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Baby gene edits could affect a range of traits

Gene targeted for its role in HIV is linked to increased severity of other infectious diseases — and has implications for learning in mice.

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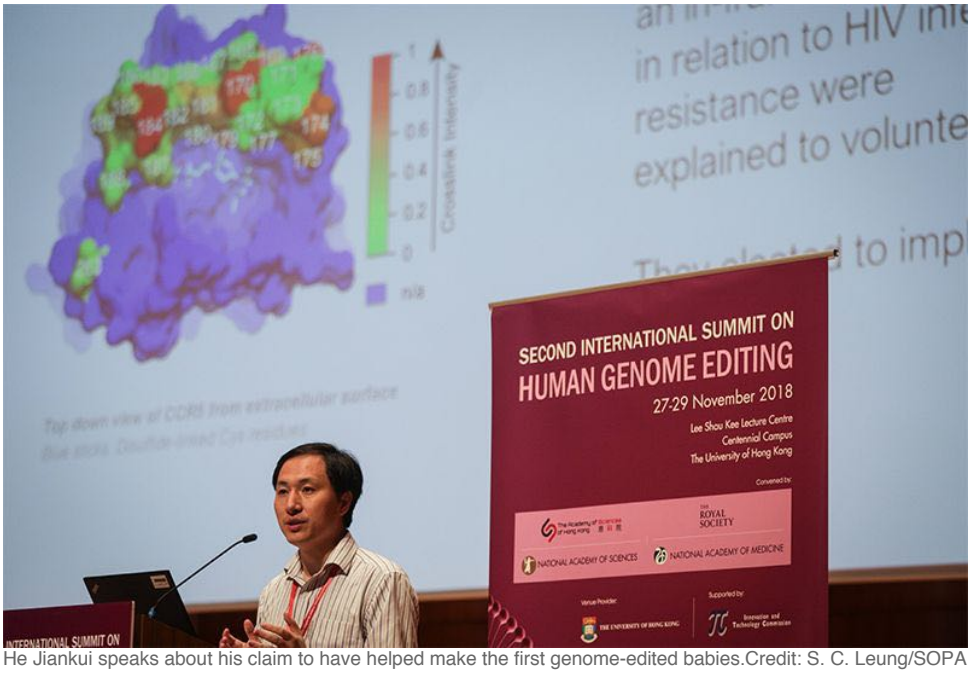

He Jiankui speaks about his claim to have helped make the first genome-edited babies.Credit: S. C. Leung/SOPA Images via Zuma

Chinese scientist He Jiankui's extraordinary claim two weeks ago that he had helped to make the first babies — twin girls — with edited genomes shocked the world. Many questions remain about the experiments, but among researchers' chief concerns are the potential effects of the genetic alterations on the girls' health.

He, a genome-editing researcher at the Southern University of Science and Technology of China in Shenzhen, says in several YouTube videosthat he impregnated a woman with embryos that had been edited to disable a gene that allows HIV to infect cells. He targeted this gene, known as *CCR5*, because it is well studied, and because its mutation offers protection against HIV infection, which still carries a significant social stigma in China.

The *CCR5* gene has been the subject of research since the mid-1990s, and has roles beyond HIV that scientists are just beginning to understand. Loss of *CCR5* function increases the risk of severe or fatal reactions to some infectious diseases, for example, and has also been shown to enhance learning in mice.

Target gene

The CCR5 protein is expressed on the surface of some immune cells, and HIV takes advantage of it to sneak into the cells. In 1996, scientists identified a mutation, known as *CCR5-Δ32*, that makes carriers highly resistant to HIV[1].

Last month, He told a meeting of genomics researchers in Hong Kong that this is the mutation — found naturally in about 10% of Europeans — that he intended to produce in the twins. Scientists analysing his presentation slides say that, instead, He seems to have produced three different mutations in the girls. It is expected that these mutations will have disabled the gene, says Kiran Musunuru, a geneticist at the University of Pennsylvania in Philadelphia. Slides from He's presentation suggest that both copies of the gene were disabled in one of the twins. The other twin seems to have at least one working copy.

Although the *CCR5-Δ32* mutation disables the gene and makes carriers resistant to the dominant strain of HIV, over the past two decades dozens of studies have shown that *CCR5* also helps to protect the lungs, liver and brain during some other serious infections and chronic diseases.

It has a well-established protective role is in West Nile virus, which is transmitted by mosquitoes and is common in Europe, Africa

and the Americas. Although most people infected exhibit no symptoms, about 20% do, with some developing potentially life-threatening complications such as meningitis or encephalitis. Philip Murphy, an immunologist at the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, has done experiments that show that people without a functional *CCR5* gene are four times more likely than those with the gene to develop these serious conditions[2]. "*CCR5* deficiency is not benign," he says.

Murphy says that the twin with one copy of the gene should be protected from these severe effects if she contracts the virus, but the other twin probably has a higher risk of complications if infected.

Virus protection

West Nile virus is rarely found in China. But the CCR5 protein also interacts with proteins called β-chemokines that help the body mount an immune response against a group of viruses called flaviviruses. These include tick-borne viruses, and the viruses that cause dengue and yellow fever, as well as West Nile virus, says Marcus Kaul an immunologist at the University of California, Riverside.

Studies have found that people with the *CCR5-Δ32* are more likely to experience severe encephalitis from tick-borne diseases, and to have a severe reaction to the vaccine for yellow fever.[7] "The absence of *CCR5*can have severe disadvantages," says Kaul.

Influenza could also pose a greater risk to the twins . Work in mice has shown that the CCR5 protein helps to recruit key immune cells to fight the virus in the lungs[3]. Without the gene, this defence system fails. A study in Spain found that that people with the *CCR5-Δ32* deletion are four times more likely than average to die from influenza[4]. And China is a hotspot for influenza outbreaks.

Scientists have also found that, among people with multiple sclerosis, those with the *CCR5-Δ32* deletion are twice as likely to die early than are people without the mutation[5]. What role *CCR5* might have in other chronic conditions, such as hepatitis C and diabetes, is unclear — studies differ on whether it helps, harms, or makes no difference to these conditions.

But, on the basis of the information in the consent form, none of these effects seems to have been communicated to the parents of the girls, or to other couples that participated in He's experiments. He's informed-consent procedure "was a disaster", says Megan Allyse, a bioethicist at the Mayo Clinic in Rochester, Minnesota.

He has not responded to *Nature's* multiple requests for comment.

Brain enhancement?

Some studies have shown that defective *CCR5* can have a positive effect — at least in mice. Mice without the gene learned to both navigate mazes and remember painful stimuli faster than rodents with the gene[6]. Overall, deletion of the gene improved the animals' cognition by 30–60%, says Kevin Fox, a neuroscientist at Cardiff University, UK, and a co-author on the study. "It was a clear and large effect," he says.

Although Fox wonders whether the twins will learn faster than they would have done without the mutation, other scientists doubt that the gene deletion will have a noticeable effect on the girls' learning. Hundreds, and possibly thousands, of genes contribute to intelligence in humans, says Kevin Mitchell, a geneticist at Trinity College Dublin. And the effect seen in mice might not translate to humans. The mutation might even have a negative effect on cognition, Mitchell says — for example, if it accelerates memory formation but makes it difficult to filter out unimportant memories. "Even if this mutation did have a cognitive effect in humans as in mice, which is not a given, it does not mean it would be a good thing," says Mitchell.

Silva Alcino, a neuroscientist at the University of California Los Angeles and Fox's co-author, agrees that any effect will likely be unpredictable. "In neuroscience the deletion of this receptor confers some advantages and very likely also results in deficits in some forms of cognitive function," he says.

Murphy thinks that despite the growing body of research on the mutation, it is difficult to draw conclusions about its overall effects. Only a small number of people have the mutation, making it difficult to recruit large numbers of participants for studies. However, the potential consequences of lacking a working *CCR5* gene are probably greater than we have established so far, says Murphy. "What we know may be the tip of the iceberg," he says.

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