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An Analysis of Genetic Risk Factors (Chromosomes 3 and 9) and Mutation of Spike COVID-19 in the Severity and Transmission Factor

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Abstract

The world was shocked by novel coronavirus disease-19 (nCoV-19) in Wuhan City which declared as a pandemic by World Health Organization (WHO). There are still some problems, especially in the appearance of both Variant of Investigations and Concerns caused second or third wave. These variants related to the Spike glycoprotein mutation and genetic risk factors on chromosome number 3 and 9. The findings of this article review was COVID-19 severity related to the genetic risk factor namely in chromosome 3p21.31 and 9q34 which its relationship is reciprocal in the level of C5a and SC5b-9 on the ABO groups with the worst severity was on A blood group. A blood group had higher increase of ferritin and procoagulant factor that reflected the severity of the disease and exaggerated complement activation leading to acute respiratory distress syndrome (ARDS). The mutations in D614G Spike glycoprotein resulted in changing aspartic acid into glycine also increased the transmission factor even though in the vaccinated persons through neutralizing antibodies of vaccine induced antibody. We review the severity and increased transmission in COVID-19 related to both genetic of host risk factors and mutation of Spike SARS-CoV-2 glycoprotein which their relationship was reciprocal.

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Introduction

New Year's Eve 2020, which is usually celebrated on December 31, 2019 is a New Year's Eve that the City of Wuhan, Hubei in the Republic of China cannot forget where Wuhan is a *wet seafood market* that sells various kinds of food made from wild animals, such as: bats, snakes, raccoon, pangolin, and other animals. At that time there was a reported case of pneumonia of unknown cause and had never

been found before. At that time, the pneumonia was identified as *novel coronavirus disease-19* (nCoV-19) and subsequently identified as *Coronavirus Disease-19* (COVID- 19). COVID-19 is a form of acute respiratory tract disorder with the causative agent being the *Severe Acute Respiratory Syndrome virus Coronavirus-2* (SARS-CoV-2). The spread of SARS-CoV-2 was very fast and reached its peak when the *World Health Organization* (WHO) declared it a pandemic outbreak that caused a world emergency or known as the *Public Health Emergency of the International Concern* (PHEIC) on January 30, 2020. This is based on the rapid spread of the virus outside China for 2 weeks which has attacked several countries¹⁻⁵.

Symptoms of COVID-19 appear after a period or incubation period that occurs on average within 5.2 days with the time from symptom onset to death ranging from 6 to 41 days with a median value of 14 days. This period depends on the patient's age and the patient's

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immune status. The clinical symptom of COVID-19 is fever accompanied by a dry cough and fatigue. Other symptoms of COVID-19 can include headache, sputum production, hemoptysis, diarrhea, dyspnea, lymphopenia, and bilateral pulmonary infiltrates on radiology³.

Comorbid	Proportion (%)	Number of cases	Recovery (%)	Number of recovered patients	Death	Number of deaths
Hypertension	52.1	314	28.7	98	19.2	6
Diabetes mellitus	33.6	220	16.3	36	15.3	3
Cardiovascular disease	20.9	137	8.9	12	10	1
Chronic lung obstructive disease	15.1	99	11.1	11	3.7	5
Kidney disease	4.9	32	0.8	0	4.1	1
Asthma	3.1	20	1.8	0	0.6	1
Cancer	2.3	15	1.1	0	1.1	1
Tuberculosis	1.8	12	1	0	0.3	1
liver disease	1.2	8	0.9	0	0.3	1
Sytemi related immunity isease	1.2	8	0.6	0	0.3	1

Table 1. Comorbid diseases found in Indonesia.

Nowadays, COVID-19 has not shown any signs of abating even though the COVID-19 vaccination process has been carried out to the world's population. In 2021, there will be a second wave and even a third wave of COVID-19 in various parts of the world, according to which according to the *Phylogenetic Assignment of Named Global Outbreak* (PANGO) there are two types of variants, namely: *Variant of Concerns* (VOCs) and *Variant of Interests* (VOIs) where in both types of variants there were several mutations that occurred in the Spike-Glycoprotein protein, especially in the *Receptor Binding Domain* (RBD) area which is the place for SARS-CoV-2 to enter and bind to the *Angiotensin Converting Enzyme* (ACE)-2 on host cells. Mutations that occur in RBD in both variants cause a decrease in the neutralization process by antibodies that have been produced after being vaccinated (*antibody-induced vaccinated person*) and also increase the transmission of COVID-19 in people even if the person has been vaccinated against COVID-19⁶⁻⁹. In addition to the phenomenon possessed by the SARS-CoV-2 agent, it turns out that there is a phenomenon in the host in the form of a genetic risk factor consisting of Chromosome numbers 3p21.31 and 9q34. Chromosome 3p21.31 is associated with the activation of the complement system and chromosome 9q34 which is associated with the ABO Blood System, where

the relationship evoked by chromosomes 3 and 9 is related reciprocally^{10,11} because the relationship between chromosome 9 and the severity of COVID¹². Host factors are also associated with the presence of comorbid diseases with comorbid diseases most susceptible to COVID-19, namely diabetes and obesity as shown in table 1¹³⁻¹⁷.

Materials and methods

This article was written using databases obtained from the Pubmed database, *Research Gate*, international journals, and books containing the relationship between chromosome numbers 3 and 9, as well as mutations that occur in COVID-19 variants of concerns (VOCs) and investigations (VOIs). This review will explain the relationship between chromosome numbers 3 and 9 and its relation to mutations in the RBD Spike protein in VOCs and VOIs.

Discussion

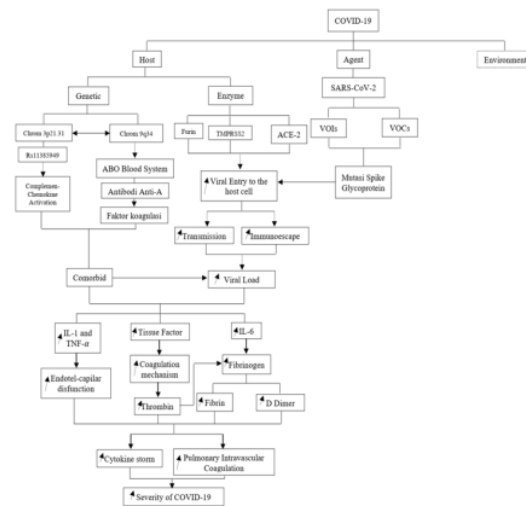


Figure 1. Concept mapping of the relationship among COVID-19, host (genetic and comorbid factor), and mutation of spike glycoprotein in the severity of COVID-19 patients.

Host Genetic Factors

Figure 1 shows the coronavirus Disease-19 (COVID-19) is viewed from the aspect of the epidemiological triangle consisting of the Host-Agent-Environment aspect with a focus on writing review articles on Host-Agent. Host factors can

be seen from two points of view, namely: genetic and enzyme point of view. Genetics that affect the host factor consist of two, namely genetics contained in chromosome 3 and chromosome 9 with a reciprocal relationship between chromosomes 3 and 9. Chromosome 3 precisely on chromosome 3p21.31 is associated with increased complement-chemokine activation. There are 6 genes on the chromosome, one of which is SLC6A20, rs11385942, LZTFL1 (leucine zipper transcription factor like-1), FYCO1 (Fab1, YOTB, Vac1, EEA1) and coiled-coil domain autophagy adapter 1, and rs11385949^{18,19}.

SLC6A20 encodes a partner for interacting with the enzyme Angiotensin Converting Enzyme-2 (ACE-2)²⁰. SLC6A20 encodes Sodium/Imino-acid (Proline) Transporter-1 (SIT-1) which functionally interacts with the enzyme ACE-2, which is a surface receptor as well as an entry point for SARS-CoV-2. SIT-1 is expressed in the lung mainly in pneumocytes, so there is involvement of SIT-1 in SARS-CoV-2 viral entry into host cells.

Chromosome Number 3

Chromosomal locus 3p21.31 is also associated with the content of clusters of genes encoding chemokine receptors (CC-motif chemokine receptor-9 /CCR-9 and CX-motivated chemokine receptor 6 /CXCR-6), complement activating factor via SLC6A20, CXCR6, CCR9, XCR1, LZTGL1. CXCR-6 regulates CD8 memory cells on lung T cells via a sustained immune response to airway pathogens. Chromosomal 3 loci rs11385942 and rs11385949 are associated with activation of the complement system in hospitalized patients. The locus rs11385949 is associated with respiratory failure through its association with modulation and recruitment and activation of inflammatory cells. The parallel activation cascade of the complement system correlates with disease severity. In addition, rs11385949 was also associated with increased circulating c5a and SC5b-9 levels. SC5b-9 correlates with viral load in the upper respiratory system and tissue damage that complement system activation and its cascades contribute to independent pathways in determining the degree of lung damage^{11,21-24}.

The spike protein in SARS-CoV-2 is able to trigger the activation of the complement system where if the activation of the complement system is inhibited it will prevent the occurrence of severe lung injury in the lungs. Complement

activation consists of three pathways with the result of activation of these three pathways the formation of C3 convertase which will split C3 into C3a and b. C3b will then undergo cleavage to become C3c and activate c5b to become c5a and c5b. C5b, together with other complement factors, forms a terminal complement complex or an attack membrane complex. Both c3 and c5a induce inflammation and coagulation processes through: 1. Platelet activation, 2. Causes the secretion of von Wille Brand factor and P selectin through endothelial cell activation, 3. Increases tissue factor activity. All three factors will be associated with increased D-dimer²⁵⁻²⁸.

The genetic variation in rs11385949 encodes several chemokine receptors that directly contribute to the increase in CCR2 expression so that rs11385949 also affects the recruitment of inflammatory cells in the lower airways or vascular tissue. In addition to activation of the complement system, an increase in circulating ferritin was also found which was parallel to viral replication^{29,30}.

Chromosome Number 9

Associated with chromosome 9, precisely on chromosome 9q34 is a chromosome that regulates the ABO blood group system. It is said that a person with blood type A has a higher level of risk when exposed to SARS-CoV-2 compared to a person with blood type O. There are several explanations to explain this relationship: 1. In blood type O there are anti-A antibodies where anti-A antibodies block the interaction between SARS-CoV-2 with entry into host cells through ACE-2, 2. The ABO blood group locus is associated with coagulation factors (von Willebrand / vWF and factor VIII). vWF at locus 12p13.31 is associated with thrombosis and coagulation. vWF is a carrier of coagulation factor VIII so that an increase in the complex between vWF and factor VIII increases the prothrombotic risk due to its intrinsic procoagulant property and natural anticoagulant effect. Pulmonary endothelial cells in the non-O blood group have a higher vWF protein level than the O blood group, so that in the non-O blood group there will be a higher probability of thrombosis than in the O blood group pulmonary endothelial cells^{26,31,32}. Related to the reciprocal relationship between chromosomes 3 and 9 lies in: 1. People with blood type O have a lower risk of COVID-19, especially with levels of the complement system c5a and SC5b-9, 2. Non-

group O blood types are more prone to exaggerated activation of the complement system that triggers the progression of tissue damage resulting in severe lung disease.

Agent Point of View

From the point of view of the agent causing COVID-19, the SARS-CoV-2 agent uses the furin, TMPRSS2, and ACE-2 entrance with the main entrance being ACE-2. Furin is present in large quantities in some tissues. Agent SARS-CoV-2 currently classified by *Phylogenetic Assignment of Named Global Outbreak* (Pango) there are two variants COVID outline-19 consisting of *Variant of Concerns* (VOCs) and *Variant of Interests* (VOIs). VOCs consist of: 1. Variant Alpha (B.1.1.7 lineage status VOC-20DEC-01), 2. Variant Beta (B.1.351 lineage status VOC-20DEC-02), 3. Variant Gamma (P.1 lineage status VOC-21JAN-02), and 4. Variant Delta (B.1.617.2/AY.1/AY.2 with status VOC-21APR-02). VOIs consist of: 1. Variant Eta (B.1525 lineage status VUI-21FEB-03 and B.1.1.318 lineage status VUI-21FEB-04), 2. Variant Lota (B.1.526 lineage), 3. Variant Kappa (B.1.617.1 lineage), and 4. Variant Lambda (C.37 lineage). This is because SARS-CoV-2 belongs to the RNA virus group that continuously evolves and has a high mutation rate ($1.05-1.26 \times 10^{-3}$) compared to SARS-CoV-1 which has a mutation rate ($0.8-2.38 \times 10^{-3}$) which is associated with increased pathogenicity and virulence^{15,16,27,30}.

Mutation on the Spike Protein

The most frequent mutation is in the Spike protein in which Spike interacts with the host ACE-2 enzyme. The result of mutations in the Spike protein is that the virus can easily immunoescape from the immune response and increase its pathogenicity. Spike has a furin cleavage site (RPAR) where RPAR is only specific for the SARS-CoV-2 strain. RPAR is cleaved by furin and contributes to viral entry in protein S. Mutations in protein S get a special issue because these mutations result in higher spread^{33,34}.

Mutations in VOIs and VOCs are double or triple mutations. The mutation in D614G is not located in the Receptor Binding Domain (RBD) but is located on the promoter surface of the S protein forming a hydrogen bond that stabilizes the mature Spike (trimeric) form on the virion surface. The existence of a mutation from what was originally encoded by Aspartic Acid to

Glycine will cause destabilization of hydrogen bonds so that it affects the interaction between the promoter and the glycosylation pattern. The D614 G mutation causes increased viral entry into host cells thereby enhancing transmission and immunoescape patterns. Another form of mutation in the Receptor Binding Domain also occurs in the Spike L452R, E484Q and P681R proteins^{28,34}.

A mutation in the amino acid encoded by L452R that causes an increase in Spike's affinity for the receptor and leads to decreased recognition by antibodies (including recognition by convalescent plasma antibodies). The L452R mutation in which the amino acid Arginine (R) replaces Leucine (L) at position 452 in the Spike protein. Arginine has a guanidine functional group so that it has polarity properties and increases hydrophilicity which the amino acid Leucine does not have. There are similarities between L452R and Y453F where the Y453F mutation is located adjacent to the upper receptor binding domain (RBD) region that is in contact with ACE-2. Y453F is associated with a predicted escape from the neutralization process by monoclonal antibodies³⁴.

Mutations in the amino acid Spike -RBD 484 which in this type of mutation terjado acid substitution glutamic by lysine (E484K) the nature of the glutamic acid is negatively charged into lysine which are positively charged. The consequences of this substitution are: 1. Decreased neutralization by convalescent antisera and binding to monoclonal antibodies, 2. Increased affinity with ACE-2. The combination of mutations in L452R and E484K in the Spike-RBD protein is called a double mutation variant. Mutations in E484Q and L452R reduce binding to monoclonal antibodies (mAb) and affect the virus neutralization process²⁸.

P681R mutation occurs at the site of furin breakdown, resulting in an increase in S1-S2 cleavage thereby increasing transmissibility because P681R is located in the "cleavage site" area between Spike 1 and Spike 2 proteins. P681R mutation occurs due to the substitution of Proline (P) into Arginine (A). This mutation causes an increase in viral infectivity by facilitating the cleavage of Protein S to the active configuration of Spike 1 and Spike 2 proteins. Mutations in spike associated with the occurrence of cytokine storm can be explained as follows. The mutation causes the Spike S1

protein to interact with the *host* enzyme *angiotensin converting enzyme* (ACE)-2. After the union of the S1 protein with ACE-2, the Spike S2 protein subunit interacts with *transmembrane serine protease 2* (TMPRSS2) and *cathepsin B/L* (CatB/L). Following the process of endocytosis or fusion with the surface of the cell membrane, the virus will place its genome in the cytoplasm. The viral genome will *hijack* the *host's* translational machinery and will directly produce polyproteins in large quantities from essential proteins. The virus will spread to the respiratory system at the bottom (*lower respiratory tract*) through the process of aspiration or infection of cells in the respiratory tract. Spike protein is *immunodominant* so that mutations in Spike protein will cause *immune evasion* caused by mutations in the *N terminal domain* (NTD) associated with *escape neutralization* because mutations in NTD crucially affect antibody sensitivity³⁴.

The process of entering the virus into *host* cells causes *host* responses in the form of: 1. *Viral pathogen-associated molecular patterns* trigger the production of pro-inflammatory interleukins followed by activation of *pattern recognition receptor* (PRR) by *toll-like receptors* (TLR). The pro-inflammatory interleukin formed is interleukin 6 (IL-6) which in turn activates the *nuclear factor kappa-beta* (Nf- κ B) transcription factor. 2. The inflammatory response due to the use of ACE-2 by the Spike S1 protein causes an increase in the serum level of Angiotensin II due to a decrease in ACE-2. An increase in angiotensin II activates the Nf- κ B pathway via the *angiotensin type II receptor* (AT1R) followed by overproduction of IL-6. AT1R is associated with the activation of the proteases ADAM 10 and ADAM 17 resulting in the production of *tumor necrosis factor* (TNF)- α , *soluble interleukin 6 receptor* (sIL-6R α). The results of both responses *host* in the form of the inflammatory cascade system Nf- κ B and STAT3 signaling pathways that cause further augmentation Nf- κ B activity and increased IL-6 inflammatory circuits, called *interleukin 6 amplifier* (IL-6 AMP). IL-6 AMP creates positive feedback for inflammatory pathways of non-immune cells (endothelial cells, and others). The final results of the IL-6 cytokine storm AMP resulting in *acute respiratory distress syndrome* (ARDS), pneumonia, multi-organ failure, and increased coagulation in blood vessels³⁵⁻³⁸.

The effect of mutations increasing *viral load* in the *host* and coupled with the presence of genetic factors on chromosomes 3 and 9 as well as the presence of comorbidities will cause an increase in the severity of COVID-19 (*severity COVID-19*) which is seen from circulating ferritin because ferritin reflects the occurrence of dysregulation in the immunity system³⁹⁻⁴¹.

Conclusion

Severity and increased transmission in COVID-19 related to both genetic of *host* risk factors and mutation of Spike SARS-CoV-2 glycoprotein which their relationship was reciprocal both in chromosome number 3 and 9. This is also aggravated by the comorbid status of the patient because of complement activation that leads the platelet activation, endothelial activation through secretion of von wille brand factor and selectin P, and increase of tissue factor. The end of these will lead the severity in COVID-19 patients.

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Declaration of Interest

The authors declare that there is no conflict of interests.

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