

POLICY & ETHICS

First CRISPR Babies: 6 Questions That Remain

Startling human-genome editing claim leaves many open questions, from He Jiankui's next move to the future of the field

By David Cyranoski, Nature magazine on December 2, 2018



Chinese Scientist He Jiankui. Credit: Anthony Kwan *Getty Images*

The meeting where He Jiankui explained his extraordinary claim to have helped produce the first babies—twin girls—born with edited genomes came to a close with a statement that came down hard on the scientist.

“We heard an unexpected and deeply disturbing claim that human embryos had been edited and implanted, resulting in a pregnancy and the birth of twins,” reads the statement released by the organizing committee of the Second International Summit on Human Genome Editing in Hong Kong on 29 November. “Even if the modifications are verified, the procedure was irresponsible and failed to conform with international norms.”

Similar criticism rained down since the revelation earlier this week that He had used the CRISPR–Cas9 to modify the CCR5 gene in two embryos, which he then implanted in a woman. The gene encodes a protein that many strains of HIV use to infect immune cells, in two embryos, which he then implanted in a woman.

As researchers take stock of the week’s events, *Nature* summarizes six big questions that are still unanswered.

1. IS HE JIANKUI IN TROUBLE?

.....

On 27 November, China’s national health ministry called on the government of Guangdong—where He’s university, the Southern University of Science and Technology is—to investigate He. Two days later, the science ministry ordered him to stop doing any science; He had already said the experiments were on hold. How the Guangdong investigation will proceed is not clear. He is accused of transgressing a 2003 health-ministry guideline, which is not a law and has no clear penalties attached to it.

Whether He’s university, the Southern University of Science and Technology, will take any action against him is also unclear. A university spokesperson told *Nature* that he “cannot disclose such information at this moment” and to wait for official statements “at an appropriate time.” He has been on leave since February 2018 and this is scheduled to last until January 2021; this week, the university criticized his claims and distanced itself from his work.

On 27 November, the laboratory webpage hosted by the university—to which He has been referring people for information about the gene-edited babies—went down although another site for He’s lab remains. Several statements praising He Jiankui’s accomplishments have also disappeared from government sites. A post on the science ministry’s site describing a genomic-sequencing technology that He developed, and a post praising He’s genomic sequencing technology on the website of the Thousand Talents Plan—a prestigious scheme to bring leading academics back to China — are both now inaccessible. It’s not clear if these actions are related to the week’s events but both posts were still accessible until recently.

He went back to Shenzhen, where he lives, after his talk at the summit, according to a statement provided by He's spokesperson, Ryan Ferrell, and missed a planned appearance at the summit on 29 November. "I have returned to Shenzhen and will not attend the conference on Thursday. I will remain in China, my home country, and cooperate fully with all inquiries about my work," the statement said.

2. ARE HE'S CLAIMS ACCURATE?

Many scientists have said that an independent body should confirm He's scientific claims by performing an in-depth comparison of the parents' and children's genes. The problem is, most everyone agrees that the babies and their parents should remain anonymous.

"He has kept them secret, and for good reasons," says Nobel-prize-winning biologist David Baltimore, chair of the summit organizing committee and former president of the California Institute of Technology in Pasadena. "We haven't even laid out how that independent investigation will happen."

He's team could supply anonymized samples. Outside scientists could also visit He's laboratory to analyse the data. In a statement released by his spokesperson, He said that he will invite other researchers to do an independent investigation. "My raw data will be made available for third-party review."



Sign up for *Scientific American's* free newsletters.

[Sign Up](#)

He also says that he has submitted studies on his human gene editing research to journals for publication. He has told some scientists that a paper will be published by the end of the year, but has not specified which journal. But even if this happens, strict Chinese genetic resources laws would prevent He from publishing the gene sequences of the parents or the children.

3. HOW EXACTLY DID CRISPR EDIT THE TWINS' GENOMES?

.....

In the absence of a peer-reviewed publication or preprint describing He's gene-editing work, some scientists are parsing his presentation to try and understand how the twins' genomes were edited—and any potential consequences of these changes.

Gaetan Burgio, a geneticist at Australia National University in Canberra who works on CRISPR gene editing, says that the raw sequencing data that He presented in his talk suggests that the babies' cells harbour multiple edited versions of the CCR5 gene, with different-size DNA deletions. Such 'mosaicism' can be caused when CRISPR edits some early embryo cells differently to others, or fails to edit some. Other researchers have reported mosaicism in efforts to edit human embryos for research purposes.

RNA researcher Sean Ryder, at the University of Massachusetts Medical School in Worcester, pointed out additional concerns in a [Twitter post](#).

He Jiankui told the gene-editing conference that he targeted the CCR5 gene because some people naturally carry a mutation in CCR5—a 32-DNA-letter deletion known as delta-32—that inactivates the gene. But Ryder says that the CCR5 deletions that He claimed to introduce into the babies' cells by CRISPR gene editing are not identical to the delta-32 mutation. "The point is that none of the three match the well-studied delta 32 mutation, and as far as I can tell, none have been studied in animal models. Unconscionable," Ryder wrote in the post.

4. WHEN WILL THERE BE ANOTHER GENE-EDITED HUMAN?

.....

As Jennifer Doudna, a pioneer of CRISPR/Cas-9 gene-editing tool, listened to He present his work on 28 November at the summer, one idea kept coming back to her. "The thought I kept having was the potential for rogue scientists to use this in unethical ways. It's a real risk," says Doudna, a biochemist at the University of California, Berkeley,

Before He's revelations, many scientist were already worried about the prospect that someone was on the brink of creating a gene-edited person. Biologist George Daley, dean of Harvard Medical School in Boston, Massachusetts, and a member of the summit organizing committee, pointed to a procedure that replaces diseased mitochondrial DNA in an embryo with healthy mitochondrial DNA of another person, eliminating the embryo's original disease-causing mutation. Although mitochondrial-replacement therapy lacks the approval of the biomedical community or the US Food and Drug Administration (FDA), doctors based in New York City used it to produce a baby in Mexico in 2016. "Similar premature practice of embryo editing by CRISPR/Cas9 is likely despite our calls for caution," Daley said.

At the Hong Kong summit, scientists discussed whether another announcement of human-germline editing—the modification of genes passed on to future generations—is nigh. "We do have reason to be concerned," said Baltimore. "If anyone working in the field gets indications that it is happening, it is important they let authorities know."

5. WILL HE'S REVELATIONS HAMPER ETHICAL EFFORTS TO DO GERMLINE EDITING?

Many researchers fear that He's revelations that could hamper the future of germline editing. "In the US some are suggesting draconian bans, which is antithetical to goals of science," says Baltimore.

In the wake of the revelations, FDA Commissioner Scott Gottlieb made comments that raised concerns among scientists. "Governments will now have to react," he told the news site Biocentury. And on 28 November, the US National Institutes of Health (NIH) director Francis Collins said in a statement that "the need for development of binding international consensus on setting limits for this kind of research, now being debated in Hong Kong, has never been more apparent."

The statement released at the summit's close makes a plea to keep open a path for safely translating gene-editing technology into treatments: "Germline genome editing could become acceptable in the future if these risks are addressed."

But the debacle has focused worldwide interest on germline gene-editing and fears of a chilling effect may be overstated. “There might be some women excited by the possibility of taking part in this research,” said Judith Dar, at the University of California Irvine School of Medicine and School of Law, at a summit satellite session when asked whether the controversy might dissuade women from donating eggs for research in the future. “The instinct is to say this is a debacle and could suppress participation. But I’m always amazed by the diverse reactions,” she added.

6. HOW WILL SCIENTISTS ENSURE BETTER OVERSIGHT OF GERMLINE EDITING IN FUTURE?

“We don’t have a blueprint, but we have been asking academies,” said Baltimore. “It is a challenge to the world.”

The statement released by the summit organizing committee suggests that science academies around the world make recommendations to their own governments, while coordinating with each other.

It also suggests the creation of an international forum that would funnel research and clinical trials through an international registry, and discuss issues like equitable access to the benefits of gene-editing. But genome editing in human embryos potentially has an unwieldy range of users, and that could make maintaining such an organization difficult. “Virtually every lab doing molecular biology is using this technique,” said Daley.

The committee also suggested the need for a “translational pathway” that would provide a rigorous and responsible way for researchers to take germline gene-editing to the clinic. Organizing committee member Alta Charo, a bioethicist at the University of Wisconsin-Madison, said expectations have to be realistic. “You can’t expect perfection. What you can do is try to minimize these incidents with enforcements that punish rogue behaviour.”

The next human genome-editing summit will take place in London in 2021.

This article is reproduced with permission and was first published on November 30, 2018.

ADVERTISEMENT

ABOUT THE AUTHOR(S)

David Cyranoski

David Cyranoski works for Nature magazine.

Nature magazine

Scientific American is part of Springer Nature, which owns or has commercial relations with thousands of scientific publications (many of them can be found at www.springernature.com/us). Scientific American maintains a strict policy of editorial independence in reporting developments in science to our readers.

© 2020 SCIENTIFIC AMERICAN, A DIVISION OF SPRINGER NATURE AMERICA, INC.

ALL RIGHTS RESERVED.