 12;28(1):9. Available from: https://doi.org/10.1186/s12929-020-00703-5
9. Dieter C, de Almeida Brondani L, Lemos NE, Schaeffer AF, Zanotto C, Ramos DT, et al. Polymorphisms in ACE1, TMPRSS2, IFIH1, IFNAR2, and TYK2 Genes Are Associated with Worse Clinical Outcomes in COVID-19. Genes (Basel) [Internet]. 2022 Dec 22;14(1):29. Available from: https://www.mdpi.com/2073-4425/14/1/29
10. Nhung VP, Ton ND, Ngoc TTB, Thuong MTH, Hai NTT, Oanh KTP, et al. Host Genetic Risk Factors Associated with COVID-19 Susceptibility and Severity in Vietnamese. Genes (Basel) [Internet]. 2022 Oct 18;13(10):1884. Available from: https://www.mdpi.com/2073-4425/13/10/1884
11. Aghamirli SS, Saleh-Gohari N. ACE2, TMPRSS2, TYK2, SLC6A20, and IFNAR2 human genes variants influence SARS-CoV-2 infection susceptibility. 2023.

12. Velavan TP, Pallerla SR, Rüter J, Augustin Y, Kremsner PG, Krishna S, et al. Host genetic factors determining COVID-19 susceptibility and severity. eBioMedicine [Internet]. 2021 Oct;72:103629. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2352396421004229
13. Ramos-Lopez O, Daimiel L, Ramírez de Molina A, Martínez-Urbistondo D, Vargas JA, Martínez JA. Exploring Host Genetic Polymorphisms Involved in SARS-CoV Infection Outcomes: Implications for Personalized Medicine in COVID-19. Pinto PM, editor. Int J Genomics [Internet]. 2020 Oct 19;2020(December 2019):1–8. Available from: https://www.hindawi.com/journals/ijg/2020/6901217/
14. Dastar S, Gharesouran J, Mortazavi D, Hosseinzadeh H, Kian SJ, Taheri M, et al. COVID-19 pandemic: Insights into genetic susceptibility to SARS-CoV-2 and host genes implications on virus spread, disease severity and outcomes. Hum Antibodies. 2022 Feb 18;30(1):1–14.
15. ASEAN Secretariat. ASEAN Member States [Internet]. 2020. Available from: https://asean.org/member-states/
16. Adimulam T, Arumugam T, Gokul A, Ramsuran V. Genetic Variants within SARS-CoV-2 Human Receptor Genes May Contribute to Variable Disease Outcomes in Different Ethnicities. Int J Mol Sci. 2023 May 13;24(10):8711.
17. Supriya R, Singh KP, Gao Y, Li F, Dutheil F, Baker JS. A Multifactorial Approach for Sarcopenia Assessment: A Literature Review. Biology (Basel). 2021 Dec 20;10(12):1354.
18. Yap PSX, Tan TS, Chan YF, Tee KK, Kamarulzaman A, Teh CSJ. An Overview of the Genetic Variations of the SARS-CoV-2 Genomes Isolated in Southeast Asian Countries. J Microbiol Biotechnol. 2020 Jul 28;30(7):962–6.
19. Rampal S, Rampal L, Jayaraj VJ, Pramanick A, Choolani M, Liew BS, et al. The epidemiology of COVID-19 in ten Southeast Asian countries. Med J Malaysia [Internet]. 2021 Nov;76(6):783–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/34806661
20. WHO. WHO Coronavirus (COVID-19) Dashboard With Vaccination Data. [Internet]. 2023. Available from: https://covid19.who.int/
21. Ruksakulpiwat S, Zhou W, Chiaranai C, Saengchut P, Vonck JE. Age, Sex, Population Density and COVID-19 Pandemic in Thailand: A Nationwide Descriptive Correlational Study. J Heal Sci Med Res [Internet]. 2021 Sep 3;40(3):281–91. Available from: https://www.jhsmr.org/index.php/jhsmr/article/view/836
22. Marzo RR, Sami W, Alam MZ, Acharya S, Jermsittiparsert K, Songwathana K, et al. Hesitancy in COVID-19 vaccine uptake and its associated factors among the general adult population: a cross-sectional study in six Southeast Asian countries. Trop Med Health. 2022 Dec 5;50(1):4.
23. Dawood FS, Ricks P, Njie GJ, Daugherty M, Davis W, Fuller JA, et al. Observations of the global epidemiology of COVID-19 from the prepandemic period using web-based surveillance: a cross-sectional analysis. Lancet Infect Dis. 2020 Nov;20(11):1255–62.
24. Hoang VT, Pham TD, Nguyen QT, Nguyen DC, Nguyen DT, Nguyen TB, et al. Seroprevalence of SARS-CoV-2 among high-density communities and hyper-endemicity of COVID-19 in Vietnam. Trop Med Int Heal [Internet]. 2022 May 25;27(5):515–21. Available from: https://onlinelibrary.wiley.com/doi/10.1111/tmi.13744
25. Sujarwoto S, Maharani A. Sociodemographic characteristics and health access associated with COVID-19 infection and death: a cross-sectional study in Malang District, Indonesia. BMJ Open [Internet]. 2022 May;12(5):e052042. Available from: https://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2021-052042
26. Ong HB, Wasiuzzaman S, Chong LL, Choon SW. Digitalisation and financial inclusion of lower middle-income ASEAN. Heliyon. 2023 Feb;9(2):e13347.
27. Rahman S, Montero MTV, Rowe K, Kirton R, Kunik F. Epidemiology, pathogenesis, clinical presentations, diagnosis and treatment of COVID-19: a review of current evidence. Expert Rev Clin Pharmacol [Internet]. 2021 May 4;14(5):601–21. Available from: https://www.tandfonline.com/doi/full/10.1080/17512433.2021.1902303
28. Rampal L, Liew BS, Choolani M, Ganasegeran K, Pramanick A, Vallibhakara SA, et al. Battling COVID-19 pandemic waves in six South-East Asian countries: A real-time consensus review. Med J Malaysia [Internet]. 2020 Nov;75(6):613–25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/33219168

29. Edouard M, Hannah R, Lucas RG et al. Coronavirus (COVID-19) Deaths. Our World in Data. [Internet]. 2023. Available from: https://ourworldindata.org/explorers/coronavirus-data-explorer?zoomToSelection=true&facet=entity&country=MYS~IDN~SGP~LAO~VNM~KHM~PHL~MMR~THA~BRN&pickerSort=asc&pickerMetric=location&hideControls=false&Metric=Case+fatality+rate&Interval=7-day+rolling+avera
30. Jiang J (Xuefeng), Cram P, Qi K, Bai G. Challenges and dynamics of public health reporting and data exchange during COVID-19: insights from US hospitals. Heal Aff Sch [Internet]. 2024 Jan 3;2(1):qxad080. Available from: https://doi.org/10.1093/haschl/qxad080
31. Rotulo A, Kondilis E, Thwe T, Gautam S, Torcu Ö, Vera-Montoya M, et al. Mind the gap: Data availability, accessibility, transparency, and credibility during the COVID-19 pandemic, an international comparative appraisal. Robinson J, editor. PLOS Glob Public Heal [Internet]. 2023 Apr 21;3(4):e0001148. Available from: https://dx.plos.org/10.1371/journal.pgph.0001148
32. Alvarez E, Bielska IA, Hopkins S, Belal AA, Goldstein DM, Slick J, et al. Limitations of COVID-19 testing and case data for evidence-informed health policy and practice. Heal Res Policy Syst [Internet]. 2023 Jan 25;21(1):11. Available from: https://health-policy-systems.biomedcentral.com/articles/10.1186/s12961-023-00963-1
33. Filip R, Gheorghita Puscaselu R, Anchidin-Norocel L, Dimian M, Savage WK. Global Challenges to Public Health Care Systems during the COVID-19 Pandemic: A Review of Pandemic Measures and Problems. J Pers Med [Internet]. 2022 Aug 7;12(8):1295. Available from: https://www.mdpi.com/2075-4426/12/8/1295
34. Sai S, Wiwanitkit V. Uncommon Atypical Presentations of COVID-19: Important and Should Not be Under Recognized! J Heal Sci Med Res [Internet]. 2020 Mar 30;38(2):153. Available from: https://www.jhsmr.org/index.php/jhsmr/article/view/733
35. Baj J, Karakuła-Juchnowicz H, Teresiński G, Buszewicz G, Ciesielka M, Sitarz R, et al. COVID-19: Specific and Non-Specific Clinical Manifestations and Symptoms: The Current State of Knowledge. J Clin Med [Internet]. 2020 Jun 5;9(6):1753. Available from: https://www.mdpi.com/2077-0383/9/6/1753
36. Bhati D, Deogade MS, Kanyal D. Improving Patient Outcomes Through Effective Hospital Administration: A Comprehensive Review. Cureus [Internet]. 2023 Oct 26;15(10):e47731. Available from: https://www.cureus.com/articles/197936-improving-patient-outcomes-through-effective-hospital-administration-a-comprehensive-review
37. Badker R, Miller K, Pardee C, Oppenheim B, Stephenson N, Ash B, et al. Challenges in reported COVID-19 data: best practices and recommendations for future epidemics. BMJ Glob Heal [Internet]. 2021 May 6;6(5):e005542. Available from: https://gh.bmj.com/lookup/doi/10.1136/bmjgh-2021-005542
38. Adam A, Tsarsitalidou S. Data misreporting during the COVID19 crisis: The role of political institutions. Econ Lett [Internet]. 2022 Apr;213:110348. Available from: https://linkinghub.elsevier.com/retrieve/pii/S016517652200043X
39. Van Gordon MM, McCarthy KA, Proctor JL, Hagedorn BL. Evaluating COVID-19 reporting data in the context of testing strategies across 31 low- and middle-income countries. Int J Infect Dis [Internet]. 2021 Sep;110:341–52. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1201971221005993
40. Ibrahim NK. Epidemiologic surveillance for controlling Covid-19 pandemic: types, challenges and implications. J Infect Public Health [Internet]. 2020 Nov;13(11):1630–8. Available from: https://www.sciencedirect.com/science/article/pii/S1876034120306031
41. Romano SD, Blackstock AJ, Taylor E V., El Burai Felix S, Adjei S, Singleton CM, et al. Trends in Racial and Ethnic Disparities in COVID-19 Hospitalizations, by Region — United States, March–December 2020. MMWR Morb Mortal Wkly Rep [Internet]. 2021 Apr 16;70(15):560–5. Available from: http://www.cdc.gov/mmwr/volumes/70/wr/mm7015e2.htm?s_cid=mm7015e2_w
42. Abdul Rashid MR, Syed Mohamad SN, Tajjudin AIA, Roslan N, Jaffar A, Mohideen FBS, et al. COVID-19 Pandemic Fatigue and Its Sociodemographic, Mental Health Status, and Perceived Causes: A Cross-Sectional Study Nearing the Transition to an Endemic Phase in Malaysia. Int J Environ Res Public Health [Internet]. 2023 Mar 2;20(5):4476. Available from: https://www.mdpi.com/1660-4601/20/5/4476
43. Xin L, Wang L, Cao X, Tian Y, Yang Y, Wang K, et al. Prevalence and influencing factors of pandemic fatigue among Chinese public in Xi'an city during COVID-19 new normal: a cross-sectional study. Front

Public Heal [Internet]. 2022 Sep 12;10:971115. Available from: https://www.frontiersin.org/articles/10.3389/fpubh.2022.971115/full
44. Yan E, Ng HKL, Lai DWL, Lee VWP. Physical, psychological and pandemic fatigue in the fourth wave of COVID-19 outbreak in Hong Kong: population-based, cross-sectional study. BMJ Open [Internet]. 2022 Dec 15;12(12):e062609. Available from: http://bmjopen.bmj.com/content/12/12/e062609.abstract
45. Casanova JL, Abel L. The human genetic determinism of life-threatening infectious diseases: genetic heterogeneity and physiological homogeneity? Hum Genet. 2020 Jun 27;139(6–7):681–94.
46. Ranjan J, Ravindra A, Mishra B. Gender and genetic factors impacting COVID-19 severity. J Fam Med Prim Care [Internet]. 2021;10(11):3956. Available from: https://journals.lww.com/jfmpc/Fulltext/2021/11000/Gender_and_genetic_factors_impacting_COVID_19.4.aspx
47. Casanova JL, Su HC, Abel L, Aiuti A, Almuhsen S, Arias AA, et al. A Global Effort to Define the Human Genetics of Protective Immunity to SARS-CoV-2 Infection. Cell. 2020 Jun;181(6):1194–9.
48. Zhang SY, Zhang Q, Casanova JL, Su HC, Abel L, Bastard P, et al. Severe COVID-19 in the young and healthy: monogenic inborn errors of immunity? Nat Rev Immunol. 2020 Aug 18;20(8):455–6.
49. Notarangelo LD, Bacchetta R, Casanova JL, Su HC. Human inborn errors of immunity: An expanding universe. Sci Immunol. 2020 Jul;5(49).
50. Casanova JL, Abel L. Mechanisms of viral inflammation and disease in humans. Science (80-). 2021 Nov 26;374(6571):1080–6.
51. Zhang Q, Bastard P, Karbuz A, Gervais A, Tayoun AA, Aiuti A, et al. Human genetic and immunological determinants of critical COVID-19 pneumonia. Nature. 2022 Mar 24;603(7902):587–98.
52. Ishak A, Mehendale M, AlRawashdeh MM, Sestacovschi C, Sharath M, Pandav K, et al. The association of COVID-19 severity and susceptibility and genetic risk factors: A systematic review of the literature. Gene [Internet]. 2022 Aug;836:146674. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0378111922004930
53. Niemi MEK, Karjalainen J, Liao RG, Neale BM, Daly M, Ganna A, et al. Mapping the human genetic architecture of COVID-19. Nature. 2021;600(7889):472–7.
54. Pathak GA, Karjalainen J, Stevens C, Neale BM, Daly M, Ganna A, et al. A first update on mapping the human genetic architecture of COVID-19. Nature [Internet]. 2022 Aug 4;608(7921):E1–10. Available from: https://www.nature.com/articles/s41586-022-04826-7
55. Kousathanas A, Pairo-Castineira E, Rawlik K, Stuckey A, Odhams CA, Walker S, et al. Whole-genome sequencing reveals host factors underlying critical COVID-19. Nature. 2022 Jul 7;607(7917):97–103.
56. Zhang Q, Bastard P, Bolze A, Jouanguy E, Zhang SY, Cobat A, et al. Life-Threatening COVID-19: Defective Interferons Unleash Excessive Inflammation. Med [Internet]. 2020 Dec;1(1):14–20. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2666634020300295
57. Wulandari L, Hamidah B, Pakpahan C, Damayanti NS, Kurniati ND, Adiatmaja CO, et al. Initial study on TMPRSS2 p.Val160Met genetic variant in COVID-19 patients. Hum Genomics [Internet]. 2021 Dec 17;15(1):29. Available from: https://humgenomics.biomedcentral.com/articles/10.1186/s40246-021-00330-7
58. Chamnanphon M, Pongpanich M, Suttichet TB, Jantarabenjakul W, Torvorapanit P, Putcharoen O, et al. Host genetic factors of COVID-19 susceptibility and disease severity in a Thai population. J Hum Genet [Internet]. 2022 May 11;67(5):295–301. Available from: https://www.nature.com/articles/s10038-021-01009-6
59. Zipeto D, Palmeira J da F, Argañaraz GA, Argañaraz ER. ACE2/ADAM17/TMPRSS2 Interplay May Be the Main Risk Factor for COVID-19. Front Immunol [Internet]. 2020 Oct 7;11. Available from: https://www.frontiersin.org/article/10.3389/fimmu.2020.576745/full
60. Chen C, Wang J, Liu YM, Hu J. Single-cell analysis of adult human heart across healthy and cardiovascular disease patients reveals the cellular landscape underlying SARS-CoV-2 invasion of myocardial tissue through ACE2. J Transl Med [Internet]. 2023 May 31;21(1):358. Available from: https://translational-medicine.biomedcentral.com/articles/10.1186/s12967-023-04224-1
61. Vazquez SE, Mann SA, Bodansky A, Kung AF, Quandt Z, Ferré EMN, et al. Autoantibody discovery across monogenic, acquired, and COVID19-associated autoimmunity with scalable PhIP-Seq. bioRxiv Prepr Serv Biol [Internet]. 2022 Mar 24; Available from: http://www.ncbi.nlm.nih.gov/pubmed/35350199

62. Gómez J, Albaiceta GM, García-Clemente M, López-Larrea C, Amado-Rodríguez L, Lopez-Alonso I, et al. Angiotensin-converting enzymes (ACE, ACE2) gene variants and COVID-19 outcome. Gene [Internet]. 2020 Dec;762:145102. Available from: https://www.sciencedirect.com/science/article/pii/S037811192030771X
63. Pairo-Castineira E, Clohisey S, Klaric L, Bretherick AD, Rawlik K, Pasko D, et al. Genetic mechanisms of critical illness in COVID-19. Nature [Internet]. 2021 Mar 4;591(7848):92–8. Available from: https://www.nature.com/articles/s41586-020-03065-y
64. Andolfo I, Russo R, Lasorsa VA, Cantalupo S, Rosato BE, Bonfiglio F, et al. Common variants at 21q22.3 locus influence MX1 and TMPRSS2 gene expression and susceptibility to severe COVID-19. iScience [Internet]. 2021 Apr;24(4):102322. Available from: https://www.sciencedirect.com/science/article/pii/S258900422100290X
65. Banday AR, Stanifer ML, Florez-Vargas O, Onabajo OO, Papenberg BW, Zahoor MA, et al. Genetic regulation of OAS1 nonsense-mediated decay underlies association with COVID-19 hospitalization in patients of European and African ancestries. Nat Genet [Internet]. 2022 Aug 14;54(8):1103–16. Available from: https://www.nature.com/articles/s41588-022-01113-z
66. Cuesta-Llavona E, Gómez J, Albaiceta GM, Amado-Rodríguez L, García-Clemente M, Gutiérrez-Rodríguez J, et al. Variant-genetic and transcript-expression analysis showed a role for the chemokine-receptor CCR5 in COVID-19 severity. Int Immunopharmacol [Internet]. 2021 Sep;98:107825. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1567576921004616
67. Dai Y, Wang J, Jeong HH, Chen W, Jia P, Zhao Z. Association of CXCR6 with COVID-19 severity: delineating the host genetic factors in transcriptomic regulation. Hum Genet [Internet]. 2021 Sep 21;140(9):1313–28. Available from: https://link.springer.com/10.1007/s00439-021-02305-z
68. Cappadona C, Rimoldi V, Maria E, Asselta R. Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID- 19 . The COVID-19 resource centre is hosted on Elsevier Connect , the company ' s public news and information . 2020;(January).
69. Yang T, Li H, Thakur A, Chen T, Xue J, Li D, et al. FOXP4 modulates tumor growth and independently associates with miR-138 in non-small cell lung cancer cells. Tumor Biol [Internet]. 2015 Oct 21;36(10):8185–91. Available from: http://link.springer.com/10.1007/s13277-015-3498-8
70. D'Antonio M, Nguyen JP, Arthur TD, Matsui H, D'Antonio-Chronowska A, Frazer KA, et al. SARS-CoV-2 susceptibility and COVID-19 disease severity are associated with genetic variants affecting gene expression in a variety of tissues. Cell Rep [Internet]. 2021 Nov;37(7):110020. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2211124721015023
71. Zhang Y, Gao X, Bai X, Yao S, Chang YZ, Gao G. The emerging role of furin in neurodegenerative and neuropsychiatric diseases. Transl Neurodegener [Internet]. 2022 Aug 23;11(1):39. Available from: https://translationalneurodegeneration.biomedcentral.com/articles/10.1186/s40035-022-00313-1
72. Coto E, Albaiceta GM, Amado-Rodríguez L, García-Clemente M, Cuesta-Llavona E, Vázquez-Coto D, et al. FURIN gene variants (rs6224/rs4702) as potential markers of death and cardiovascular traits in severe COVID-19. J Med Virol [Internet]. 2022 Aug 12;94(8):3589–95. Available from: https://onlinelibrary.wiley.com/doi/10.1002/jmv.27748
73. Nguyen A, David JK, Maden SK, Wood MA, Weeder BR, Nellore A, et al. Human Leukocyte Antigen Susceptibility Map for Severe Acute Respiratory Syndrome Coronavirus 2. J Virol [Internet]. 2020 Jun 16;94(13):510–20. Available from: HLA
74. Ramos-Benitez MJ, Strich JR, Alehashemi S, Stein S, Rastegar A, de Jesus AA, et al. Antiviral innate immunity is diminished in the upper respiratory tract of severe COVID-19 patients. medRxiv Prepr Serv Heal Sci [Internet]. 2022 Nov 13; Available from: http://www.ncbi.nlm.nih.gov/pubmed/36415460
75. van Moorsel CHM, van der Vis JJ, Duckworth A, Scotton CJ, Benschop C, Ellinghaus D, et al. The MUC5B Promoter Polymorphism Associates With Severe COVID-19 in the European Population. Front Med [Internet]. 2021 Nov 23;8:668024. Available from: https://www.frontiersin.org/articles/10.3389/fmed.2021.668024/full
76. Dhangadamajhi G, Rout R. Association of TLR3 functional variant (rs3775291) with COVID-19 susceptibility and death: a population-scale study. Hum Cell [Internet]. 2021 May 22;34(3):1025–7. Available from: https://doi.org/10.1007/s13577-021-00510-6

77. Palacios Y, Ruiz A, Ramón-Luing LA, Ocaña-Guzman R, Barreto-Rodriguez O, Sánchez-Monciváis A, et al. Severe COVID-19 Patients Show an Increase in Soluble TNFR1 and ADAM17, with a Relationship to Mortality. Int J Mol Sci [Internet]. 2021 Aug 5;22(16):8423. Available from: https://www.mdpi.com/1422-0067/22/16/8423
78. Stikker B, Stik G, Hendriks RW, Stadhouders R. Severe COVID-19 associated variants linked to chemokine receptor gene control in monocytes and macrophages. bioRxiv Prepr Serv Biol [Internet]. 2021 Jun 11; Available from: http://www.ncbi.nlm.nih.gov/pubmed/33501435
79. Horowitz JE, Kosmicki JA, Damask A, Sharma D, Roberts GHL, Justice AE, et al. Genome-wide analysis provides genetic evidence that ACE2 influences COVID-19 risk and yields risk scores associated with severe disease. Nat Genet [Internet]. 2022 Apr 3;54(4):382–92. Available from: https://www.nature.com/articles/s41588-021-01006-7
80. Saad MI, Jenkins BJ. The protease <scp>ADAM17</scp> at the crossroads of disease: revisiting its significance in inflammation, cancer, and beyond. FEBS J [Internet]. 2024 Jan 11;291(1):10–24. Available from: https://febs.onlinelibrary.wiley.com/doi/10.1111/febs.16923
81. Friberg C, Björck K, Nilsson S, Inerot A, Wahlström J, Samuelsson L. Analysis of Chromosome 5q31–32 and Psoriasis: Confirmation of a Susceptibility Locus but no Association with SNPs within SLC22A4 and SLC22A5. J Invest Dermatol [Internet]. 2006 May;126(5):998–1002. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0022202X15328797
82. Liu W, Mahdessian H, Helgadottir H, Zhou X, Thutkawkorapin J, Jiao X, et al. Colorectal cancer risk susceptibility loci in a Swedish population. Mol Carcinog [Internet]. 2022 Mar 10;61(3):288–300. Available from: https://onlinelibrary.wiley.com/doi/10.1002/mc.23366