

CRISPR-Cas9 Editing Can Cause Unexpected Mutations, Researchers Say

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As CRISPR-Cas9 gene editing starts to move into clinical trials, a research team led by scientists at Columbia University Medical Center has found that this technology can introduce hundreds of unintended mutations into the genome.



CRISPR-Cas9 gene editing can cause hundreds of unintended mutations. Image credit: Lisichik.

CRISPR-Cas9 editing technology has been a boon for scientists trying to understand the role of genes in disease.

The technique has also raised hope for more powerful gene therapies that can delete or repair flawed genes, not just add new genes.

The first clinical trial to deploy CRISPR-Cas9 is now underway in China, and a trial in the United States is slated to start next year.

But even though CRISPR-Cas9 can precisely target specific stretches of DNA, it sometimes hits other parts of the genome.

Most studies that search for these off-target mutations use computer algorithms to identify areas most likely to be affected and then examine those areas for deletions and insertions.

“These predictive algorithms seem to do a good job when CRISPR-Cas9 is performed in cells or tissues in a dish, but whole genome sequencing has not been employed to look for all off-target effects in living animals,” said Prof. Alexander Bassuk, from the University of Iowa.

In the new study, Prof. Bassuk and his colleagues sequenced the entire genome of mice that had undergone CRISPR-Cas9 gene editing in the team’s previous study and looked for all mutations, including those that only altered a single nucleotide.

The scientists determined that CRISPR-Cas9 had successfully

corrected a gene that causes blindness, but they also found that the genomes of two independent gene therapy recipients had sustained more than 1,500 single-nucleotide mutations and more than 100 larger deletions and insertions.

None of these DNA mutations were predicted by computer algorithms that are widely used by researchers to look for off-target effects.

“Researchers who aren’t using whole genome sequencing to find off-target effects may be missing potentially important mutations. Even a single nucleotide change can have a huge impact,” said [Prof. Stephen Tsang](#), from [Columbia University Medical Center](#) and Columbia’s Institute of Genomic Medicine and the Institute of Human Nutrition.

“We’re still upbeat about CRISPR-Cas9. We’re physicians, and we know that every new therapy has some potential side effects — but we need to be aware of what they are,” said [Dr. Vinit Mahajan](#), of Stanford University.

Researchers are currently working to improve the components of the CRISPR-Cas9 system — its gene-cutting enzyme and the RNA that guides the enzyme to the right gene — to increase the efficiency of editing.

“We feel it’s critical that the scientific community consider the potential hazards of all off-target mutations caused by CRISPR-Cas9, including single nucleotide mutations and mutations in non-coding regions of the genome,” Prof. Tsang said.

“We hope our findings will encourage others to use whole-genome sequencing as a method to determine all the off-target effects of their

CRISPR-Cas9 techniques and study different versions for the safest, most accurate editing.”

The team’s findings will be published in an upcoming issue of the journal *Nature Methods*.