The Risk of COVID-19 in People Having a Particular Set of Gene
Dhakal B, Makaju R, Dhakal R

Department of pathology
Dhulikhel Hospital, Kathmandu University Hospital, Kathmandu University School of Medical Sciences, Dhulikhel, Kavre, Nepal.

Corresponding Author
Binod Dhakal
Department of pathology
Dhulikhel Hospital, Kathmandu University Hospital, Kathmandu University School of Medical Sciences, Dhulikhel, Kavre, Nepal.
E-mail: dbinod@gmail.com

Citation

INTRODUCTION
The reported number of Coronavirus disease of 2019 (COVID-19) cases globally now exceeds 183 million and the number of deaths is almost 4 million.1 We are all living in these difficult times and the virus is surprising us in many ways. The virus is showing a considerable variation in disease behavior among patients. It is strangely and tragically selective.2 Early in the pandemic, it was believed that morbidity and mortality due to COVID-19 rise dramatically with advancing age, male gender and co-existing health conditions like cancer, cardiovascular diseases or hypertension, and also diabetes and obesity.3 These risk factors, however, do not fully explain why some people have no or mild symptoms whereas others have severe symptoms. Even young people and those who do not have other preexisting chronic disease are facing serious consequences.4 Thus, this lead to the hypothesis, those human genetic factors may contribute to a high risk of Corona virus.

COVID-19 AND GENE
Researchers are now looking inside the genomes for DNA variations. Genome wide association study (GWAS) done by Ellinghouse et al. identify a 3p21.31 gene cluster as a genetic susceptibility locus in patients with COVID-19 with respiratory failure.5 The frequency of the risk allele of 3p21.31 was higher among patients who received mechanical ventilation than among those who received oxygen supplementation.5 They also found a higher risk among persons with blood group A and protective effect for blood group O than among patients with other blood groups. The particular haplotype in a region of chromosome 3 is contributed to modern humans by neandertals. Another Neanderthal haplotype on chromosome 12 is associated with a 22% reduction in relative risk of becoming severely ill with COVID-19. The ApoE e4e4 homozygous genotype was found to increase the risk of severe COVID-19. Change in angiotensin converting enzyme (ACE) 2 gene was also found to be associated with increased risk of COVID-19, cardiovascular and pulmonary conditions.

ABSTRACT
These risk factors of advancing age, male gender and co-existing health conditions like cancer, cardiovascular diseases, diabetes and obesity do not fully explain why some people have no or mild symptoms whereas others have severe symptoms. Genomewide association study (GWAS) identify a 3p21.31 gene cluster as a genetic susceptibility locus in patients with COVID-19 with respiratory failure. They also found a higher risk among persons with blood group A and protective effect for blood group O than among patients with other blood groups. The particular haplotype in a region of chromosome 3 is contributed to modern humans by neandertals. Another Neanderthal haplotype on chromosome 12 is associated with a 22% reduction in relative risk of becoming severely ill with COVID-19. The ApoE e4e4 homozygous genotype was found to increase the risk of severe COVID-19. Change in angiotensin converting enzyme (ACE) 2 gene was also found to be associated with increased risk of COVID-19, cardiovascular and pulmonary conditions.

KEY WORDS
Blood group, Chromosome 3, Chromosome 12, Angiotensin converting enzyme
evolved in western Eurasia at least 200,000 years ago. The Neanderthals and the Denisovans (their Asian sister group) then became extinct about 40,000 years ago. However, they continue to have a biological impact on humans even today. The biological impact may reflect adaptations to environments outside Africa. These genes may have helped human adapt to infectious diseases and to several pandemics that have infected earth.

Another Neanderthal haplotype on chromosome 12 is protective for severe disease in the current Covid pandemic. This haplotype on chromosome 12 is associated with a 22% reduction in relative risk of becoming severely ill with COVID-19. This gene is carried in populations of Eurasia and the Americas that often reach and exceed 50%. This Neanderthal haplotype has also been found to be protective for RNA viruses that include hepatitis C virus and West Nile virus. The Neandertal haplotype protective against severe COVID-19 contains parts or all of the three genes OAS1, OAS2, and OAS3. Neandertal OAS locus variants may thus have been advantageous to modern humans since the humans have been facing pandemics involving RNA viruses since eternity.

There are some genes that protect humans against some pathogens however some genes have detrimental effects. Those who have each copy of the haplotype in chromosome 3 have double the risk of requiring intensive care. Such gene is almost absent in East Asia. This gene may have been eliminated in East Asia by negative selection. This particular set of inherited gene may have been beneficial in pandemics or epidemics of earlier times.

Various other studies also suggest the genetic susceptibility to COVID-19. A twins study studied by Williams FM estimated that total heritability of COVID-19 risk was 50%.

Study done by Van Der Made et al. in severe COVID-19 patients, found the loss-of-function variants of X chromosomal TLR7. TLR 7 was associated with impaired type I and II IFN responses. This explains the risk of COVID-19 in males more than in females. Similarly, Testosterone in males upregulates anti-inflammatory cytokines (interleukin-10, IL-10), thus acts as an immune suppressor. Estrogen enhances the immune system by upregulating pro-inflammatory cytokines (tumor necrosis factor alpha (TNFα)). Females tend to have higher antibody responses, but are also more prone to developing autoimmunity.

The ApoE e4e4 homozygous genotype was found to increase the risk of severe COVID-19. ApoE e4 allele moderates macrophage pro-/anti-inflammatory phenotypes. ApoE is one of the highly expressed genes in type II alveolar cells in the lungs.

COVID-19 infection depends on the host cell factors angiotensin-converting enzyme 2 (ACE2) for entry into cells and the host transmembrane serine protease TMPRSS2. ACE2 are the receptors present in lung that receive Corona virus and aids in its multiplication is highly expressed in lungs. These genes impact severity of Covid-19.

Yet another study done in Cleveland (USA) by Hou et al. concludes that ACE2 or Trans membrane serine protease TMPRSS2, DNA polymorphisms were likely associated with genetic susceptibility of Corona virus. Change in ACE 2 gene was also found to be associated with cardiovascular and pulmonary conditions. These conditions are by altering the angiotensinogen (AGT)-ACE2 interactions. The localization of ACE2 to the X chromosome may also help explain the increased risk of COVID-19 to males compared to females. ACE2 receptors are also found in other vital organs like heart, kidney and Stomach. This explains multi organ failure as an important cause of mortality in severe COVID-19 patients.

In addition to genetic factors non-genetic factors like age, medical conditions, and environmental factors like air pollution, are likely to contribute to differing susceptibility to COVID-19.

Still, which and to what extent genetic factors are involved remains unclear. Most of the studies mentioned above have many limitations. The precautions taken by individuals, precautions taken by country for prevention of the disease and the viral load also play a significant importance in the virulence of COVID-19. So much is yet to be known.

CONCLUSION

We can conclude that some people with particular gene have been protected by the virus however some people have the opposite. The findings are the interpretations of various studies conducted outside Nepal. In Nepal the study are very rare. However we can learn from the studies of abroad. We never know who have those particular sets of gene so we all have to be cautious and at least follow the basic health protocol that is needed against the virus.

REFERENCES


