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Chromothripsis: Bad News for Gene Editing

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CRISPR gene editing is often presented as a straightforward, precise, and safe procedure. But recent research findings on CRISPR gene editing for gene therapy applications show it can lead to massive damage to chromosomes. The phenomenon is known as chromothripsis.

An article in Nature Biotechnology about the new findings describes chromothripsis as "an extremely damaging form of genomic rearrangement that results from the shattering of individual chromosomes and the subsequent rejoining of the pieces in a haphazard order".

And now there are signs that the findings are hitting gene editing companies' stock.

"You cannot make this go away"

The authors of the new study, published in Nature Genetics, conclude that "chromothripsis is a previously unappreciated on-target consequence" of the double-strand breaks in the DNA that CRISPR gene editing is designed to bring about. The fact that the damage occurs "on-target" – at the intended edit site – means that any attempts to target the CRISPR gene editing more precisely will not solve this problem, as pointed out in the Nature Biotechnology article by one of the researchers on the study, David Pellman of the Dana-Farber Cancer Institute and Harvard Medical School. He said, "You cannot make this go away by making the cutting more specific."

Cancer worries

The major worry with chromothripsis in therapeutic settings is that it can lead to cancer or an inherited disease in any children of the affected patient. It would only take a single cell to be affected by chromothripsis to result in a cancer.

This has implications for animal gene editing, as edited animals could be prone to cancer. But it also spells bad news for plant gene editing, where chromosomal damage would lead to changes in the function of genes that could in turn result in unexpected toxicity or

allergenicity, as well as unpredictable effects on wildlife.

Effect "cannot be completely avoided"

While an expert interviewed for the Nature Biotechnology article is upbeat about the ability of the gene editing field to "innovate its way around" this and any other problems that arise from CRISPR processes, the researchers on the original paper seem less convinced.

This is evident from the preprint version of their article, which appeared on BioRxiv before the peer-reviewed version was published in Nature Biotechnology. In the preprint version, the authors bluntly call chromothripsis "a catastrophic mutational process" and warn that it is "an on-target toxicity that may be minimized by cell manipulation protocols or screening but cannot be completely avoided in many genome editing applications".

However, this wording is absent from the final published version. The original downbeat conclusion on the impossibility of avoiding chromothripsis has been watered down to the bland statement, "As genome editing is implemented in the clinic, the potential for extensive chromosomal rearrangements should be considered and monitored."

Investors running scared

Others who remain unconvinced that this inherent problem of CRISPR can be solved may include investors in CRISPR-based companies. An article for the investment news outlet Seeking Alpha says that the "new data concerning chromothripsis may affect the long-term outlook of companies such as Crispr Therapeutics". The stock of these companies (collected in a fund known as ARKG), which was previously surging, suddenly slumped in July this year, the same month that the Nature Biotechnology study was published.

The Seeking Alpha article continues, "The long-term impact on health of gene editing may not be known until around 2040." It concludes, "Given the uncertain outlook, investors may be wise to re-evaluate their positions in companies employing DNA double strand breaks to edit the genome."

Seeking Alpha does not go so far as to blame the chromothripsis findings as the sole or main cause of ARKG's slump, but notes it as "one contributory factor".

Chromothripsis is just the latest in a long list of unintended CRISPR-induced outcomes that can occur at the intended edit site and thus cannot be avoided by improving CRISPR targeting. In spite of this, policymakers in the UK and the EU persist in echoing industry lobbyists' narratives that CRISPR gene editing is precise and the outcomes predictable.

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