Researchers link death in gene-editing study to a virus used to deliver the treatment, not CRISPR

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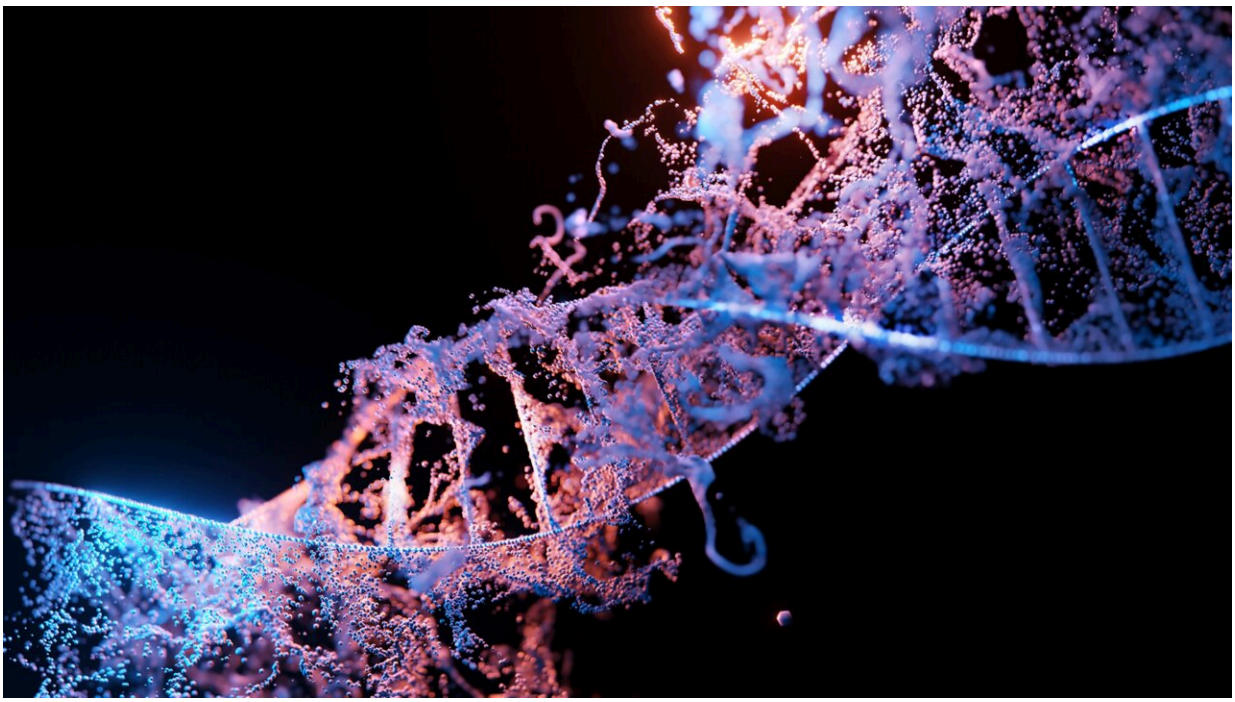

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The lone volunteer in a gene-editing study targeting a rare form of Duchenne muscular dystrophy likely died after having a reaction to the virus that delivered the therapy in his body, researchers concluded in an early study.

Terry Horgan, 27, of Montour Falls, New York, died last year during one of the first tests of a gene-editing treatment designed for one person. Some scientists wondered if the gene-editing tool CRISPR played a part in his death. The tool has transformed genetic research, sparked the development of dozens of experimental drugs, and won its inventors the Nobel Prize in 2020.

But researchers said the virus—one used to carry treatment into the body because it doesn't usually make people sick—combined with his condition, triggered the problems that ultimately killed him.

Horgan appears to have had a more severe immune reaction "than others receiving similar or slightly higher doses" of the virus, the authors wrote in the study, which has not yet been peer-reviewed.

Horgan was enrolled in an early-stage safety trial approved by the Food and Drug Administration. It was sponsored by Cure Rare Disease, a Connecticut-based nonprofit founded by his brother, Rich, to try and save him from the muscle-wasting disease caused by a mutation in the gene needed to produce a protein called dystrophin.

In a statement, Rich Horgan thanked the research team led by the University of Massachusetts Chan Medical School and Yale University for a "thorough, comprehensive" investigation that provided valuable insights. He added, "On a personal note, this study is another important step toward honoring Terry's legacy and his commitment, as well as our entire family's, to the rare disease community."

The therapy Horgan got aimed to use CRISPR to increase a form of the dystrophin protein. The process began with suppressing Horgan's immune system to prepare his body for the therapy, which was delivered by IV with "a high dose" of what's known as an adeno-associated viral vector, or AAV, according to Cure Rare Disease.

But Horgan soon began experiencing problems, went into cardiac arrest six days after the treatment and died two days later from organ failure and brain damage. Because of the timing of symptoms, and the fact researchers could find little of a gene-editing enzyme in his body, they concluded that the therapy hadn't been activated yet.

This isn't the first time viral vectors have been implicated in a gene therapy trial death. In a major setback for the field, 18-year-old Jesse Gelsinger died in 1999 during a study aimed at combatting his rare metabolic disease. Scientists later learned that his immune system overreacted to the virus used to carry the treatment. The virus used in Horgan's trial is considered safer but it is not without problems.

"People have been trying to make safer vectors … but they still remain challenging," said Arthur Caplan, a medical ethicist at New York University who was not involved in the study but has followed the case closely. "We don't really understand why some people run into trouble and others don't. We don't know whether it's their underlying disease, some co-morbidity, or some strange immunology."

Rich Horgan said they plan to submit the study to a peer-reviewed journal. Meanwhile, Cure Rare Disease said it will use alternative viruses for the other treatments it is trying to develop.

Dr. Terence Flotte, dean of the UMass medical school and senior author of the study, said he hopes it leads "to further research into how to identify subsets of patients who might be prone to severe, unexpected reactions like this."

More information: Angela Lek et al, Unexpected Death of a Duchenne Muscular Dystrophy Patient in an N-of-1 Trial of rAAV9-delivered CRISPR-transactivator, *medRxiv* (2023). DOI: 10.1101/2023.05.16.23289881