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BIOTECHNOLOGY

An ode to gene edits that prevent deafness

Gene editing can prevent inherited deafness in mice by disabling a mutant version of a gene that causes hearing loss. Is this a turning point on the path towards treating some types of human deafness? SEE LETTER P.217

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When the 32-year-old composer Ludwig van Beethoven realized that his hearing was failing, he wrote to his brothers that "as the leaves of autumn wither and fall, so has my own life become barren". Although the cause of Beethoven's deafness is unknown, there are many examples of hearing loss in later life that are linked to inherited DNA changes. Two centuries later, techniques to prevent inherited forms of deafness are finally getting closer to implementation in the clinic. On page 217, Gao *et al.*[1] report progress in using gene-editing technology to treat a mouse model of inherited deafness. Given the growing momentum in using genetic engineering for human therapy, the path needed to take this approach to the clinic is clear.

The remarkable process of sensing sound occurs in the inner ear[2]. Tiny, hair-like structures called cilia on the surface of hair cells in the cochlea respond to sound waves. Ciliary motion evokes an electrical signal because the properties of a protein assembly at the base of each cilium change when such motion occurs. The TMC1 protein is thought[3] to be part of this assembly in humans, and some *TMC1* mutations cause people to lose their hearing over time. The symptoms start in childhood, and deafness, along with associated degeneration and death of hair cells, ensues within 10 to 15 years[4].

Gao and colleagues analysed the Beethoven mouse strain, in which the animals have a *Tmc1* mutation that causes them to grow deaf over time[5]. The mouse mutation they studied matches a mutation in human *TMC1* that is also linked to progressive hearing loss[6]. The mutation is dominant, which means that even if only one of a person's two copies of the gene has the mutation, they will become deaf. The mutant copy of the gene produces a defective protein that somehow impairs cell function, even though the cell also has a wild-type copy of the gene[7].

The repair of dominant-mutation-associated deafness is a delicate matter — the mutated gene must be disabled while preserving the wild-type gene within the same cell. This is no trivial undertaking, because only one nucleotide of DNA distinguishes the two versions of the *TMC1* gene from each other (Fig. 1). One way to understand this is to imagine a duet between two people trying to sing in unison. If one person is off-key, this offender must be selectively silenced to allow the correct tune to be heard, because if both singers are stopped, the music will cease.

Gene editing is the technique of choice to rid a hair cell of the mutant version of a gene[8]. This involves using a nuclease enzyme to cut a targeted DNA sequence in the specific gene inside the living cell. The cut causes a double-strand DNA break and the repair process often results in mistakes in which nucleotides are added or lost. Such a change can alter the sequence in a way that might cause translation to prematurely arrest and thereby prevent gene expression.

The authors used the nuclease Cas9, which cuts DNA at a specific site by using a snippet

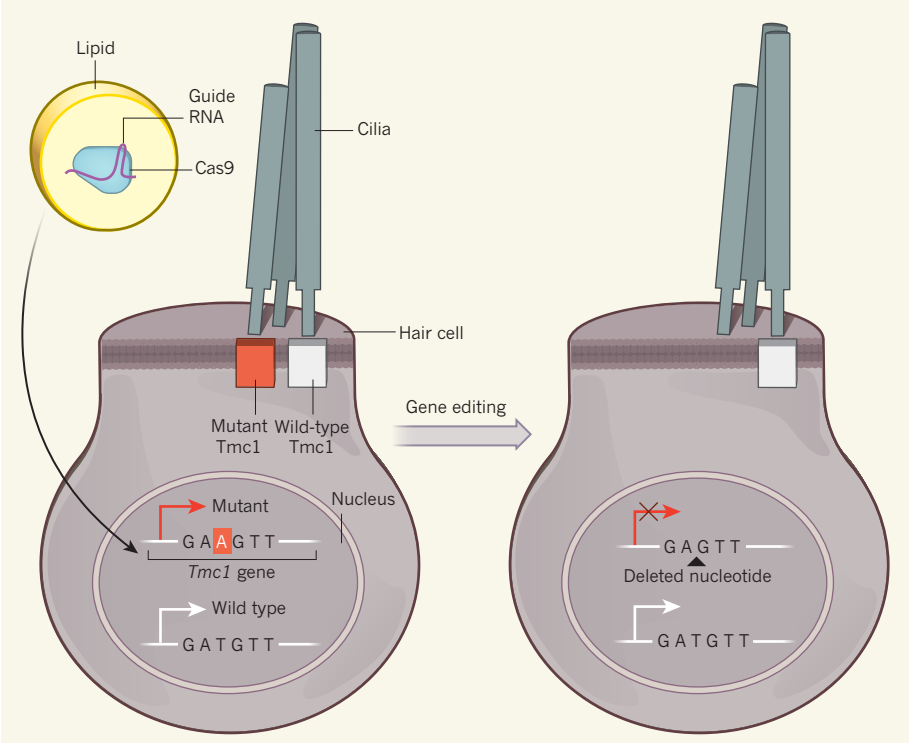

Figure 1 | Gene editing in mice can prevent inherited hearing loss. Gao *et al.*[1] investigated a mouse model of later-life deafness that is caused by a mutant version of the *Tmc1* gene. This mutation is identical to one in the human version of the gene that is linked to deafness. Hearing loss is accompanied by the death of inner-ear hair cells that sense sound using their ciliary projections. The authors injected the ears of newborn mice with gene-editing components: the nuclease enzyme Cas9 that can cut DNA, and a guide RNA that targets Cas9 to the mutant version of *Tmc1* in hair-cell nuclei. These were packaged in a lipid droplet that fuses with cells to enable the gene-editing components to enter. The mutant version of *Tmc1* has an adenine nucleotide (A, highlighted in red in the mutant nucleotide sequence) at a position that is a thymidine nucleotide (T) in the wild-type version. Gene editing selectively inactivated the mutant version of the gene through mechanisms such as nucleotide deletion. Edited cells express only the wild-type Tmc1 protein (white) and don't express the mutant version (red).