Structure-function analysis of CNGA3-associated achromatopsia patient variants complements clinical genomics in pathogenicity determination

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Introduction

Achromatopsia

- Loss of color perception, photophobia, nystagmus
- Cone-specific dysfunction
- Autosomal recessive retinal disease
- Six associated genes, mainly in the phototransduction cascade
  - CNGA3 and CNGB3 together covers 95% of achromatopsia cases

CNGA3

- Key player in glutamaric phototransduction regulation
- Forms cone-specific cone cyclic nucleotide-gated (CNG) channel with CNGB3

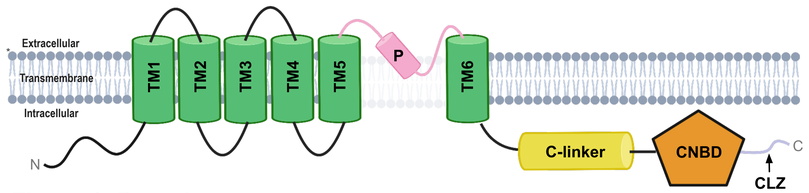


Figure 1: Domain topology

Study objective and design

- In this study, we present an achromatopsia patient with a novel homozygous variant in the *CNGA3* gene.
- We established a three-dimensional protein structure-based proteotype analysis of the CNGA3/CNGB3 complex to better understand CNG channel-dependent achromatopsia pathology and determined the pathogenicity and potential disease pathology of our patient's mutation.
- Our proteotype analysis was further extended to study the structural and functional consequences of known pathogenic variants, and finally
- Applied to variants of unknown significance displaying similar molecular and structural consequence

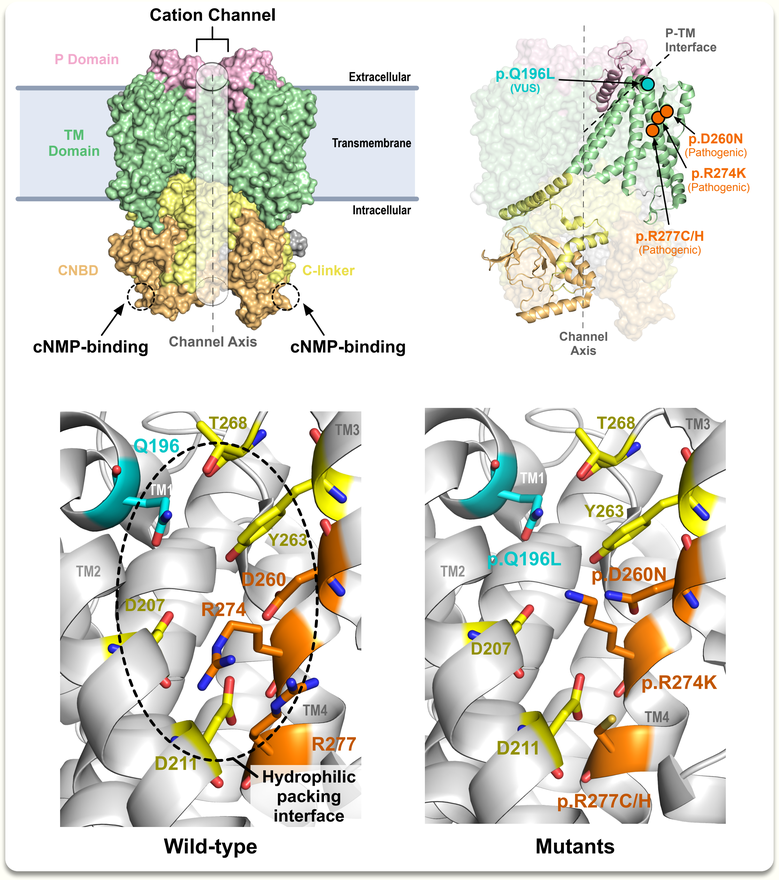
Proof of concept	Pathological molecular mechanism	Variants of unknown significance
Our novel patient variant was compared to established pathogenic variants with similar molecular and structural consequence as well as proximity in 3D	Molecular and structural consequence of 52 pathogenic variants identified in literature were mapped and characterized within six clusters	Variants of unknown significance were assessed and compared to nearby pathogenic variants, which reinforced the mechanism clusters

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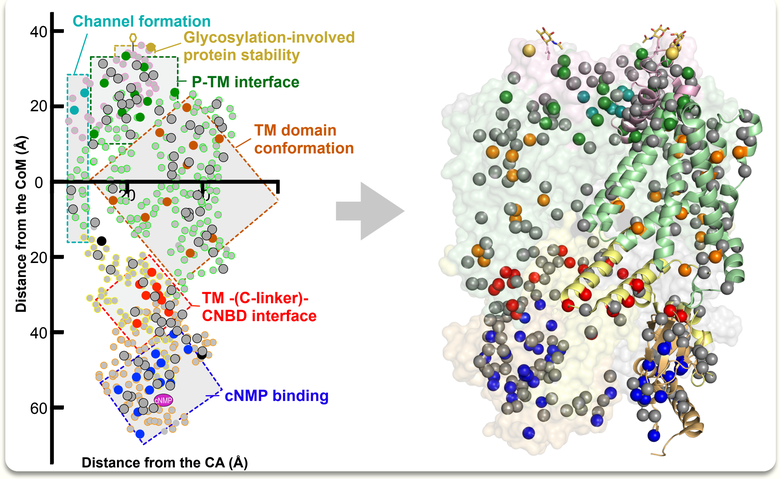
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Results

Three-dimensional proteotype analysis of our patient's variant reveals its potential molecular pathology

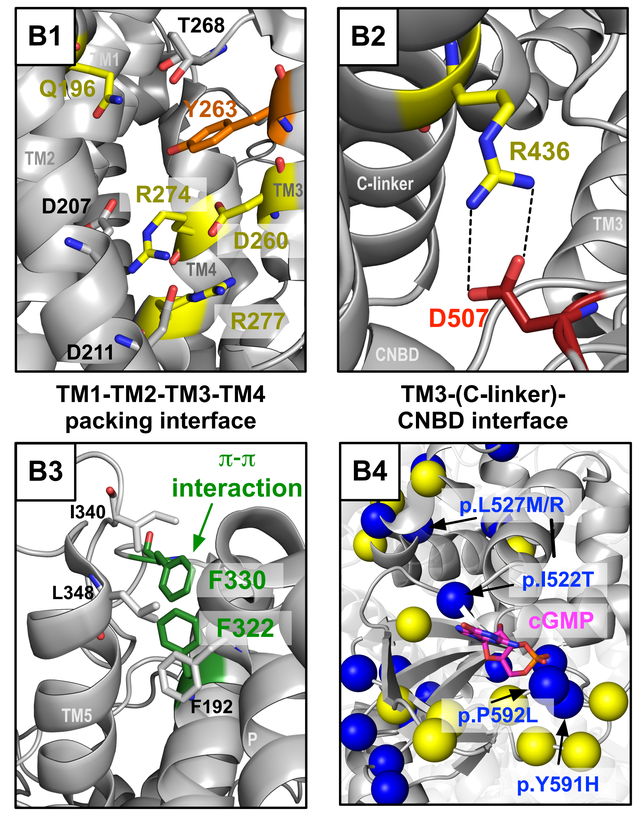


Structure-function based prototype analysis can be applied to other *CNGA3* variants of unknown significance



Results

Molecular consequence of CNGA3 variants



Conclusions

- ★ Pathogenic *CNGA3* variants can be parsed into six prototypic groups with distinctive functional consequences and spatial proximity in 3D protein structure
- ★ 86.4% of VUS had similar/identical functional consequence to nearby pathogenic variants
- ★ Proteotype-based structure-function analysis complements clinical genomics in pathogenicity determination
- ★ Our analysis strongly supports the notion that gene supplementation may be the most widely applicable therapeutic option for *CNGA3*-associated achromatopsia patients.

Acknowledgements

Funding/Support: DKR is supported by the DARE fellowship, which is sponsored by the Lundbeck Foundation and the VRSF Fellowship. VBM is supported by NIH grants (R01 EY031952, R01 EY030151, R01NS98950, and R01EY031360). VBM is also supported by P30EY026877, Research to Prevent Blindness (RPB), and the Stanford Center for Optic Disc Drusen. Jonas Children's Vision Care is supported by 5P30CA013696, U01 EY030580, U54OD020351, R24EY028758, R24EY027285, 5P30EY019007, R01EY033770, R01EY018213, R01EY024698, the Schneeweiss Stem Cell Fund, New York State (SDHDOH01-C32590GG-3450000), the Foundation Fighting Blindness New York Regional Research Center Grant (TA-NMT-0116-0692-COLU), Nancy & Kobi Karp, the Crowley Family Funds, the Rosenbaum Family Foundation, Alcon Research Institute, and the Gebroe Family Foundation. SHT receives grant support from Abeona Therapeutics, Inc and Emendo . YS is supported by R01EY032159, R01EY025295, VA Merit I01CX001481, I01BX BX005831, P30EY026877, and Stanford Maternal & Child Health Research Institute (MCHRI). YJS is supported by BrightFocus Foundation's Macular Degeneration Research program.