through extensive recombination — in which viruses swap chunks of RNA with each other — or the sequences are the result of contamination in the lab. Richard Neher, a computational biologist at the University of Basel in Switzerland, thinks that recombination is unlikely and not consistent with what has been observed in the evolution of SARS-CoV-2 so far.

An alternative explanation that needs further investigation is that samples containing very small amounts of Delta variant were contaminated with Omicron, says Darren Martin, a computational biologist at the University of Cape Town in South Africa.

"I consider this the more likely explanation," says Neher. "Given how rapidly Omicron spread once it entered the general population, it is unlikely that it had circulated for several months undetected" across Africa.

Drexler says he and his team used several techniques to ensure their sequencing was as robust as possible. He says they are now re-checking their data carefully. "Should there have been a mistake despite all our precautions, we will handle this appropriately, of course."

Several researchers have requested detailed sequencing data from the paper's authors, and many are withholding judgement until they have interrogated the raw data. Drexler says they are preparing to upload those data to a public repository.

SCIENTISTS WELCOME $3.5-MILLION DRUG — BUT QUESTIONS REMAIN

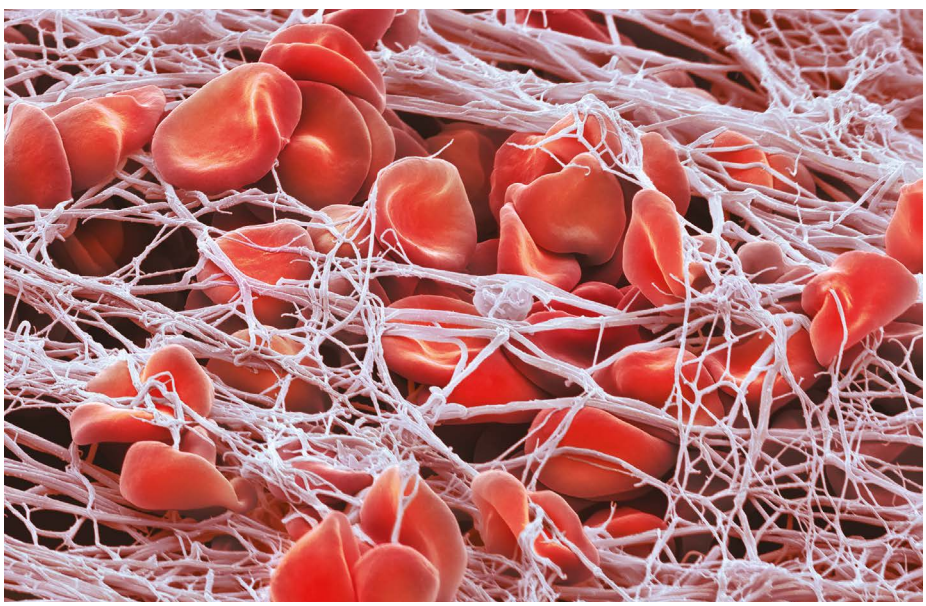
Haemophilia gene therapy could save lives. But it cannot treat the most common form of the disease.

By Miryam Naddaf

On 22 November, the US Food and Drug Administration (FDA) approved the first gene therapy for the genetic blood-clotting disorder haemophilia B — a one-time treatment that costs US$3.5 million.

Hemgenix — developed by the pharmaceutical company CSL Behring, based in King of Prussia, Pennsylvania — uses a modified virus to deliver a gene to the recipient's liver cells. The gene codes for a protein involved in blood clotting called factor IX, which people with the disease are unable to produce.

Clinical trial data suggest that the single dose of Hemgenix will provide people with moderate to severe haemophilia B with adequate protection from uncontrolled bleeding for eight years, and potentially longer.



Haemophilia is a genetic condition that affects the formation of blood clots (pictured).

STEVE GSCHMEISSNER/SPL

But the treatment's hefty price tag makes it the most expensive drug in the world. And gene-replacement therapies for the most common form of haemophilia remain elusive.

Significant savings

CSL Behring says the cost is justified. In a statement, the company said that even at a cost of $3.5 million, Hemgenix could save the US health-care system $5 million to $5.8 million per person treated, because of its proven effectiveness at decreasing or eliminating the need for regular injections of factor IX. People with haemophilia B are currently given factor IX once or twice a week. The protein is required to form blood clots, but people with the disease lack the gene required to make it in sufficient quantities. If the condition is left untreated, people experience uncontrolled bleeding that can be life-threatening.

"Living with haemophilia is all about where one is born," says Glenn Pierce, vice-president of the World Federation of Hemophilia in Montreal, Canada. "In the United States, the treatment of an adult with haemophilia B averages $700,000–800,000 per year. The high price of Hemgenix will pay for itself in a relatively short time, assuming it lasts."

But scientists worry that the price will not be affordable in low- and middle-income countries, where most people with haemophilia live and where supplies of treatments and factor IX are often insufficient. "As new technologies such as gene therapy emerge on the scene, those who would benefit most can least afford to pay. We cannot leave the majority of the world behind," says Pierce. CSL Behring declined to comment on the drug's pricing beyond its public statement.

Promising results

The latest clinical trial of Hemgenix, which included 54 people with haemophilia B, reported a 54% reduction in the number of bleeding episodes per year, with 94% of participants discontinuing any prophylactic therapy within two years of receiving the single dose. "The patients start making factor IX very quickly … in seven to eight months after the single dose, for nearly all patients, the level of factor IX had stabilized," says Andrew Nash, CSL Behring's chief scientific officer.

Even the lowest response in the clinical trial, a 10% increase in factor IX levels, is sufficient to prevent spontaneous bleeding. But patients might require top-up treatments after injuries, or if they're having major surgery.

"If you're in the 10–40% range, you could still get a problem with major trauma or surgery. But you can pretty much forget about haemophilia," says Edward Tuddenham, a consultant haematologist at University College London and part of the research group that designed the viral vector that CSL Behring licensed.

Tuddenham and his colleagues, in an

eight-year follow-up study of a clinical trial of a similar drug for haemophilia B, showed that there are good reasons to consider gene therapies a stable and durable treatment (A. C. Nathwani *et al. Blood* **132** (S1), 491; 2018).

"The approval of Hemgenix is a key milestone on the road to a cure, and it appears likely some recipients will indeed be cured for many years," says Pierce.

Immunity issues

The FDA's approval highlights difficulties in the quest to develop gene therapies for haemophilia more generally. Only 15% of people with haemophilia have haemophilia B. Most have haemophilia A, caused by a deficiency in a different blood-clotting protein called factor VIII, which is encoded by a different gene.

Finding an effective gene therapy for haemophilia A has proved challenging, because a greater increase in factor VIII production is needed to get a good therapeutic effect, and some clinical trial participants have shown strong immune responses to the viral vector used to deliver the gene.

"In haemophilia A, there is an obvious waning off with time and [the gene expression] may only last for eight years," says Michael Makris, who studies haemostasis and thrombosis at Sheffield University, UK. "Once you have adeno-associated viral gene therapy, you make antibodies to the [viral] vector, so you cannot have it again."

On 24 August, the European Medicine Agency approved a gene therapy for haemophilia A by BioMarin Pharmaceutical, based in San Rafael, California. After rejecting their first application, the FDA is now considering BioMarin's resubmission.

"Gene therapy — while exciting and promising — should not be considered lightly," says Leonard Valentino, a former haemotologist who is chief executive of the US National Hemophilia Foundation in New York City. "With any life altering decision, there can be positive and negative effects."

SEVERE COVID COULD CAUSE MARKERS OF OLD AGE IN THE BRAIN

Key genes are active in the brains of both older people and people with serious COVID-19.

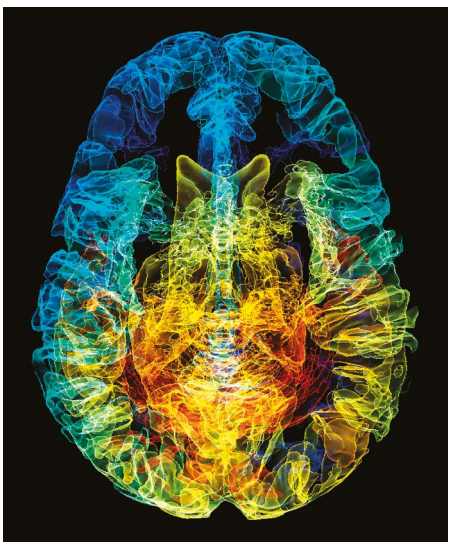
By Heidi Ledford

Severe COVID-19 is linked to changes in the brain that mirror those seen in old age, according to an analysis of dozens of post-mortem brain samples[1].

The analysis revealed changes in gene activity in the brain that were more extensive in people who had had severe SARS-CoV-2 infections than in uninfected people who had been in an intensive care unit (ICU) or put on ventilators to assist their breathing — treatments used in many people with serious COVID-19.

The study, published on 5 December in *Nature Aging*, joins a bevy of publications cataloguing the effects of COVID-19 on the brain. "It opens a plethora of questions that are important, not only for understanding the disease, but to prepare society for what the consequences of the pandemic might be," says neuropathologist Marianna Bugiani at Amsterdam University Medical Centers. "And these consequences might not be clear for years."

Maria Mavrikaki, a neurobiologist at the Beth Israel Deaconess Medical Center in Boston, Massachusetts, embarked on the study after seeing a preprint, later published as a paper[2], that described cognitive decline after COVID-19. She decided to look for changes in the brain that might trigger the effects.



K. H. FUNG/SPL

A human brain (artificially coloured).

She and her colleagues studied samples taken from the frontal cortex — a region of the brain closely tied to cognition — of 21 people who had severe COVID-19 when they died and one person with an asymptomatic SARS-CoV-2 infection at death. The team compared these with samples from 22 people with no known history of SARS-CoV-2 infection. Another control group comprised nine people who had no known history of infection but had spent time on a ventilator or in an ICU — interventions that can cause serious side effects.

The team found that genes associated with inflammation and stress were more active in the brains of people who had had severe COVID-19 than in the brains of people in the control group. Conversely, genes linked to cognition and the formation of connections between brain cells were less active.

The scientists also analysed brain tissue from 20 further uninfected people: 10 who were 38 years old or younger at death, and 10 who were 71 or older. A comparison revealed that people in the older group had brain changes that were similar to those seen in people with severe COVID-19.

The work needs to be confirmed, says Daniel Martins-de-Souza, head of proteomics at the University of Campinas in Brazil. But it is informative, he says, and such research could guide treatment for people who have lingering cognitive difficulties after COVID-19.

Inflammatory effect

Mavrikaki suspects that COVID-19's effects on gene activity are caused indirectly, by inflammation, rather than by viral infiltration of the brain. Supporting this interpretation, she and her colleagues found that exposing laboratory-cultured neurons to proteins that promote inflammation affected the activity of a subset of the ageing-related genes.

But it's possible that other infections might trigger this response, she says. And the study could not fully control for obesity or other conditions that might both increase a person's chances of developing severe COVID-19 and generate an inflammatory state that affects gene expression in the brain.

Another key question is whether the gene-expression changes can be caused by milder disease as well as by severe infections, says Bugiani. In March, a study[3] of hundreds of brain images collected by the UK Biobank found that even mild disease could cause changes in the brain.

It will take time to determine whether the changes observed in the study are transient, Bugiani says. "The duration of the pandemic has now been long enough to see these things, but not long enough to establish if they are permanent," she says. "We don't yet know what their real consequences will be."

1. Mavrikaki, M., Lee, J. D., Solomon, I. H. & Slack, F. J. *Nature Aging* https://doi.org/10.1038/s43587-022-00321-w (2022).
2. Hampshire, A. *et al. eClinicalMedicine* **39**, 101044 (2021).
3. Douaud, G. *et al. Nature* **604**, 697–707 (2022).