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A MINI-EDITORIAL VIEW ON THE LATEST DEVELOPMENTS REGARDING THE GENETICS OF COVID-19

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Abstract. COVID-19, caused by SARS-CoV-2, has led to a global health crisis with devastating consequences. The disease exhibits diverse clinical manifestations, affecting multiple organs and systems. Understanding the genetic basis of SARS-CoV-2 and host susceptibility is crucial for developing effective treatments. Key genes like ACE2 and TMPRSS2 offer potential targets for therapeutic intervention. Further research into viral and host genetics is essential for devising personalized approaches to disease management and prevention.

Keywords: COVID-19, SARS-COV-2, GENES, GENETICS

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THE CURRENT STATE OF KNOWLEDGE REGARDING COVID-19

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes COVID-19, an infectious disease highly contagious, with devastating effects worldwide., claiming over 6 million lives. It represents one of the most significant global health crises since the influenza pandemic of 1918. With the virus continuously mutating, treatment protocols evolve to incorporate the most effective therapies **[1].**

First discovered in late December 2019 in Wuhan, China and later declared an outbreak pandemic by The World Health Organization (WHO) on March 2020, it was reported that as of April 1, a total of 127,877,462 were confirmed COVID-19 cases and 2,796,561 deaths. Apart from severe pneumonia, the SARS-CoV-2 virus can affect multiple organs and lead to physical symptoms, along with causing psychological harm **[2, 3].**

CLINICAL MANIFESTATIONS

People of all ages can catch this infection, but those aged 60 and above, as well as individuals with certain underlying health conditions (such as obesity, heart disease, kidney disease, diabetes, chronic lung issues, smoking, cancer, or those who have had organ or stem cell transplants), are more likely to develop severe COVID-19 illness **[1].**

The typical symptoms the infection with SARS-CoV-2 include fever in 83%-98% of the cases, fatigue in 25%-44%, cough in 50%-82%, shortness of breath in 19%-55%, and muscle soreness in 11%-44%. Some individuals may also exhibit symptoms like sputum production, chest tightness, runny nose, nausea, headache, vomiting, sore throat, diarrhea, loss of taste and loss of smell, only a few days before fever onset. This indicates that while fever is a significant early symptom, it may not always be the first one. Furthermore, some patients might only experience mild symptoms, such as slight fever, mild fatigue, or even no symptoms at all **[4].**

While respiratory symptoms are common among COVID-19 patients, SARS-CoV-2 can also cause various extrapulmonary manifestations, such as neurologic deficits, cardiac injury, acute coronary syndromes, arrhythmia, gastrointestinal (GI) symptoms, acute renal injury, hyperglycemia, impaired liver function, diabetic ketosis and dermatologic issues **[4].**

NEUROLOGIC MANIFESTATIONS

Neurologic symptoms, ranging from mild to severe, have been observed in COVID-19 patients, affecting approximately 36% of severe cases. Symptoms include headache, dizziness, anosmia, anorexia, ageusia and fatigue. It is important to mention more severe manifestations such as confusion, acute stroke, meningoencephalitis, Guillain-Barré syndrome and acute necrotizing encephalopathy affecting regions such as the brainstem and basal ganglia **[4].**

CARDIOVASCULAR MANIFESTATIONS

Causing not only direct but also indirect cardiovascular injury, patients that experiment COVID-19 are prone to acute coronary syndrome, myocardial injury, cardiomyopathy, cardiac arrhythmias, and thromboembolic complications. Approximately 20% to 30% of hospitalized patients experience myocardial injury, with higher troponin levels associated with worse outcomes. Cardiac arrhythmias are also prevalent among hospitalized COVID-19 patients, affecting up to 44% of cases **[4].**

RENAL AND GASTROINTESTINAL MANIFESTATIONS

Acute kidney injury occurs in a significant percentage of COVID-19 patients, ranging from 0.5% to 37%, with higher rates observed in critically ill patients. Gastrointestinal symptoms may include nausea or vomiting, diarrhea, anorexia and

abdominal pain, are reported in 12% to 61% of cases, with associated risks of prolonged illness and increased COVID-19 identification **[4].**

ENDOCRINOLOGIC AND DERMATOLOGIC MANIFESTATIONS

Endocrinologic abnormalities, such as hyperglycemia and diabetic ketoacidosis, affect around 6.4% of hospitalized patients.

Dermatologic manifestations, including rashes and lesions, are observed in around 20% of hospitalized patients, with acro-cutaneous lesions being the most common **[4].**

GENETICS OF SARS-COV-2 AND VARIATIONS

Being similar to additional coronaviruses and also placed among the largest known RNA genome, the SARS-CoV-2 not only possesses a single-stranded genomic RNA with a positive-sense orientation, but also contains the inclusion of a 5′-cap and a 3′-poly(A) tail enables the genomic RNA (gRNA) of SARS-CoV-2 to function as messenger RNA (mRNA), serving for the prompt translation of viral polyproteins. The genomic RNA (gRNA) of the virus has important structured untranslated regions (UTRs) at its 5′- and 3′- ends. These UTRs play a crucial role in regulating RNA replication and transcription. The structures that are significant for viral functions, having overlapping sequences are the 5′-UTR, that consists of seven stem-loop structures, and the 3′-UTR that contains a pseudoknot and a stem-loop. It is suggested that the alternative formation of either structure plays a role in transcriptional regulation. The open reading frames (ORFs), each preceded by transcriptional regulatory sequences (TRSs) are included in the SARS-CoV-2 genome. ORF1a and ORF1ab encode replicase polyproteins 1a (PP1a) and polyprotein 1ab (PP1ab), respectively, being the primary transcriptional units. The largest polyprotein is PP1ab and it contains non-structural proteins (Nsp1-16), key factors in the generation of the replicase machinery complex. In other families of positive-stranded RNA viruses, this complex does not houses enzyme activities. The envelope, membrane, spike, and nucleocapsid are four crucial structural proteins being encoded by the viral genome's 3′ end. These are vital for maintaining the virus's structural integrity. The viral entry into the host is promoted by the spike protein. The 3′ end of the genome carries nine putative ORFs for accessory factors, alongside the structural genes. Both structural and accessory proteins are synthesized from nested sub-genomic RNAs, all culminating with the 3′-end of the full-length gRNA. The TRSs are regulating the production of these sub-genomic RNAs, stemming from negative-sense RNA intermediates. The viral RNA polymerase pauses at each TRS sequence during minus-strand RNA synthesis. The continuation of synthesis through the TRS into the nearby gene or the termination of transcription with the generation of a sgRNA can be resulted by this pause. The exact molecular mechanisms determining either outcome is yet to be fully elucidated **[5]**.

A globally predominant D614G variant emerged, linked to heightened transmissibility but lacking severe illness-causing capability. In Denmark, another variant, originating from infected farmed mink was identified but did not exhibit heightened transmissibility. Due to their potential for increased transmissibility or virulence, numerous SARS-CoV-2 variants have been documented, some classified as variants of concern **[1]**.

Variations in SARS-CoV-2 arise primarily due to recombination events, facilitating cross-species transmission. Despite a high mutation rate, the virus maintains relatively low mutation levels (10^-10) compared to other viruses, thanks to its proofreading mechanism. The viral genome was sequenced early in 2020, suggesting a likely origin from bats, particularly Rhinolophus affinis, which serves as the natural reservoir. Through spontaneous mutations and recombination events, the virus gained pathogenicity and successfully crossed into humans, leading to subsequent human-to-human transmission. While the exact transmission vector remains unknown, animals sold at the Huanan market in Wuhan, such as Pangolins (Manis javanica), were initially suspected. However, Pangolins were later excluded as potential intermediaries since the virus is harmful to them. SARS-CoV-2 shares 96% homology with the bat virus RaTG13 but less with the Pangolin virus **[6]**.

The majority of genetic studies on COVID-19 in hosts have concentrated on detecting genomic variations linked to susceptibility to infection, severity of the illness, and disease-related symptoms **[7]**.

The genome-wide association studies (GWAS) and direct gene sequencing are human genetics techniques that helped the researchers to identify both common and rare genetic variations. These variations occur in genes responsible for producing proteins involved in specific biochemical pathways linked to COVID-19 development. These investigations have unveiled alleles detected in both coding and non-coding sections of genes correlated with heightened susceptibility or a partial immunity to COVID-19. A notable breaktrough, particularly prevalent among patients under 65 years old, highlighter the errors affecting both innate and interferon-mediated immunity due to mutations in genes such as TLR3, TLR7, and IRF7. It was also revealed that congenital errors of immunity (IEI) were present in approximately 3% of individuals suffering from severe COVID-19 pneumonia. Furthermore, the consortium noted that at least 10% of other severe cases harbored autoantibodies capable of neutralizing interferon type I **[8]**.

THE GENETICS OF HOST AND IMPORTANT GENES

The genetics of the host represents another significant source of variation in the clinical and epidemiological aspects of COVID-19. This field encompasses various aspects, including the immunological features of innate or adaptive responses, as well as physiopathological mechanisms. Host genetics play a crucial role in COVID-19, with ACE2 and TMPRSS2 being the most studied genes. **[6]**.

ACE2, located on chromosome Xp22.2 [6] plays a crucial role in the infection process and post-infection inflammatory responses and it is also a receptor for SARS-CoV-2. These receptors are widely expressed throughout the body, including in the heart, gut, vessels lungs, kidneys, testes, and brain. By binding its viral S-protein to ACE2 receptors, SARS-CoV-2 gains entry into cells. ACE2 receptors serve to mitigate the adverse effects of angiotensin II in several ways. The first step ist o degrade angiotensin II, thereby reducing its harmful impact. Additionally, they generate angiotensin (1–7), which works in opposition to angiotensin II's regulatory effects. Heart diseases like heart failure, hypertension, diabetes, and most likely older age are conditions that can result in ACE2 deficiency. In the pathogenesis of SARS-CoV-2 infection it is believed that these conditions play a significant role, promoting the progression of inflammatory and thrombotic processes **[3].**

TMPRSS2, located on chromosome 21q22.3, facilitates spike protein priming and is highly expressed in lung cells. Genetic disparities between males and females in COVID-19 severity may be attributed to an androgen-responsive enhancer upstream of TMPRSS2 **[6]**.

The TMPRSS2 inhibitor presents a potential treatment avenue by impeding viral cell entry. The SARS-CoV-2 infection can be effectively blocked in lung cells by inhibiting TMPRSS2. This is offering a promising strategy to halt the progression of the disease **[3]**.

Additional studies have identified IFNAR2, TMEM189, and UBE2V1 as potential genes linked to COVID-19 susceptibility and severity. These genes play roles in immune response pathways, including interleukin-1 (IL-1) signaling. Further research is needed to elucidate the precise mechanisms underlying the genetic contributions to COVID-19 outcomes **[6]**.

Various genes linked to SARS-CoV-2, including TNF, EGFR, and P53, play pivotal roles in the virus's functionality, pathogenesis, and survival. Research indicates that TNF may play a crucial role in driving inflammation among patients with severe COVID-19. Existing immunomodulatory therapies could potentially target TNF to mitigate its inflammatory effects. These genes are deemed potential therapeutic targets due to their significance in SARS-CoV-2 infection. Prioritizing and identifying the most critical genes among those associated with COVID-19 from recent research can aid researchers in concentrating on specific gene sets for deeper analysis. A promising approach to COVID-19 treatment it is linked to developing drugs that target these essential genes to obstruct their normal functions and affiliated physiological pathways **[9]**.

A recent bioinformatics study reviewed potential genes associated with COVID-19 pathogenicity, drawing parallels with conditions such as Herpes simplex encephalitis, ARDS caused by Influenza virus, and infections by Varicella Zoster viruses, along with certain immunodeficient syndromes. The study identified 40 candidate genes implicated in Toll-like Receptor (TLR), lectin, and inflammasome

pathways. When compared with genes related to insulin resistance and Metabolic Syndrome (MetS), only a few genes overlapped, including HLA-B, CCL5, ABO, MBL2, and TRAF3, suggesting a potential link between cytokine-related genes and severe COVID-19 **[10]**.

CONCLUSIONS

In conclusion, the genetics of both the virus (SARS-CoV-2) and the host (human) play crucial roles in determining susceptibility, severity, and response to COVID-19. Genetic variability influences how individuals may react to the virus, ranging from asymptomatic carriers to severe cases requiring intensive care. Variations in human genes, particularly those involved in the immune response (e.g., ACE2, TMPRSS2), can impact susceptibility to infection and disease severity. Understanding these genetic factors can be seen as a key point in identifying individuals at elevated risk and developing targeted interventions. Continuous monitoring of viral genetic mutations and variants is essential for tracking the evolution of SARS-CoV-2 and understanding its transmission dynamics, immune evasion strategies, and potential impacts on diagnostics, treatments, and vaccine effectiveness. Insights from genetics can inform personalized approaches to COVID-19 management, and unraveling the genetics of COVID-19 is essential for elucidating disease mechanisms, identifying at-risk populations, guiding treatment strategies, and developing effective public health interventions to mitigate the impact of the pandemic.

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