Abstract 31

CRISPR DNA BASE EDITING STRATEGIES FOR TREATING RETINITIS PIGMENTOSA CAUSED BY MUTATIONS IN RHODOPSIN

Poster

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Purpose:

Pathogenic variants in the Rhodopsin (RHO) gene are major cause for autosomal dominant RP (adRP). Despite extensive attempts, the disease still lacks standardized curative treatment. Recently developed CRISPR DNA base editors offer an exciting opportunity to correct pathogenic variants and hence could be utilised to develop therapy for RHO-associated adRP.

Methods:

All disease-associated RHO variants were downloaded from the Leiden Open Variation Database (LOVD), ClinVar and Genome Aggregation Database and analysed for their amenability to base editing first based on the variant types. Then, suitable PAM sites were searched for the currently available base editors utilizing the Streptococcus pyogenes Cas9 (SpCas9), Staphylococcus aureus Cas9 (SaCas9) or the KKH variant of SaCas9 (KKH-SaCas9) utilising the Benchling software. Finally, unwanted bystander edits were analysed for each guideRNA to assess the safety of the approach.

Results:

Of all the reported pathogenic RHO variants (n=247), 55% could in theory be corrected with base editors. Importantly, nine of the ten most common disease-associated RHO variants were editable. However, PAM sites were available for only 32% of the editable variants and unwanted bystander edits were predicted for the majority of the designed guide RNAs.

Conclusions:

Base editing offers exciting possibilities to treat RHO-associated adRP in future. However, further research is needed to develop base editing constructs that will provide available PAM sites for more variants and that will not introduce potentially harmful bystander edits.