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Mutated DNA Restored to Normal in Gene Therapy Advance

The small study in patients with a rare disorder that causes liver and lung damage showed the potential for precisely targeted infusions.

By Gina Kolata

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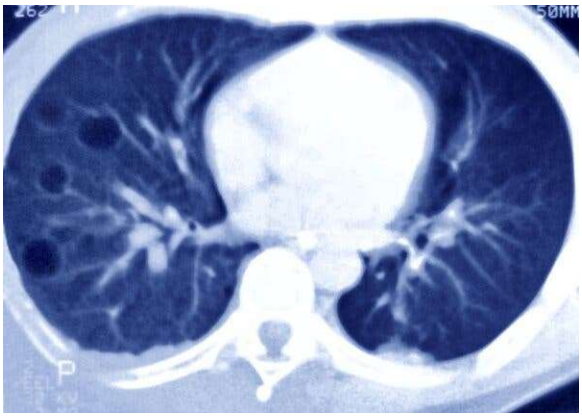

People with the condition AATD are prone to developing emphysema in their lungs, as shown in the scan above. A new gene therapy corrected the genetic mutation that drives AATD.Credit...

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Researchers have corrected a disease-causing gene mutation with a single infusion carrying a treatment that precisely targeted the errant gene.

This was the first time a mutated gene has been restored to normal.

The small study of nine patients announced Monday by the company Beam Therapeutics of Cambridge, Mass., involved fixing a spelling error involving the four base sequences — G, A, C and T — in DNA. The effect was to change an incorrect DNA letter to the right one. The result was a normal gene that functioned as it should, potentially halting liver and lung damage of patients with a rare disorder.

“This is the beginning of a new era of medicine,” said Dr. Kiran Musunuru, a gene therapy researcher at the University of Pennsylvania’s Perelman School of Medicine.

He added that the method offers the hope of treating other genetic diseases precisely by fixing mutations — an alternative to current gene therapies, which either add new genes to compensate for mutated ones, or slicing DNA to silence genes.

Dr. Musunuru is a co-founder and equity holder of Verve Therapeutics, a gene therapy company, and receives funding from Beam Therapeutics for research, but not for this study.

Dr. Richard P. Lifton, president of Rockefeller University and head of its Laboratory of Human Genetics and Genomics, said the sort of gene editing Beam did, rewriting genes with an infusion, “is a holy grail” that “has the promise for being a one-and-done kind of therapy.”

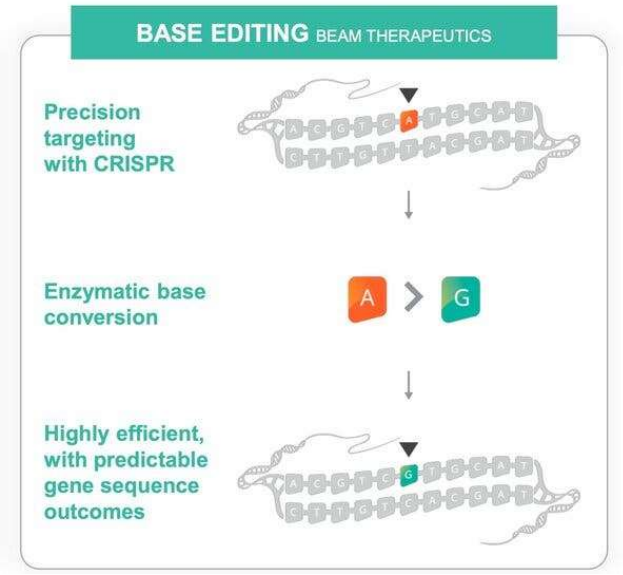
Dr. Lifton is a director of Roche Pharmaceuticals and its subsidiary Genentech.

Despite the study’s small size, he said the results are “a very impressive advance and very promising.”

The study involved patients who have alpha-1 antitrypsin deficiency, or AATD, a genetic disease that affects an estimated 100,000 Americans, mostly of European ancestry. That makes it as common as sickle cell in this country. It is progressive and incurable.

The alpha-1 antitrypsin protein is made in the liver and normally goes to the lungs and protects them from inflammation from inhaled irritants like smoke or dust. But in people with the disease, a single change in a DNA letter in the gene results in a misshapen and nonfunctional protein. The result is often emphysema or chronic obstructive pulmonary disease in unprotected lungs.

Image



Base editing, which corrects misspellings in DNA, offers an alternative to existing forms of gene therapy, which either add or remove things from the genome.

But many of the aberrant alpha-1 antitrypsin proteins never get to the lungs and instead build up in patients' livers, often causing cirrhosis.

The gene editing was simple for patients. They sat in a chair for a couple of hours while lipid nanoparticles, like those used in Covid vaccines, were infused into their blood. The nanoparticles did not hold vaccines, though. Instead, they encased a microscopic gene editor. The lipid casing protected the editor on a journey to the liver.

When the nanoparticles reached the liver, the lipid layer peeled off, releasing the editor — a disabled CRISPR molecule that acted like a GPS for the genome and an enzyme to fix the mutation. The CRISPR molecule crawled along the patient's DNA until it found the one incorrect letter that needed to be repaired among the three billion DNA letters in the genome. Then the editing enzyme replaced that letter with the correct one.

The study divided the patients into three groups and tested three different doses of the gene editor. Those who got the highest dose made enough normal alpha-1 antitrypsin to be in a range where no more damage should occur. There were no serious side effects, said John Evans, Beam's chief executive officer.

Beam will now be offering the higher dose to the patients who got the lower doses in the company's study. Beam will also study the treatment in more patients, and test an even higher dose of its gene editor.

"And then we immediately have to think about how we can get this approved," Mr. Evans said.