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Genetics and Pathogenic of (SARS-Covid-19) Coronavirus (Article Review)

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ABSTRACT

Background: *Coronaviruses are a group of enveloped viruses with non-segmented, single-stranded, and positive-sense RNA genomes. These viruses can infect various important vertebrates such as pigs and chickens, as well as humans, causing respiratory diseases. Among them, there are two highly pathogenic coronaviruses that have resulted in global outbreaks: the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV). The name "coronavirus" comes from the outer fringe, or "corona," of embedded envelope protein. The Coronaviridae family can cause a wide range of animal and human diseases. The RNA genome replication process is unique in that it generates a nested set of viral mRNA molecules. Human coronavirus (H-CoV) infection can cause respiratory diseases with varying degrees of severity. COVID-19 can cause a variety of symptoms that vary in severity. While many cases may not result in any symptoms or only mild ones, some patients may experience a more severe form of the disease that can lead to acute respiratory distress syndrome and other complications affecting multiple organs.*

Keywords: Human coronavirus, (SARS-CoV), Genetics and Pandamic COVID-19

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INTRODUCTIN

Coronaviruses are a large group of viruses that can cause illness in both animals and humans According to the World Health Organization (WHO,2020). While seven types of coronaviruses can infect people globally, the most common ones are 229E, NL63, OC43, and HKU1. These viruses usually lead to respiratory infections that can range from a common cold to more severe illnesses like Middle East Respiratory Syndrome (MERS) or Severe Acute Respiratory Syndrome (SARS). The most recent coronavirus, COVID-19, is also causing an infectious disease (WHO,2020; Huang, C. *et al*, 2020).

Common symptoms of this virus include fever, cough, sneezing, and shortness of breath. It can lead to complications such as pneumonia, throat pain, and acute respiratory distress syndrome. Currently, there is no specific antiviral treatment or vaccine available, so efforts focus on treating symptoms and providing supportive therapy (WHO, 2020). These viruses have caused several outbreaks globally, including the

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severe acute respiratory syndrome (SARS) pandemic of 2002-2003 and the Middle East respiratory syndrome (MERS) outbreak in South Korea in 2015. The recent outbreak of a novel coronavirus (SARS-CoV-2), also known as COVID-19, originated in China in December 2019 and has raised international concern. While some coronaviruses can cause severe epidemics, others cause mild to moderate respiratory infections similar to the common cold (WHO, 2020;. Zhou, F. *et al*,. 2020). Discovering genetic factors in hosts that affect infection susceptibility and disease severity is crucial. This knowledge deepens our understanding of viral infections, the pathophysiological changes caused by disease, and potential drug targets. It also reveals causal relationships between risk factors, biomarkers, and disease outcomes, which can inform prevention strategies. The identification of the CCR5Δ32 mutation for protection against HIV infection is a well-known example of a successful human genetic study of infectious diseases (Samson, M. *et al*,. 1996). Additionally, individuals who carry a sickle cell allele of the hemoglobin-β (HBB) gene and are heterozygous have protection against Plasmodium falciparum infection, which causes malaria disease. For a more comprehensive understanding of human genetic influences on infectious diseases, please refer to the review by (Kwok et al., 2021). When it comes to studying human genetics of infectious diseases, such as COVID-19, there are unique challenges to consider. These challenges include differences in exposure to the virus within a population, varying treatment of patients with severe disease during a pandemic emergency, and the implementation and uptake of vaccination programs. Despite these challenges, experts around the world have been able to conduct rapid, large-scale studies on the host genetics of COVID-19. In this review, we provide an overview of the current study designs that enable the discovery of human genetic variations associated with COVID-19. We focus on large-scale, population-based association studies, the genetic discoveries that have been made so far, and what we have learned in terms of biology and public health impact. Finally, we discuss some of the key challenges that the field faces during this pandemic and beyond.

Coronaviruses Types

Coronaviruses are part of the Coronavirinae subfamily in the Coronaviridae family. The severity of the disease and the extent of its spread differ depending on the type of human coronavirus. There are currently seven known types of coronavirus that can infect humans. (Shrikrushna *etal.*,2020).

- Common types

1. 229E (alpha coronavirus)
2. NL63 (alpha coronavirus)
3. OC43 (beta coronavirus)
4. HKU1 (beta coronavirus)

There are several strains of viruses that can cause respiratory illnesses, some of which are more rare and severe than others. Two of these strains are MERS-CoV, which causes Middle East respiratory syndrome (MERS), and SARS-CoV, which leads to severe acute respiratory syndrome (SARS). In 2019, a new and dangerous strain called SARS-CoV-2 emerged and began circulating, causing the disease COVID-19. This information is depicted in Figure 1 (Shrikrushna et al., 2020).

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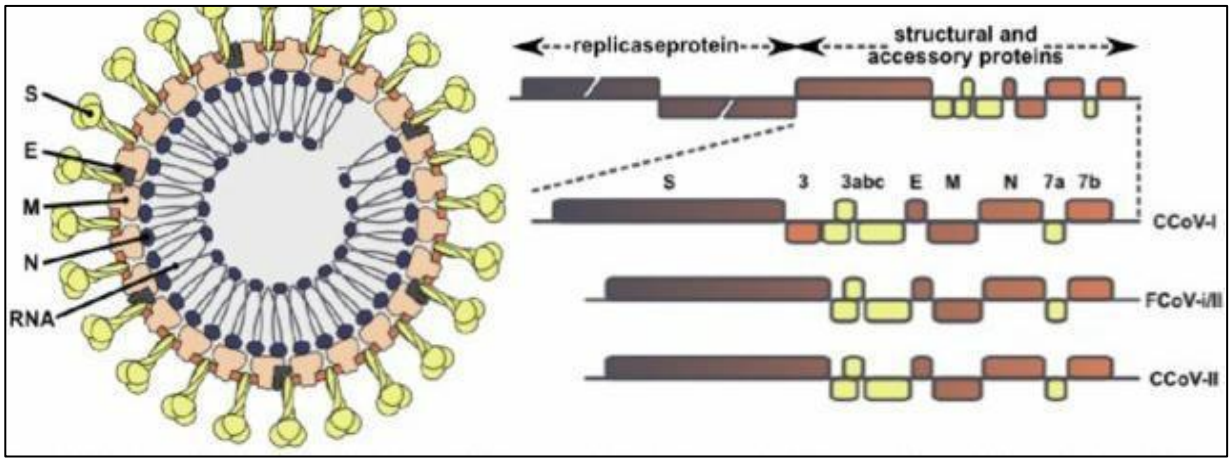

Figure.1: Coronavirus structure and comparison of C-CoV and F-CoV genome.

(Shrikrushna et al., 2020).

Researching COVID-19 host genetics study designs.

A variety of studies have contributed to investigations into host genetics for COVID-19 during the pandemic:

Clinical studies: are an important tool for gathering in-depth and relevant information about COVID-19 (Nakanishi, T. *et al.*2021; Pairo-Castineira, E. *et al.* 2021). Typically, these studies focus on patients with severe cases of the disease and collect phenotypic data. While most studies are relatively small, with only a few thousand patients, one of the largest studies, GenOMICC/ISARIC Pairo-Castineira, E. *et al.* 2021 was already studying genetics related to critical illness before the pandemic began. By leveraging existing frameworks and resources, researchers were able to quickly adapt their studies to study COVID-19. To understand the genetic factors that contribute to disease severity, clinical studies often rely on whole-exome sequencing (WES) and/or whole-genome sequencing (WGS) data analysis, while also collecting appropriate controls. These studies are an important way to investigate how genetic factors may affect a patient's clinical outcomes after infection.

Biobank and cohort studies: One way to study COVID-19 is by utilizing existing biobank and cohort studies. These studies can provide a large enough sample size and sufficient infection rate within the population. Typically, COVID-19-positive cases are identified through electronic health records or questionnaires while individuals who are not positive or tested negative are used as controls. Although these studies may not fully represent the general population, they can provide a more representative sample of

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COVID-19 patients than clinical studies. Some established epidemiological cohorts have even been extensively recontacted to collect longitudinal information about COVID-19 symptoms (Mc Intyre, K. *et al*,. 2021). Most studies, for example, the UK Biobank and DiscovEHR collaboration, utilize genotyping microarrays which are not ideal for analyzing variants with a population frequency below 0.1%. (Kosmicki, J. A. et al., 2021).

Genetic companies: Several direct-to-consumer genetic companies have been actively involved in COVID-19 research. Two of the leading companies in this field, 23andMe and AncestryDNA, have developed surveys that allow for the collection of detailed self-reported information (Shelton, J. F. *et al*, 2022). With a large customer base, these companies have been able to identify new genetic variants associated with various COVID-19 symptoms, including vaccination side effects. However, it should be noted that these studies rely on self-reported COVID-19 positive status, which may not accurately represent severe cases. Nonetheless, PCR test results and hospitalization related to COVID-19 are presumed to be reliably self-reported(Bolze, A. *et al.*, 2022).

COVID-19 Phenotypes: The majority of host genetic studies regarding COVID-19 have concentrated on identifying genetic variations in the genome that are linked to susceptibility to infection, severity of disease, and symptoms associated with the illness.

Symptoms related to diseases: Symptoms related to diseases have been the focus of genetic studies. Some studies have concentrated on a single symptom, such as loss of taste and smell, while others have focused on a combination of symptoms that can help identify undiagnosed COVID-19 cases (Shelton, J. F. *et al*, 2022). These study designs were especially useful when testing for the virus was not widely available, which was the case at the beginning of the pandemic (Van Blokland, I. V. *et al*,.2020).

Discovering Genetic Associations

Studies on genetic associations can reveal specific regions of the genome that are related to susceptibility to disease and infection. However, such research can be affected by various biases during sample collection, data generation, and processing. Additionally, further analysis and functional follow-up are necessary to identify the precise variants and genes that impact the observed phenotypes. In this article, we will explore the latest findings from the most comprehensive genetic studies on SARS-CoV-2 infection and COVID-19 disease. We have compiled the most reliable and understandable associations in[Table 1], along with our confidence in the presumed causal gene.

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Table 1 | Genetic loci associated with SARS-CoV-2 infection susceptibility and COVID- -19 severity, including the putative causal genes.

Chr.	Position[a]	Genes in linkage disequilibrium	Suspected causal genes	Phenotype	Confidence for suspected gene[b]
1	155127096	*THBS3, EFNA1, SLC50A1, DPM3, KRTCAP2, TRIM46, MUC1, THBS3, MTX1, GBA, FAM189B, SCAMP3, CLK2, HCN3, PKLR, FDPS, RUSC1, ASH1L, MSTO1*	*MUC1*	Disease severity	++
3	45796521	*SLC6A20*	*SLC6A20*	Susceptibility to infection	++
3	45823240	*LZTFL1, CXCR6, CCR9, XCR1*	*LZTFL1*	Disease severity	++
3	101780431	*NFKBIZ, ZBTB11, RPL24, CEP97, NXPE3*	*NXPE3*	Susceptibility to infection	+
6	33076153	HLA region	*HLA-G, HLA-DRB1, HLA-DQA1*	Disease severity	+
6	41534945	*FOXP4*	*FOXP4*	Disease severity	++
9	133274084	*ABO*	*ABO*	Susceptibility to infection	+++
10	79946568	*SFTPD*	*SFTPD*	Disease severity	++
11	1219991	*MUC5B*	*MUC5B*	Disease severity	++
11	34507219	*ELF5*	*ELF5*	Disease severity	++
12	112919388	*OAS1, OAS3, OAS2*	*OAS1*	Disease severity	+++
12	132564254	*FBRLS1*	*FBRLS1*	Disease severity	+
19	4719431	*DPP9*	*DPP9*	Disease severity	++
19	10317045	*ICAM1, ICAM4, ICAM5, ZGLP1, FDX2, RAVER1, ICAM3, TYK2*	*TYK2*	Disease severity	+++
21	33242905	*IFNAR2, IL10RB, IFNAR1*	*IFNAR2*	Disease severity	++
X	12867072–12890361	*TLR7*	*TLR7*	Disease severity	+++
X	15602217	*ACE2*	*ACE2*	Susceptibility to infection	+++

Loci reported in this table were discovered or replicated using genome-wide genetic approaches, and relevant studies are listed. Owing to the extensive heterogeneity of study designs and ascertainment of cases and controls we are not able to provide an accurate numerical estimate of the risk associated with each locus. aPosition based on the Genome Reference Consortium Human Build 38 (GRCh38) version of the human reference genome. bConfidence for suspected genes is subjectively rated by the authors and includes current evidence from cross-functional work in addition to the genetic studies listed here. Chr., chromosome; COVID-19, coronavirus disease 2019; HGI, COVID-19 Host Genetics Initiative; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WES, whole-exome sequencing; WGS,whole-genome sequencing (Niemi,*M.E.K etal.*, 2022).

The studies mentioned above have focused on candidate genes rather than using a hypothesis-free genomewide approach, which requires a larger sample size and a more stringent significance threshold. As a result, the results need to be carefully scrutinized and replicated. The only gene with an association reaching exome-wide significance is TLR7, according to unpublished work by the COVID-19 HGI WES/WGS working group, which now includes up to 23,000 cases and 500,000 controls (G. Butler-Laporte, personal

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communication). A smaller study of 7,491 critically ill patients and 48,400 controls did not identify any significant rare variant associations(Kousathanas, *A. et al*., 2022). Two other studies have also failed to replicate the rare variant associations with the 13 immune genes reported by Zhang *et al*.,(2020) despite substantially larger sample sizes. These differences may be due to different definitions of COVID-19 severity, age distribution, and in silico versus experimental validation of non-synonymous variants (Zhang, Q. *et al*., 2021; Povysil, G. *et al*., 2021). The power of rare variant discovery in COVID-19 will be improved by increased sample sizes of WES and WGS data sets, which in time may provide definitively conclusive associations. In summary, TLR7 is currently the only gene uniformly replicated for association of rare non-synonymous variants with severe COVID-19, although it is expected that more findings will be confirmed as studies increase in power.

The immune system's regulation is managed by the human leukocyte antigen (HLA) system. In the largest GWAS of common infections, HLA has been implicated in several of them (Tian, C. *et al*.,2017). This led researchers to believe that HLA would play a significant role in explaining the variability of COVID-19 severity and infection susceptibility. However, it is not the strongest signal in GWAS. Nevertheless, GenOMICC/ISARIC28 and COVID-19 HGI51 have now detected associations for HLA class II. Smaller targeted studies have also found that HLA class I genotypes are implicated when HLA genotypes are imputed to gain better resolution of the region (Douillard, V. *et al*.,2021). Definitive large-scale studies are still required that account for the complexity in linkage disequilibrium (LD) and ancestry differences in the region. Therefore, the lack of HLA associations in some GWAS of COVID-19 severity might be due to limitations of study designs rather than a lack of biological association. Much-needed activity can be facilitated with the recent availability of multi-ancestry HLA imputation panels and integration with imputation servers (Luo, Y. *et al*.,2021).

Transmission, **Symptoms and life cycle of Coronavirus**

The transmission of coronavirus occurs through fluids in the respiratory system, such as mucus. The transmission can occur in several ways, including coughing and sneezing without covering the mouth, which can disperse droplets into the air. Also, touching or shaking hands with a person who has the virus can pass the virus between individuals. Additionally, making contact with a surface or object that has the virus and then touching the nose, eyes, or mouth can also lead to transmission.

While some animal coronaviruses, such as feline coronavirus (FCoV), may spread through contact with feces, it is unclear

whether this also applies to human coronaviruses. According to the National Institutes of Health (NIH), several groups of people have the highest risk of developing complications due to COVID-19 (WHO,2020; Shrikrushna *et al*., 2020). These groups include:

1. Young children
2. People aged 65 years or older
3. Women who are pregnant

IN 2019 COVID-19, The Centers for Disease Control and Prevention (CDC) began monitoring the outbreak of COVID-19, a respiratory illness caused by a new coronavirus called SARS-CoV-2. The virus was first identified in Wuhan, China, and can result in varying symptoms from person to person. While some individuals may experience no symptoms, others can become severely ill and even die. Common symptoms include fever, breathlessness, and coughing, and it may take anywhere from 2 to 14 days for symptoms to appear after infection (Shrikrushna *et al*., 2020).

Symptoms resembling those of a cold or flu typically appear 2-4 days after someone contracts the coronavirus. These symptoms are usually not severe, but they can differ from person to person. It's important to note that certain strains of the virus can potentially be fatal. Symptoms include(Sneezing, Runny nose, Cough, Watery diarrhea, Fever in rare cases, Sore Throat and Exacerbated asthma). It is difficult for scientists to cultivate human coronaviruses in a lab, unlike the rhinovirus which is known to cause common colds. The replication process of coronaviruses is depicted in [figure,3] as demonstrated by (Abdul Hafeez *et al*., 2020).

Corona virus life cycle Steps auch as Attachment and entry, Replicas protein expression, Replication and transcription and Assembly and release as mentioned in [figure,1] (Abdul Hafeez*etal*.,2020).

Respiratory infections are prevalent human diseases that can vary from mild colds to severe lower respiratory tract infections like bronchitis and pneumonia. Coronaviruses, which are easily transmitted through respiratory droplets in the air and on surfaces, cause many respiratory infections. The current global pandemic is caused by the novel strain COVID-19. In some cases, moderate upper respiratory infections can progress into serious lower respiratory infections within a few weeks. Patients who initially experience a mild cough may eventually require ventilator support to breathe due to respiratory failure [figure, 2] as demonstrated by (Sonja Bartolome, M, 2020).

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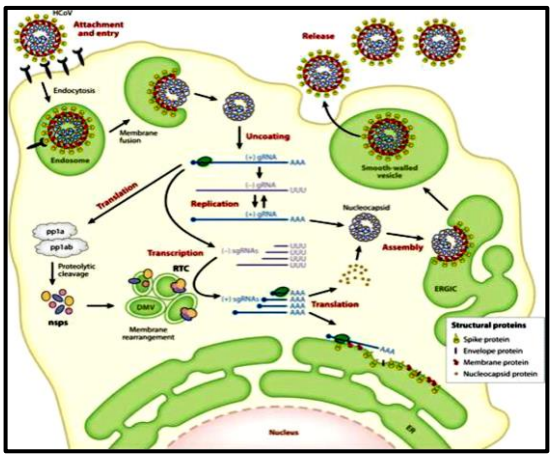

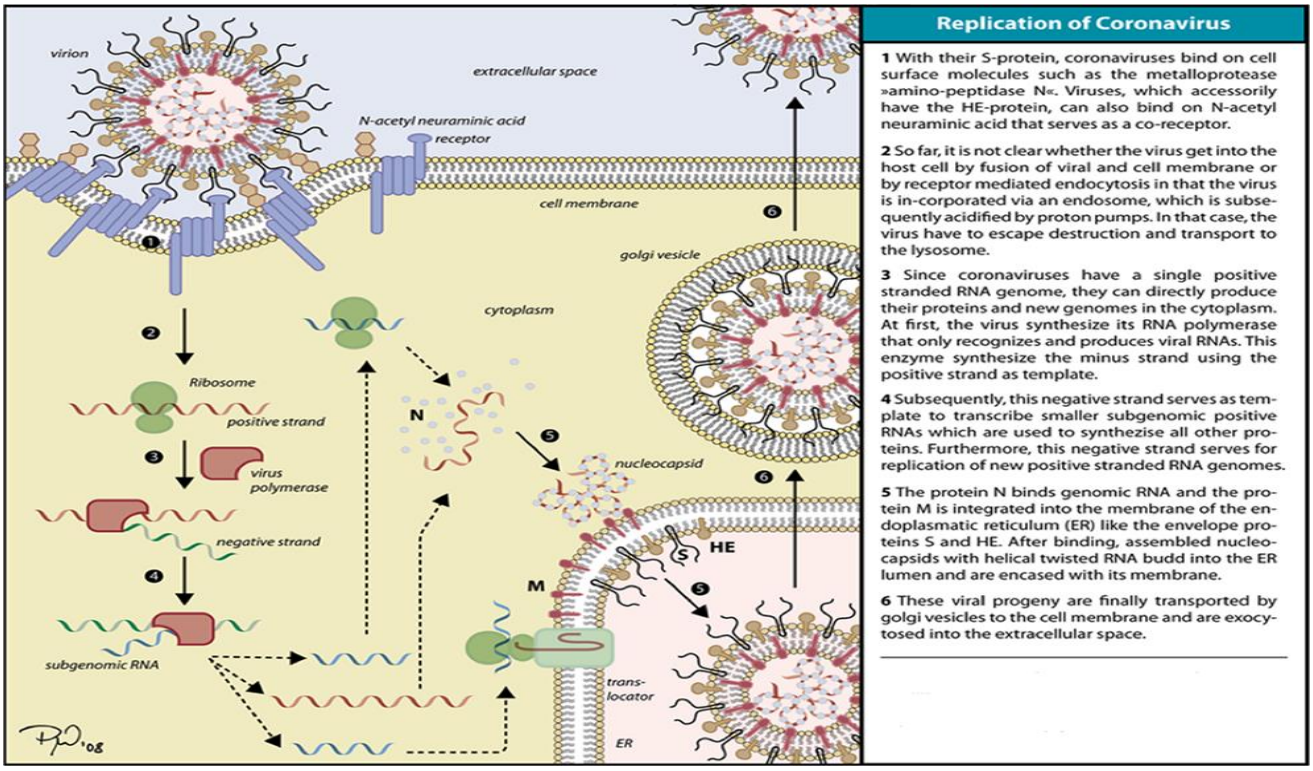

Figure 1: Life cycle of Corona virus (Abdul Hafeez *et al.,* 2020)

Figure 2: Respiratory infections like COVID-19 typically originate in the upper respiratory tract and can progress to the lower respiratory tract in severe cases (Sonja Bartolome, M, 2020).

Figure 3: Replication process Coronaviruses (Abdul Hafeez *et al.*, 2020).

Epidemiology of COVID-19

In December of 2019, a number of pneumonia cases were reported in Wuhan city, with Huanan Seafood Market being identified as the likely source. The first case of the COVID-19 epidemic was discovered on December 12th, 2019, with 27 cases of viral pneumonia (7 of which were severe)

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being officially announced on December 31st of that same year. Investigations into the cause of the illness have indicated that it was likely transmitted from animals to humans. On January 22nd, 2020, it was declared that the novel CoV originated from wild bats and belongs to Group 2 of beta-coronavirus, which also includes Severe Acute Respiratory Syndrome Associated Coronavirus (SARS-CoV), (Shrikrushna *et al.* 2020). The disease, which originated in China, quickly spread and the number of cases increased rapidly. On January 11, the first case was reported in Thailand, outside of mainland China. Within a few months, the disease had spread to all continents except for Antarctica. India reported its first case of COVID-19 on January 30, 2020, which increased to three cases by February 3, 2020. No additional cases were reported in February 2020. However, starting in mid-March, the number of infected cases began to rise, and cases were reported from all over India. The first COVID-19 related death in India was reported on March 12, 2020. By the second week of April, the disease had spread to all states in India except for Sikkim. As of writing this, there have been 2,170,265 cases and 135,163 deaths globally, and 15,712 cases and 507 deaths in India (WHO,2020). A study of viral dynamics in mild and severe cases has shown that mild cases tend to clear the virus quickly while severe cases can have a longer period of viral shedding(Liu Y, *et al.*, 2020). Studies using both respiratory and fecal samples have found that the virus can persist in stools for over four weeks even when respiratory samples are negative. Wu et al,, (2020) found that being male, delaying hospitalization after becoming ill, and requiring invasive mechanical ventilation were all factors that increased the likelihood of prolonged viral shedding (Wei W E, et al., 2020). Additionally, transmission during the asymptomatic phase has been reported. A study conducted in Singapore found that 6.4% of the 157 locally acquired cases of COVID-19 were caused by transmission during this phase.

Risk Factors Associated with Adverse Outcome:

Although the illness can strike any age group, serious illness is more likely in the elderly and those with comorbidities. The rates of hospitalization, ICU use, and mortality are higher among older persons, according to data from China and the United States(Wu and McGoogan,2019 ; CDC, 2019). Comorbidities include cancer, chronic lung disease, diabetes mellitus, cardiovascular disease, and hypertension have been linked to unfavorable outcomes, according to the Chinese Center for Disease Control and Prevention (Wu and McGoogan,2019).To identify risk factors that are causal, use genetic methods. Genetic analysis can be used to find risk factors and biomarkers associated with COVID-19. causal relationships between current and potential dangers factors (Burgess, S. *et al*., 2018; Van Rheenen, W. *et*

al., 2019). For instance, extensive genetic investigations can demonstrate the genetic impact of COVID-19 and among others. Genes are frequently employed in this.Genetic correlations' main advantage is correlations (Van Rheenen, W. *et al.,* 2019). Unlike phenotypic connections, Neither COVID-19 phenotypes nor risk factors call for to be assessed on the same population. Genetic susceptibility and SARS-CoV-2 infection links, or more serious illness has mostly mirrored the acknowledged linkages between clinical (phenotypic) severe COVID-19 (such as an increase in body weight body mass, diabetes, ischemia, smoking, and achievement in school(Pairo-Castineira, E. *et al,* 2021).

Prevention and Diagnose 2019-nCoV

Diagnoses are crucial in areas where there is a serious CoV outbreak going on, like the Middle East right now, where MERS-CoV is still spreading. The creation of public health strategies to contain outbreaks will be guided by the case identification process. The diagnosis of severe veterinary CoV-19 cases is very crucial. Since multiplex real-time RT-PCR assays have been created, are capable of detecting all four respiratory HCoVs, and might be further modified to detect additional CoVs, they have become the method of choice for diagnosis of human CoV. Serologic assays are crucial for epidemiological investigations and situations where RNA may be difficult to isolate or is no longer present. Molecular tests to Diagnose 2019-nCoV, a number of tests that both internally and externally detect the 2019-nCoV (e.g. SARS-CoV) that are genetically similar (WHO,2019). A polygenic score, also known as a polygenic risk score, is a way to measure an individual's genetic risk for a particular trait or disease based on their genotypes at multiple loci from GWAS. This score is typically constructed using variants in loci that are statistically significant in association with the trait, as well as variants across loci that did not reach genome-wide statistical significance (Chatterjee, N. *et al.,* 2016; Torkamani, A. *et al*., 2018). At a population level, the polygenic score can be used alone or in combination with other risk factors to estimate an individual's risk. While some studies have attempted to calculate polygenic scores for COVID-19, these have generally been underpowered, with most of the variation in the phenotype explained by a few highly significant signals, such as (Kosmicki, J. A. *et al* ., 2021).

As we continue to learn more about COVID-19, genetic studies may expand their focus to investigate specific symptoms associated with the infection or severe comorbid conditions. Some individuals who have contracted COVID-19 may experience long-term symptoms that can be a significant health burden in the years to come. The symptoms experienced by those affected by post (long) COVID-19 can vary greatly (Menges, D. *et*

al., 2021). Human genetics research can be helpful in this context, as some post-COVID-19 symptoms have been studied by GWAS. For example, researchers may test the hypothesis that COVID-19 accelerates existing genetic predispositions to some of the symptoms. Observational epidemiological analysis, along with MR, can be used as additional pillars to triangulate evidence of a causal relationship between COVID-19 and downstream consequences (Ayoubkhani, D. *et al*., 2021).

The relationship between host genomes and viral genomes is not fully understood due to a lack of research in both scientific communities and studies that collect information on both types of genomes at a large scale (Callaway, E. 2020; Jones, J. *et al*., 2021). A recent report revealed that the sickle cell allele of host HBB does not provide protection against severe malaria when certain alleles are present in the parasite's genome, which is often found in African strains (Band, G. *et al*., 2022). This highlights the importance of analyzing host-pathogen interactions to understand disease epidemiology and selective pressures. Variability in symptoms and disease severity has also been observed in SARS-CoV-2 strains, but it is unclear if the underlying host genetic factors are the same. One initial study combined viral and human genetic data but did not yield significant results. To overcome the lack of large samples, targeted studies could focus on genome-wide significant loci or PSs.

It is important to continue investigating the role of host genetics in severe COVID-19 and susceptibility to SARS-CoV-2 viral infection. This can help us discover new therapeutic options for the disease, such as drug repurposing or new drug development. Combining these findings with multi-omics results can provide valuable biological insights. Genetic risk prediction can also aid in identifying patients who may develop severe symptoms, which can be beneficial in a hospital setting. While host genetics is not the only factor in treating COVID-19, collaboration between academic, industry, healthcare providers, and policy-makers through open science can lead to significant progress in finding effective treatments.

Antiviral Drugs and RNA Vaccines

A group of antiviral drugs, including interferon α (IFN-α), lopinavir/ritonavir, chloroquine phosphate, ribavirin, and arbidol, have been deemed therapeutically useful for the prevention, diagnosis, and treatment of Novel Coronavirus-induced Pneumonia by the National Health Commission (NHC) of the People's Republic of China for tentative treatment of COVID-19. Vaccines made of messenger RNA are a promising alternative because they prompt host cells to produce many copies of the proteins they encode, leading to a stronger immune response than proteins delivered alone. Messenger RNA can

encode viral antigens, but the simplest means of delivering these antigens to a specific body part must be found to ensure they generate an immune response and promote appropriate immune stimulation for a robust response. RNA vaccines can also swiftly target different viral proteins, as long as the sequence encoding the protein is understood. The main challenge in developing these vaccines is finding effective and safe delivery methods to the site of action (Bolze *et al*.,2022)**.** The rollout of COVID-19 vaccines presents both challenges and opportunities for studying the genetic epidemiology of the disease. The various vaccination strategies employed by different countries can alter the demographics of those affected by the virus, potentially complicating genetic discoveries. However, vaccination also allows for the examination of potential side effects and breakthrough infections. A study by Bolze et al.(2022) found that individuals with the HLA-A✳ 03:01 allele may experience more severe difficulties with daily routines after vaccination. For more severe and rare side effects, international collaboration will be necessary to obtain reliable and reproducible findings.

CONCLUSION

In conclusion, this review highlights the ongoing evolution of COVID-19's disease profile. Despite progress, numerous questions remain unanswered. The impact of COVID-19 on society is significant, with proper medication, sanitation, and social distancing being crucial steps towards mitigating its effects.

RECOMMENDATIONS

Based on previous research, investing in the study of how coronaviruses cause disease and the body's immune response can greatly enhance our ability to create effective vaccines and decrease the impact of the disease.

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