Gene editing in photoreceptor progenitors prevents visual function loss in a mouse model of retinal degeneration.

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Purpose: Currently, there is no known cure for *Retinitis pigmentosa* (RP). Even if some treatments can slow down the progression of the disease, none of them can effectively stop retinal degeneration. We exploited the possibility of an early intervention in photoreceptor progenitors aiming at preventing cell death. For our purpose, we selected the Rd10 mouse model, which carries a point mutation in a gene associated with human RP. We designed a CRISPR/Cas9 gene editing system to repair the mutation taking advantage of the increased activity of the homologous directed repair mechanism in dividing cells.

Methods: The efficiency of the editing system (composed of guide RNA, Cas9, and DNA repair template) was first tested *in vitro* in neural progenitor cells (NPCs) derived from Rd10 mice (n=3). The constructs were then injected *in vivo* in the subretinal space of Rd10 pups at postnatal day (P) 1.5 (single treated, ST) or at P1.5 and P8 (multiple treated, MT). One eye was injected, while the other one was kept as internal control. The injection was followed by electroporation (electric field: 40 V/cm). The visual acuity was measured at P28 with the optomotor test in ST (n=43), MT (n=12), sham (n=20), untreated Rd10 (NT, n=13), and WT (n=18) mice. One tailed Student's t-test was used to compare control and treated eyes, while one-way ANOVA was used to compare different groups. Moreover, the flash visually evoked potentials (fVEPs) were recorded from the visual cortex of ST (n=19), MT(n=12), sham (n=17), NT (n=4), and WT(n=10) mice at P33.

Results: The net efficiency of the CRISPR/Cas9-mediated DNA editing in NPCs was 52.8±11.1%. The visual acuity in the treated eye was significantly higher compared to the control eye in ST (0.22±0.02c/d vs 0.12±0.01c/d, p<0.01) and MT mice (0.27±0.02c/d vs 0.15±0.02c/d, p<0.01). ST and MT mice had a significantly higher visual acuity compared to sham (0.11±0.01c/d, p<0.01) and NT mice (0.11±0.07c/d, p<0.01). Preliminary measurements of the fVEPs showed a partial recovery of the light-evoked response in MT mice.

Conclusions: Our results strongly suggest a positive effect of the CRISPR/Cas9-based therapy on photoreceptor survival in our model of RP. However, additional morphological analyses and electrophysiological tests at different time points are needed to assess the preservation of the retinal outer nuclear layer and the functionality of the visual pathways.

Layman Abstract (optional): Provide a 50-200 word description of your work that non-scientists can understand. Describe the big picture and the implications of your findings, not the study itself and the associated details.: