ORIGINAL ARTICLE | VOLUME 31, ISSUE 8, P2439-2453, AUGUST 02, 2023 Download Full Issue

Rescue of hearing by adenine base editing in a humanized mouse model of Usher syndrome type 1F

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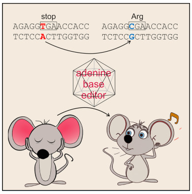
Published: June 12, 2023 • DOI: https://doi.org/10.1016/j.ymthe.2023.06.007 • Check for updates

Usher syndrome type 1F (USH1F), characterized by congenital lack of hearing and balance and progressive loss of vision, is caused by mutations in the *PCDH15* gene. In the Ashkenazi population, a recessive truncation mutation accounts for a large proportion of USH1F cases. The truncation is caused by a single C→T mutation, which converts an arginine codon to a stop (R245X). To test the potential for base editors to revert this mutation, we developed a humanized *Pcdh15*^{R245X} mouse model for USH1F. Mice homozygous for the R245X mutation were deaf and exhibited profound balance deficits, while heterozygous mice were unaffected. Here we show that an adenine base editor (ABE) is capable of reversing the R245X mutation to restore the PCDH15 sequence and function. We packaged a split-intein ABE into dual adeno-associated virus (AAV) vectors and delivered them into cochleas of neonatal USH1F mice. Hearing was not restored in a *Pcdh15* constitutive null mouse despite base editing, perhaps because of early disorganization of cochlear hair cells. However, injection of vectors encoding the split ABE into a late-deletion conditional *Pcdh15* knockout rescued hearing. This study demonstrates the ability of an ABE to correct the *PCDH15* R245X mutation in the cochlea and restore hearing.

Graphical abstract



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Keywords

Usher syndrome • PCDH15 • hair cell • cochlea • deafness • blindness • gene therapy • gene editing • base editor • AAV

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Article info

Publication history

Published online: June 12, 2023
Accepted: June 8, 2023
Received: December 31, 2022

Identification

DOI: https://doi.org/10.1016/j.ymthe.2023.06.007

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