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Analysis of Epigenetic Effect on COVID-19

Deming Wang

The Experimental High School Attached to Beijing Normal University, Beijing, China, 100032

13801270323@139.com

Abstract. The global spread of coronavirus illness (COVID-19) has been the most serious public health hazard to human life since 2019. For approximately three years, the COVID-19 pandemic has spread over the world, causing individuals to suffer not only from the virus's anguish but also from the consequences once they recover. Symptoms such as pneumonia, hypoxia, and severe respiratory distress emerge as the condition advances. The impact of gender, age, and genetic differences on the outcome of COVID-19 symptoms has piqued the interest of researchers in this field. Scientists from all over the world have established that the sequel is related to the epigenetic mechanism. As a result, the author examines the epigenetic effect on COVID-19 using a literature review method.

Keywords: COVID-19, epigenetic mechanism, epidemic, disease

1. Introduction

The global spread of coronavirus illness has been the most serious public health hazard to human life since 2019. The sickness begins with symptoms similar to typical influenza. Symptoms such as pneumonia, hypoxia, and severe respiratory distress emerge as the condition advances. Furthermore, if the condition progresses, it can cause respiratory failure, sepsis, septic shock, and multiple organ failure. However, the severity of symptoms varied greatly between younger and older persons, as well as between men and women. The impact of gender, age, and genetic differences on the outcome of COVID-19 symptoms has piqued the interest of researchers in this field. Most scientists now believe that a mix of hereditary and non-genetic factors may determine illness severity.

Several investigations have demonstrated that SARS-CoV-2 entrance mechanism and host innate immune response genes influence its severity. Furthermore, epigenetic mechanisms influence COVID-19 through the regulation of the IFN signaling system, angiotensin-converting enzyme 2, and immune-related genes associated with the X chromosome.

Because scientists all across the world have determined that the sequel has something to do with epigenetic mechanisms, the author addresses the epigenetic effect on COVID-19 using a literature review method. It attempts to provide some insightful research proposals.

2. Life cycle is effected by the corona virus

Some studies have found that the corona virus has an effect on life expectancy. According to Chinese researcher Huichuan Yu and his team from Zhongshan University, infection with Covid-19 reduces life expectancy, implying that the virus alters the epigenetic life of humans [1].

Previous research has demonstrated that viral infections, such as HIV or coronavirus, can affect

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epigenetic age [2]. Chronological age is a major risk factor for COVID-19 infection, severe illness, and mortality. However, epigenetic aging in COVID-19 patients has received little attention.

Yu's team used five distinct types of epigenetic clocks and a telomere length estimator to obtain their findings [1]. The experiment compares the epigenetic lifetimes of healthy people with those affected with the Corona virus. The team then utilized the data they gathered to compare the lengths of epigenetic lives and real lives of those afflicted to determine whether the acceleration of aging of epigenetic lives was related to whether they were infected by the virus and the severity of symptoms.

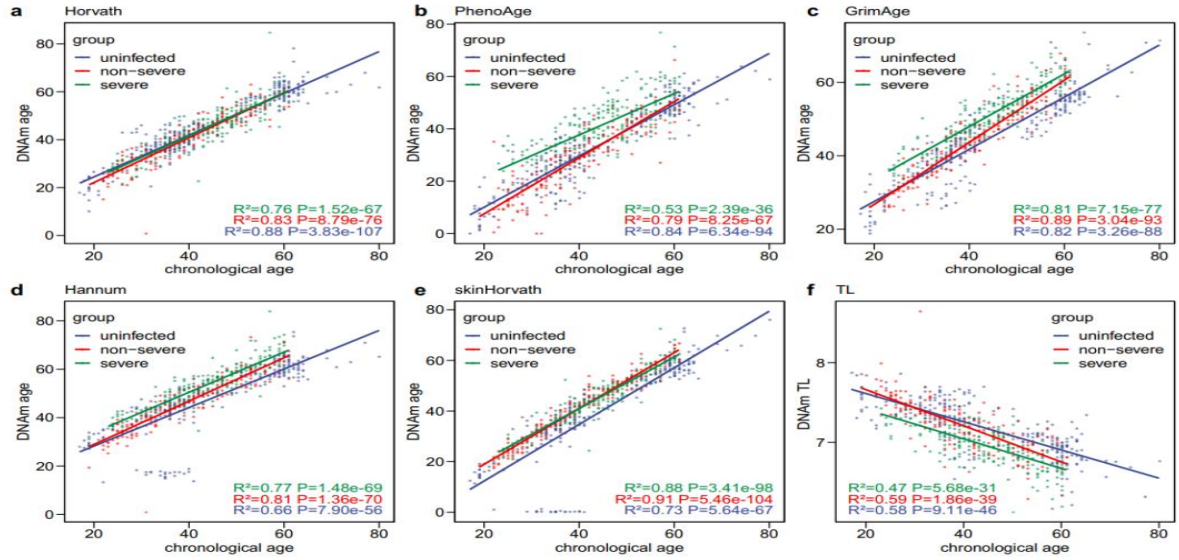


Figure 1. The effect of COVID-19 on genetic age [1].

In Figure 1, (a) (b) (c) (d) (e) and (f), epigenetic clocks Horvath, PhenoAge, GrimAge, Hannum, skinHorvath, Telomere Length Estimator are used to study the actual age of the individual and the genetic age difference, actual age and genetic positively related to age, based on individual health, mild and severe individual data analysis. It manifests that as infection severity increases, genetic differences between age and actual age increase slightly or significantly.

3. Analysis of the results of the experiment

At the conclusion of the experiment, scientists concluded that the corona virus infection and severity of the symptoms accelerated epigenetic aging [3]. According to scientists, COVID-19 infection can affect the epigenetic clock and telomere length estimation, speeding epigenetic aging and having other repercussions.

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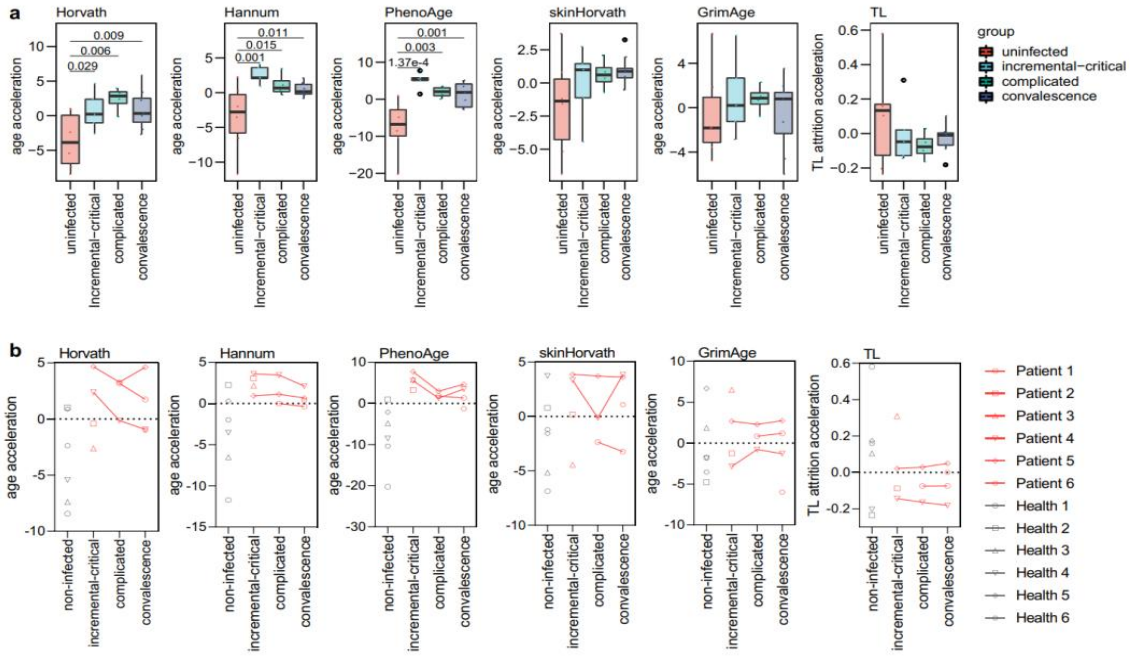


Figure 2. The trend of epigenetic aging in different stages of COVID-19 patients[1].

Figure 2 (a) depicts the progression of epigenetic aging in COVID-19 patients at various stages of development, severe stage, and recovery. (b) depicts the epigenetic aging trend in six COVID-19 patients at various stages of the initial, developing, severe, and recovery stages.

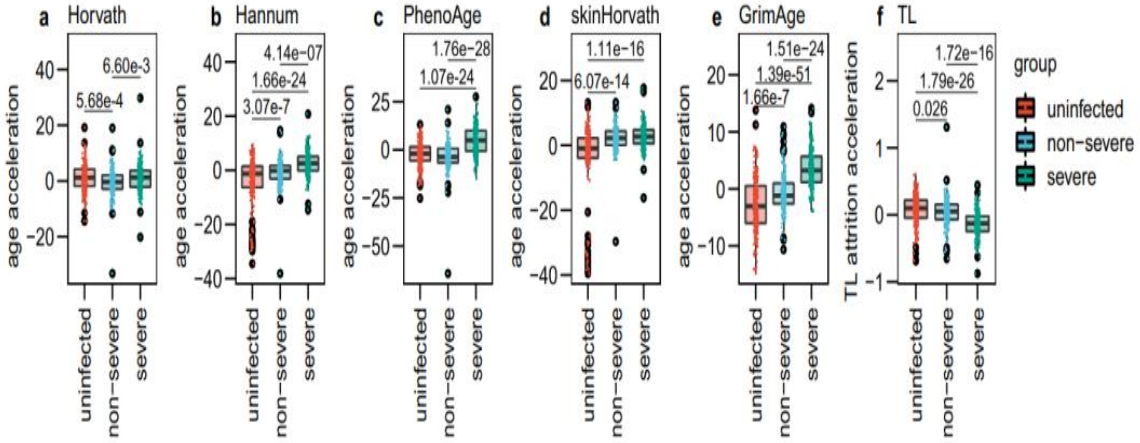


Figure 3. The relationship between the degree of COVID-19 infection and aging[1].

Figure 3 shows an investigation of the relationship between the degree of COVID-19 infection and the degree of accelerated genetic aging in individuals using different epigenetic clocks. (a) demonstrates no significant association. (b), (c), (d), and (e) demonstrate a positive link between infection level and genetic aging acceleration, whereas (f) reveals a negative correlation between infection level and genetic aging acceleration.

However, this is not always the case. According to studies, this effect of infection can be reversed in some patients, and the epigenetic aging of those persons can be partially reversed throughout the restoration process [4].

Further discussion revealed the study's potential outlook, stating that it will help people detect those who may get seriously ill and provide better health treatment to such patients.

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3.1. Immune response to SARS-COV-2

On COVID-19, Rwik Sen, Michael Carbati, Kevin Bryant, and Yuan Lu investigate epigenetic inheritance. Individuals infected with COVID-19 displayed dysregulated immunological and inflammatory responses to SARS-COV2 [5]. Cytokines are signaling proteins that bind to receptors on target cells, causing immune cells to congregate at the site of infection. Cytokines are responsible for inflammation and the release of immune cells.

This cytokine storm activates various proinflammatory pathways, with the JAK-STAT pathway serving as a hub for several cytokine signals [6]. JAK protein and STAT3 are downstream effectors of IL-6, a cytokine related with illness severity. Clinical trials of tocilizumab, a neutralizing antibody against IL-6 receptors, have benefited patients with severe COVID-19 pneumonia.

3.2. Effects of DNA methylation on ACE2

A study of five chromosomal locations in the ACE2 promoter of 96 essential hypertension (EH) patients revealed the importance of moderate epigenetic control [4]. Because CpG DNA methylation in promoter regions is a characteristic of transcriptional repression, it has an inverse association with gene expression [4]. According to M.J. Corley and L.C. Ndhlovu's preprint paper, there was also a negative connection between promoter CpG island methylation and expression, with ACE2 promoter methylation being higher in the gut, liver, pancreas, brain, and blood than in the lung epithelium. Furthermore, the degree of ACE2 expression in lung tissue was found to be positively associated to disease severity.

The putative regulators of ACE2 were predicted to be epigenetic modifiers such as HAT1, HDAC2, and KDM5B by connection and web mining of the lung transcriptome of 700 patients with high ACE2 and COVID-19 comorbidity [7]. The analysis predicted a strong relationship between human HDAC2 and SARS-COV2 NSP5. Epigenetic ACE2 modulation via DNA methylation, histone modification, and chromatin modification enzymes may aid in understanding the pathophysiological process of severe COVID-19 patients in order to develop epigenetic-based therapeutics.

3.3. Severity and X-chromosome

According to the sex-related analysis of 23,39,709 patients by Sanita Institute for Advanced Research in Italy, the infection rate of females was higher than that of males, accounting for 54.2%[4]. The higher expression of ACE2 and higher infection rate in females may be due to the ACE2 locus being located in the part of the X chromosome that avoids X inactivation.

3.4. ACE2 and histone modification

Histone alterations can also affect ACE2 epigenetically. Histone [4] tail amino acids are modified post-translationally. Depending on histone modifications, chromatin is open, condensed, or inaccessible to transcription factors, causing transcriptional suppression. EZH2 catalyzes the repressive marker H3K27me3. Loss of EZH2 function decreases H3K27me3, increasing ACE2 expression in mouse germ lines [4].

Correlation and network analysis of the lung transcriptomes of 700 individuals with high ACE2 and severe COVID-19 suggest that epigenetic modifiers may regulate ACE2. Proteomic study indicated human HDAC2 and SARS-COV2 NSP5 interacted.

3.5. Locus

HLA proteins help in antigen presentation and genetic diversity. HLA's polymorphic genetic locus helps the immune system deal with infections.

Severe COVID-19 respiratory failure was associated with rs11385942 and rs657152. Decreased expression of chemokine recepto-6 affects increased expression of sodium/imine transporter-20 in rs11385942 GA allele as well.

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3.6. Regulation of inflammatory pathway genes

The involvement of genes that produce immune responses to coronavirus infection can be modulated by histone modifications. During an infection, Toll-like receptors identify viral pathogen-associated molecular patterns [8], triggering innate immune responses. Dendritic cells and macrophages detect pathogens and activate a quick, specialized immune response.

This reaction activates IFN and TNF. IFN and TNF stimulate the innate immune system's initial reaction. Interferon-induced interferon promotes gene expression and synthesis. These proteins contribute to severe COVID-19's cytokine storm.

H3K9me2 is a restrictive chromatin marker on the type I interferon promoter. It favors euchromatin by preventing histone acetylation and promoting heterochromatin development. H3K9me2 is a transcriptional regulator, hence its presence on the IFN promoter in DCS reduces ISG expression.

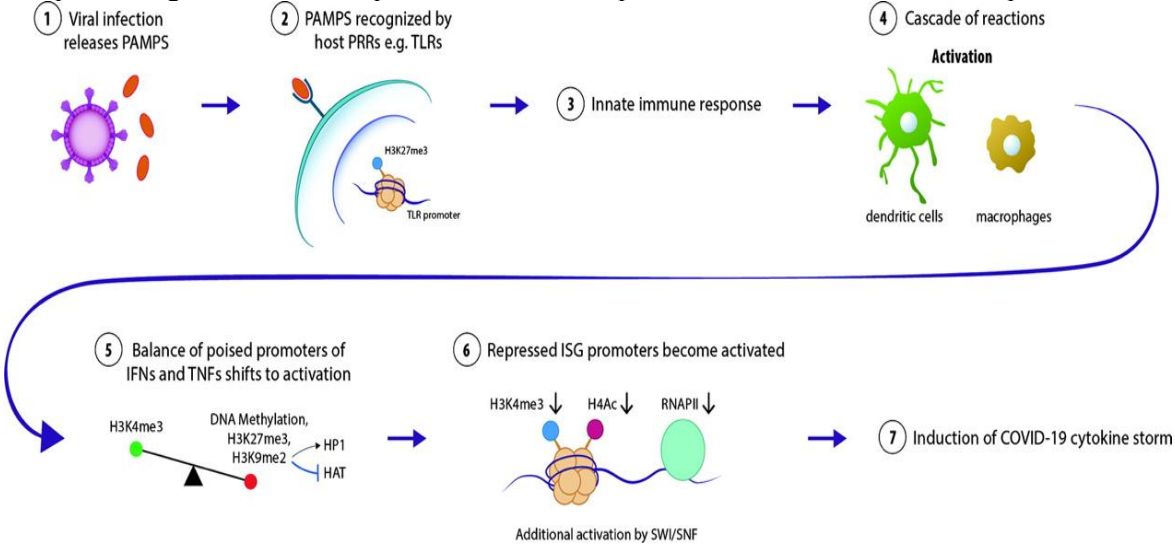


Figure 4. After an individual is infected with the virus, activated interferons lead to an activation process of interferon-stimulated genes (ISGs) [4].

Viral infections emit pathogen-associated molecular patterns (PAMPs), which are recognized by pattern recognition receptors such as Toll-like receptors (TLRs). This is innate immunological response. Dendritic and macrophages are stimulated. Interferon (INF) and tumor necrosis factor (TNF) promoters are stable, and transcriptional activation marks like histone H3K4me3 and repressive marks like CpG methylation H3K27me3 and H3K9me2 are present. H3K9me2 recruits HP1 and suppresses HAT activity. Activated IFN causes ISG activation [4].

3.7. Histone citrullination and Covid 19

Citrullination of H3-hiton was another epigenetic change discovered in COVID-19 individuals. Decoding arginine residues on histones aids in the transcription of chromatin structure. CIT-H3 is an extracellular trap marker for neutrophils [9]. Local microbicides and antioxidants are abundant in NETs.

In COVID-19 patients, the level of citrullinated histone H3 is elevated, which correlates with an increase in white blood cell count, granulocyte count, and the cytokine IL-8. NETs in COVID-19 tracheal aspirates, patients' plasma, lung epithelium, alveolar cavity, and other tissues exhibit enhanced features.

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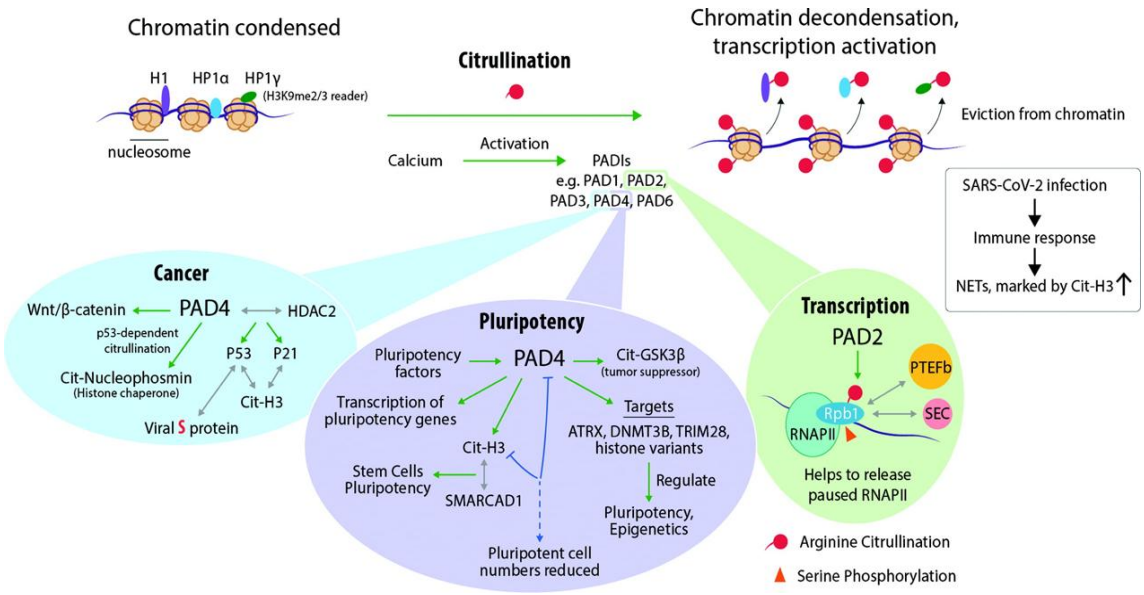


Figure 5. The characteristics of gene transcription disorder in COVID-19 patients[4].

Histone citrullination is upregulated in COVID-19 patients, and it is related to cancer, stem cell pluripotency and transcription. The expression of citrullinated histone H3, a NETs marker, is up-regulated in patients with COVID-19. Citrullination of histones has also been associated with cancer, pluripotency, and transcription. These three processes have the following relevance to COVID-19. Bioinformatics studies have found that tumor suppressor p53 has a variety of associations with histone citrullination and interacts with viral S protein [10]. Citrullination, used in COVID-19 clinical studies, boosts stem-cell pluripotency. Histone citrullination causes transcription-affecting chromatin condensation. Since COVID-19 patients have disordered gene transcription and citrullination is elevated in them, it is vital to explore how citrullination impacts the aforementioned three processes [4].

3.8. Stem cell pluripotency

Early embryogenesis has fewer pluripotent cells after PAD4 or histone citrullination suppression [4]. Oct4, Klf4, and Sox2 interact with PAD4 to reprogramme somatic cells into pluripotent cells [4]. In mouse stem cells, Oct4, Klf4 and Sox2 bind to Pad4's promoter.

COVID-19 links stem cell pluripotency, reprogramming, and histone citrullination. In the U.S., nine stem cell treatment studies for COVID-19 are ongoing.

SARS-CoV-2 protein-epigenetic factor interactions.

SARS-CoV-2 proteins interact with epigenetic factors. Affinity purification mass spectrometry was used to map the interactome of 26 SARS-CoV-2 proteins. 8 epigenetically changed human proteins were SARS-CoV-2 binding partners.

BRD2 and BRD4 interact with viral E proteins, which read acetylated histones and activate transcription. E and BRD proteins may interact because the C-terminal region of E mirrors the N-terminal area where histone H3 binds with BRD.

4. Therapies and clinical trials

Epigenetic mechanisms have begun to receive attention in two clinical trials [11]. Many additional clinical studies are underway for COVID-19 treatments that use epigenetic pathways, but we focus primarily on those. One of these clinical trials will examine smoking biomarkers, immune cell signatures, and transcriptional and DNA methylation patterns.

The second research examined the relationship between COVID-19 severity and circulating epigenetic markers in the presence and absence of pneumonia and severe acute respiratory syndrome

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[11]. ACE2, TMPRSS2 and PARP genes, crucial players in triggering cytokine storm interleukins, were tested for DNA methylation. This study examines prognostic epigenetic markers.

5. Discussion

Yu′s team and their article provided enough experimental evidence showing that the aging caused by the infection of Covid 19 virus truly existed [1]. However, the passage has not clearly shown the mechanism behind this shifting of epigenetic lives, leaving only the phenomenon. Moreover, this uncertainty of mechanism doubt the result of study because it is merely based on the data collected from patients but not chemical analysis.

To go further, the researchers should use chemical method to analysis the phenomenon they discovered in the data and try to discover the mechanism behind the epigenetic change in life cycle and figure out whether it can be used by people to imped the spread of the pandemic as researchers Rwik Sen, Michael Carbati, Kevin Bryant and Yuan Lu did in their study. Furthermore, the researchers could try to analysis genome of those patients to find whether the infection of Covid 19 differs the DNA component.

Although the article mainly focus on the Covid 19 pandemic, the result will not only be useful to stop the spreading of the corona virus but also be practical to prevent other type of disease from spreading if we can fully understand the mechanism and using the experience when we meet other types of bacteria, fungus, or disease.

6. Conclusion

It has been demonstrated that the novel coronavirus pneumonia (COVID-19) is highly contagious, with rapid transmission capabilities prior to virus infection but no visible symptoms. The virus's disguised propagation makes early detection of asymptomatic illness challenging, and it is impossible to identify and isolate all affected people. Certain flaws exist in the prevention and treatment strategy of limiting the spread of the virus by isolating the infected. To overcome this sickness, new approaches and technologies must be researched in order to improve the virus's potential to be defeated.

People all throughout the world must work together to put an end to the global COVID-19 outbreak as soon as possible. The level of economic development varies around the globe; people in poor places, in particular, cannot afford the high costs of viral prevention, vaccine, and disease treatment, and hence cannot respond to the virus rapidly. Because of this scenario, the administrative branches of the national government must collaborate with manufacturing enterprises and institutions, as well as health insurance plans, to provide citizens all over the world with easier and more cheap access to medical treatment.

The increased prevalence of severe COVID-19 in black, Asian, and other minority populations cannot be explained solely by behavioral features, socioeconomic level, cardiovascular disease risk, or vitamin D status. According to one case report, the COVID-19 virus caused the deaths of three previously healthy people who lived in different parts of the country and had no history of cancer. A new report from a large familial cluster adds to the evidence that a family history of severe disease may contribute to genetic risk. These cases show that underlying genetic and epigenetic factors can cause significant COVID-19 consequences.

Genetic variation in genes involved in the SARS-CoV-2 entry mechanism, genes involved in the host immune response, and other putative genetic loci may be able to explain both the genetic propensity to severe COVID-19 as well as the disease process. The COVID-19 Host Genetics Initiative aims to strengthen research on the fundamental biology of SARS-CoV-2 and kindred viruses by bringing together the research power of human genetics. The purpose of this research is to identify the genetic determinants that influence the severity, susceptibility, and outcome of COVID-19 infection. Using effective approaches seeks to stop the pandemic and ensure that humanity is well prepared to deal with any unexpected future virus outbreaks.

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