CORONAVIRUS VARIANTS ABOUND IN THE US — BUT THE THREAT IS UNCLEAR

Ramped-up sequencing spots mutations that might boost contagion or help virus evade immune system.

By Ewen Callaway

Despite having world-leading genome-sequencing infrastructure and experiencing more COVID-19 infections than any other country, the United States has lagged far behind in sequencing coronavirus genomes and spotting worrying variants.

But, in recent weeks, US researchers have identified a host of new variants (see 'US sequencing ramps up'). That has brought another challenge: making sense of the variants that are discovered. They carry potentially troubling mutations and might be becoming more common, but a dearth of data on how they are spreading means that the threat they pose is unclear.

"It's a Wild West," says Jeremy Kamil, a virologist at Louisiana State University in Shreveport who co-led a team that, last month, spotted a fast-rising variant in Louisiana, New Mexico and elsewhere. In the absence of clear data on a variant's behaviour, "it's as if there's an unofficial policy that every variant is a variant of concern until proven otherwise", says Kamil.

Part of the challenge is the decentralized nature of US sequencing and surveillance efforts. "Right now it's individual labs or states or cities doing their part," says David Ho, a virologist at Columbia University in New York City, whose team last week identified a variant in the city with a mutation that could compromise immune responses. States such as New York, California and Washington have contributed thousands of sequences each, while others such as Iowa, Tennessee and New Hampshire have obtained many fewer.

Ho and other US researchers look enviously at the United Kingdom, where a nationwide sequencing effort — which works closely with public-health, medical and research institutions — has generated more than 300,000 coronavirus genomes. Thanks to the fine granularity of its data, the UK effort showed in late 2020 that the variant called B.1.1.7 clearly spread faster than other circulating strains; research has since suggested that B.1.1.7 might be deadlier, but does not compromise vaccines.

"I don't think we have anything like that," says Ho. He hopes that the US National Institutes of Health and the Centers for Disease Control and Prevention (CDC), the federal agencies responsible for biomedical research and public health, "will get the country moving in a more concerted fashion". A CDC-led effort launched in November aims to sequence around 7,000 samples per week — a goal met for the first time in late February — and eventually 25,000.

Worrying mutations

In the absence of clear-cut epidemiological or medical data, scientists can gauge some of a variant's potential threat by the mutations it carries. Researchers have drawn up a growing list of mutations that might boost transmission or help a virus to evade immune responses.

The variant that Ho's team identified in New York, also known as B.1.526, carries a notorious mutation called E484K that has been identified in South Africa and Brazil. Studies by multiple laboratories have shown that E484K — a change in a portion of the coronavirus's 'spike' protein that recognizes host cells — weakens the potency of antibodies that can ordinarily disable the virus. That could help to explain observations that similar variants in South Africa and Brazil are behind cases of reinfection and reduced vaccine efficacy in field trials.

On the basis of those concerns, a team led by Ho and Columbia University microbiologist Anne-Catrin Uhlemann set up a surveillance network to identify viruses carrying E484K in New York City. Pamela Bjorkman and Anthony West, structural biologists at the California Institute of Technology in Pasadena, spotted it in public sequencing data from New York.

Ho concedes that B.1.526 needs much more study. It has not yet been shown to dodge immune responses and its apparent rise in frequency might be unrelated to any biological property. "It's taken months for the UK variant [B.1.1.7] to be shown to be more transmissible and more virulent. I think we would need to do the same," he says.

Rarer variants

Beefed-up US sequencing efforts are turning up variants with new or rarely seen mutations that are harder to make sense of. Kamil teamed up with researchers in New Mexico because they had also observed a variant bearing a mutation called Q677P, which they hadn't seen before. It sits near a region of the spike protein that needs to snap in two to allow the viral particle to enter a host cell. Mutations in this region occur in fast-spreading variants such as B.1.1.7, but Kamil says the variant is, for now, one to watch rather than worry over.

Last week, researchers in California raised a red flag over variants that carry a spike-protein mutation called L452R (J. Peng *et al*. Preprint at medRxiv https://doi.org/fx87; 2021). A team at the University of California, San Francisco (UCSF), found that a variant with the mutation was rising rapidly in one city neighbourhood. Another UCSF team reportedly found, in lab tests, that a variant with the mutation was more infectious and less susceptible to antibodies.

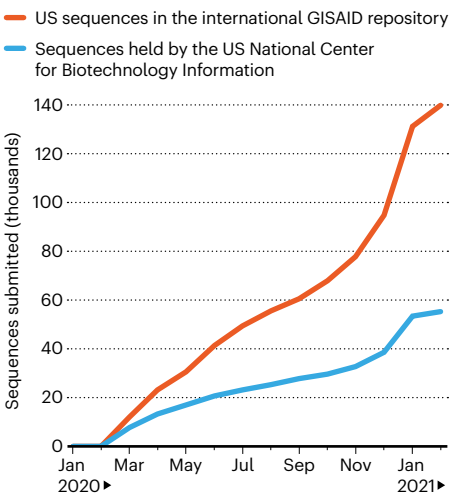
But many researchers have expressed scepticism about the significance of the L452R variants. The mutation hasn't turned up in lab studies that have flagged several other worrisome changes, such as E484K, and the same L452R mutation has popped up elsewhere in the United States and not grown rapidly, says Jeffrey Barrett, a statistical geneticist at the Wellcome Sanger Institute in Hinxton, UK. "It's probably not going to be one of these ones that is fundamentally problematic," he says.

So far, researchers in the United States have uncovered only a handful of cases linked to immune-evading variants identified in South Africa and Brazil. But cases of the B.1.1.7 variant identified in the United Kingdom are rising steadily — a pattern repeated in other countries in Europe and the Middle East.

Which of these variants will predominate is anyone's guess, say researchers, but as vaccination coverage increases, susceptible variants such as B.1.1.7 could dwindle, whereas those that can partly evade immunity might spark regional flare-ups. "I don't think we're going to have years of 'New York variants' and 'California variants'," says Barrett. Working out what is happening will depend not only on sequencing more samples, but also on building the capacity to understand them. "The US must do a better job along these lines," says Ho.

US SEQUENCING RAMPS UP

Since November 2020, the number of SARS-CoV-2 sequences submitted to open-access repositories by US laboratories has grown significantly.



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