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Antiviral drug for COVID-19 infections linked to SARS-CoV-2 mutations

Researchers at the University of Cape Town (UCT) were part of a collaboration that has uncovered a link between an antiviral drug for COVID-19 infections called molnupiravir and a pattern of mutations in the SARS-CoV-2 virus.

Other researchers who formed part of the group were from Francis Crick Institute, University of Cambridge, Imperial College London, University of Liverpool and UK Health Security Agency

Molnupiravir works by inducing mutations in the virus's genetic information, or genome, during replication. Many of these mutations will damage or kill the virus, reducing viral load in the body. It was one of the first antivirals available on the market during the COVID-19 pandemic and was widely adopted by many countries.

In research published in *Nature* on Monday, 25 September, the scientists used global sequencing databases to map mutations in the SARS-CoV-2 virus over time. They analysed a family tree of 15 million SARS-CoV-2 sequences so that at each point in each virus's evolutionary history they could see which mutations had occurred.

Although viruses mutate all the time, the researchers identified mutational events in the global sequencing database, which looked very different from typical patterns of COVID-19 mutations and were strongly associated with individuals who had taken molnupiravir.

These mutations increased in 2022, coinciding with the introduction of molnupiravir. They were also more likely to be seen in older age groups, consistent with the use of the antivirals to treat people who are more at risk, and in countries known to have high molnupiravir use. In England, the researchers analysed treatment data and found that at least 30% of the events involved the use of molnupiravir.

The causes of mutational events can be traced by looking at their 'mutational signature': a preference for mutations to occur at particular sequences in the genome. The researchers found a close match between the signature seen in these mutational events and the signature in clinical trials of molnupiravir.

The researchers also saw small clusters of mutations, suggesting onward transmission from one person to another, although no established concern variants are currently linked to this signature.

Ryan Hisner, a master's student in bioinformatics at UCT, said: "Our findings show that molnupiravir creates genetically divergent viruses capable not only of replicating but transmitting, with unknown consequences for the global public. This should have been of greater concern when molnupiravir was tested in clinical trials, and now that we have this evidence, regulators need to be proactive in monitoring virus sequencing databases for the effects of drugs that work by mutagenesis."

Understanding the impact of molnupiravir treatment on the risks of new variants, and any impact they might have on public health, is difficult. It is also important to consider that chronic COVID-19 infections, which molnupiravir is used for, can themselves result in new mutations.

Theo Sanderson, lead author and postdoctoral researcher at the Francis Crick Institute, said: "COVID-19 is still having a major effect on human health, and some people have difficulty clearing the virus, so it's important we develop drugs that aim to cut short the length of infection. But our evidence shows that a specific antiviral drug, molnupiravir, also results in new mutations, increasing the genetic diversity in the surviving viral population."

"Our findings are useful for ongoing assessment of the risks and benefits of molnupiravir treatment. The possibility of persistent antiviral-induced mutations needs to be taken into account for the development of new drugs which work in a similar way. Our work shows that the unprecedented size of post-pandemic sequence datasets, collaboratively built by thousands of researchers and healthcare workers around the world, creates huge power to reveal insights into virus evolution that would not be possible from analysis of data from any individual country.'"

Christopher Ruis from the Department of Medicine at the University of Cambridge shared: "Molnupiravir is one of a number of drugs being used to fight COVID-19. It belongs to a class of drugs that can cause the virus to mutate so much that it is fatally weakened. But what we've found is that in some patients, this process doesn't kill all the viruses, and some mutated viruses can spread. This is important to take into account when assessing the overall benefits and risks of molnupiravir and similar drugs."

Read the paper.

ENDS

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