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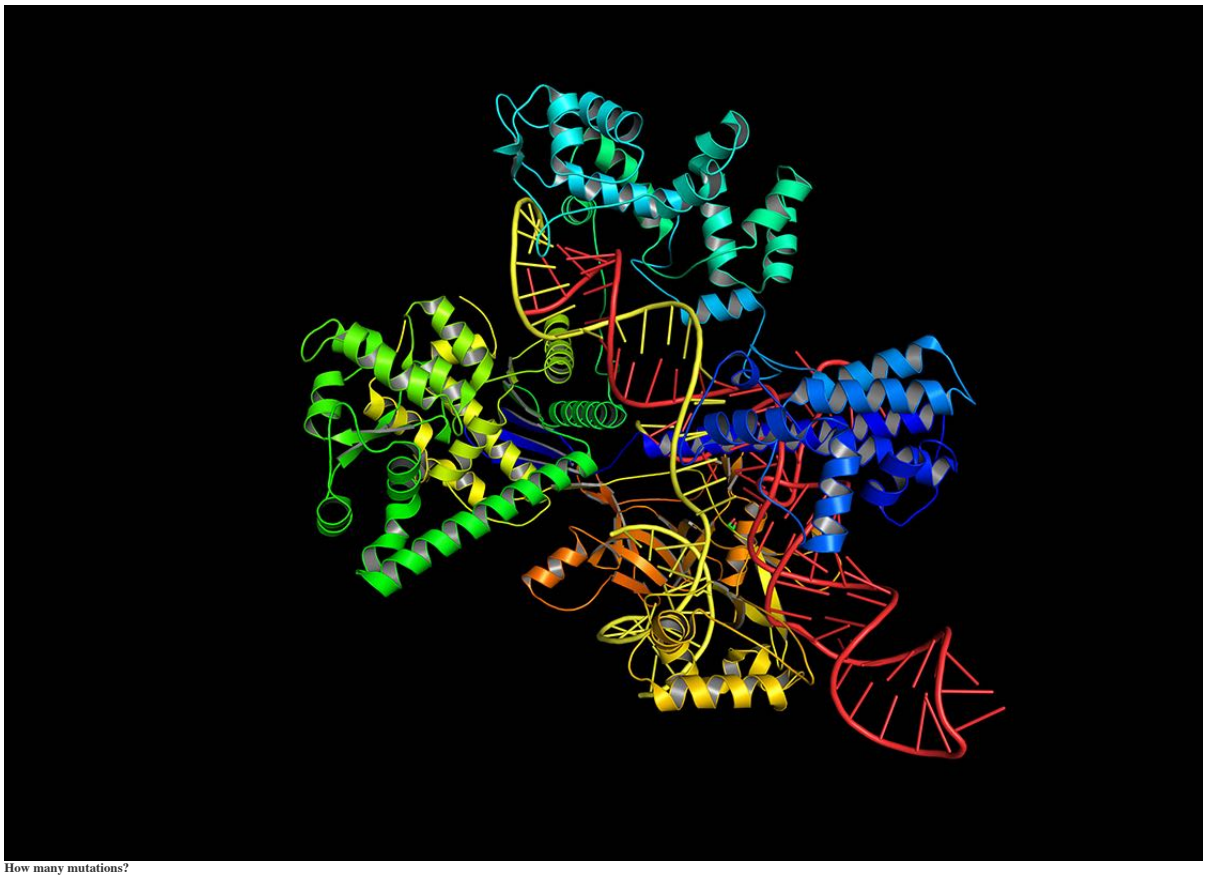
CRISPR gene editing technique is probably safe, study confirms



How many mutations?

By **Michael Le Page**

As you were. In May, a study claimed that the revolutionary CRISPR gene editing technique can cause thousands of unwanted and potentially dangerous mutations. The authors called for regulators to reassess the safety of the technique.

But doubts were raised about these claims from the very beginning, not least because it was a tiny study involving just three mice. Some critics have called for the paper to be withdrawn. Now a paper posted online on 5 July has proposed a simple and more plausible explanation for the controversial results. If it's right, the authors of the original study were wrong.

"We strongly encourage the authors to restate the title and conclusions of their original paper or provide properly controlled experiments that can adequately support their claims," write the team behind the new study. "Not doing so does a disservice to the field and leaves the misleading impression that the strong statements and recommendations found in their paper are adequately supported by the data presented."

Unwanted mutations

The aim of gene editing is to make a precise change in a DNA sequence while leaving the rest of the genome untouched. Gene editing can be used to introduce desirable changes into plants and animals (and perhaps people too one day), and to treat a range of disorders in people.

Gene editing has been around for decades but it remained extremely difficult and expensive until the revolutionary CRISPR technique was discovered in 2013. CRISPR is so cheap and easy that it is already widely used by researchers around the world, and nearly 20 clinical trials in people are already getting underway. The rapid pace of development has been unprecedented.

But have doctors been rushing to use it too soon? When Stephen Tsang of Columbia University Medical Center and colleagues compared the entire genomes of two CRISPR-edited mice with a third one, they found thousands of shared mutations in the two edited mice.

Tsang and co attributed to these mutations to CRISPR, and issued a widely-covered press release that suggested CRISPR is far riskier than dozens of other studies had suggested.

It has always been clear that CRISPR, like other gene-editing techniques, can sometimes make alterations other than the intended one. These "off-target" changes are most likely to occur when the CRISPR machinery binds to DNA sequences very similar to the target one.

Related mice

For this reason, studies on the safety of CRISPR have usually looked to see if any sequences resembling the target sequences have been altered. Most have found few unwanted changes, suggesting CRISPR is safe. And some teams have already tweaked the CRISPR machinery to reduce these off-targets effects even more.

Tsang and colleagues claimed that by sequencing the entire genome, they found off-target mutations missed by studies that only looked at sites resembling the target sequence. But there is a much simpler explanation, says the latest study: the two CRISPR-edited mice just happened to be more closely related and thus shared more mutations.

Tsang and colleagues assumed the three mice they studied were essentially genetically identical because their parents were very closely related, but the way the colony of mice was maintained means this was probably not the case, the team, which includes Luca Pinello of Harvard University, say.

This explanation makes sense for another reason, too. The shared mutations in the edited mice were nowhere near DNA sequences resembling the one were targeted for editing, Pinello and colleagues point out, so it's far from clear why CRISPR would cause mutations in these same sites in two different mice.

"I agree the two mice are indeed more likely to be closely related," says geneticist Gaetan Burgio of the Australian National University, one of the many critics of the original paper. He says its publication in a prominent journal was a failure of peer review.

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Read more: CRISPR causes many unwanted mutations, small study suggests