**Genetic variation in the virus**

**[Khalid Munir, Isra Munir and M. Akram Muneer](https://nation.com.pk/Columnist/khalid-munir-isra-munir-and-m-akram-muneer)**

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A new Coronavirus disease was reported to the World Health Organisation (WHO) on December 31, 2019. It is referred to as Covid-19 and is primarily caused by severe respiratory syndrome coronavirus 2 (SARS-CoV-2). Recently a new strain of it was reported in the United Kingdom (UK). Coronaviruses contain large RNA genomes with limited proof-reading ability and, like many other RNA viruses, they acquire random mutations over time. Although the mutation rate in SARS-CoV-2 is less than that of influenza-A viruses, this virus is acquiring approximately one mutation in its genome every two weeks.

Many mutations are silent and do not affect the function and structure of viral proteins. Some, however, may be non-silent and impact viral protein structure and function. The critical concept among ‘corona-virologists’ is that human coronaviruses are non-pathogenic in their natural reservoir hosts but become pathogenic after their transmission to a new host species. With further evolution, the viruses adapt to the new host and tend to become more transmissible and less pathogenic or virulent over time. Virulence is the disease-producing power of the virus, whereas pathogenicity is the potential ability of the virus to produce disease in the susceptible host population. Therefore, it is possible that a progenitor of SARS-CoV-2 jumped from bats through pangolins, and perhaps another unknown intermediate host, and into humans. From there, it adapted from the more pathogenic strain to a more transmissible viral strain which is responsible for the current pandemic.

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It is important to note that SARS-CoV-2 shows less pathogenicity than SARS-CoV-1 and MERS-CoV. Viruses such as SARS-CoV-2 aim to attain a point of equilibrium with their host and become endemic without causing high mortality in the susceptible host population. SARS-CoV-2 in humans is likely to continue evolving on these lines and become adapted further to humans to become less pathogenic or virulent.

Since early December 2020, a new variant strain of the SARS-Cov-2 virus, known as SARS-Cov-2 VUI 2020120/01 or B117, is spreading rapidly in London and the south-eastern region of the UK. The emergence of a variant strain containing at least one mutation identical to the UK strain has also been detected in South Africa. The UK variant has been associated with higher transmission rates, meaning it spreads more quickly among humans, as compared to the South African variant and other previously identified strains. However, there have been no links between the new variant strain and enhanced pathogenicity. The new variant, reported in the UK, has accounted for more than 60% of London’s recent infections. The presence of this SARS-CoV-2 variant has also been confirmed very recently in Ottawa and some areas of the Ontario Province of Canada. The concern is that this virus variant strain might have already spread to other regions due to ongoing travel between the UK and other countries.

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Scientists and researchers are working to sequence the genomes of SARS-CoV-2 isolates from millions of cases. The current knowledge is that the UK variant strain of SARS-CoV-2 contains many mutations in its genome. The projections based on structural modelling, considering the mutations associated with the viral Spike protein and it’s Receptor-Binding Domain (RBD), have several important implications. First, they may lead to more effective binding of RBD of the Spike protein to the Angiotensin-Converting Enzyme (ACE2) receptor on host cells.

Second, the mutation near the furin cleavage site of the Spike protein may lead to a conformational change in the Spike protein leading to high infectivity of the virus. These mutation-induced enhanced functions may increase SARS-COV-2 variant strain’s transmissibility. They may also change the ability of the virus to cause disease among humans either positively or negatively—they may result in a silent infection, a milder or more severe disease.

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Third, these mutations may give the variant strain the ability to evade vaccine-induced immune responses. The consequence of such immune evasion could be potentially devastating as the population starts to get vaccinated and builds immunity, which could theoretically be destroyed by the emergence of ‘escape mutants’. However, mutations in the Spike protein of the UK variant strain account for about one percent of amino acid sequence change. Thus, viral evasion of the vaccine-induced immunity is less likely because antibody-mediated immunity produced by the Covid-19 vaccines approved so far would be polyclonal. Polyclonal antibodies are a heterogeneous mixture that are usually made by different B lymphocyte-clones in the body. They can recognise and bind to many different epitopes (part of an antigen molecule to which an antibody attaches) present on a single antigen. In other words, antibodies target various epitopes on the Spike protein of SARS-CoV-2. Additionally, the local immunity and the cell-mediated component of the adaptive immune responses would also play a role in conferring protective immunity to individuals vaccinated against SARS-CoV-2.

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Fourth, mutations may make the variant strain less prone to therapy with certain monoclonal antibodies.

Finally, the variant strain may not be accurately detectable by the diagnostic tests specifically developed for the parental or original strain of SARS-CoV-2.

Presently, it is not conclusively known how significantly these mutations affect the clinical or epidemiological manifestations of Covid-19. The projections based on structural modelling are sometimes not entirely correct. They require confirmation through further studies in humans or animal models. The characterisation of mutations in various viral genes is vital not only for understanding the viral drug resistance, immune evasion, and disease development mechanisms but also for developing effective vaccines, antiviral drugs, and diagnostic assays.

Thus, more research is needed to decisively link the genetic makeup of different variants of the virus with the severity and presentation of disease in patients infected with SARS-CoV-2, and fathom differences in transmissibility or virulence caused by mutations in various SARS-CoV-2 genes. The type of mutations in SARS-CoV-2 that allow for human infection, transmission, and the impact of these viral mutations on specific vaccines’ long-term efficacy requires further investigations. Moreover, the relatively rapid changing genetic makeup of the virus may limit the efficacy of newly developed vaccines with time. As more mutations emerge in SARS-CoV-2 over time, the COVID-19 vaccines may need to be updated to match them with the circulating field strain. This also happens with seasonal flu or influenza virus in the UK and USA and some other countries. This virus accumulates mutations throughout the year, and the antigen in the flu vaccine is adjusted accordingly every year or so. It is important to note that the US has confirmed its first case of UK COVID-19 variant strain earlier in a 20-year-old patient in the state of Colorado. Pakistan has also reported its first case of UK COVID-19 variant strain just recently.

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