Eye (2021) 35:2901–2902
https://doi.org/10.1038/s41433-020-01212-3

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CORRESPONDENCE

CDHR1-related late-onset macular dystrophy: further insights

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Received: 1 September 2020 / Revised: 21 September 2020 / Accepted: 23 September 2020 / Published online: 1 October 2020

To the Editor:

We read with interest the series of patients described by Ba-Abbad et al. [1]. Whilst biallelic truncating *CDHR1* variants result in cone-rod or rod-cone dystrophies—consistent with the *Cdhr1*$^{-/-}$ knockout mouse [2]—it is intriguing that certain biallelic splice or missense variants in *CDHR1* may result in late-onset macular dystrophy.

Variants in *CDHR1* described in association with late-onset macular dystrophy [1] appear to affect the ectodomains of CDHR1. Although the six extracellular cadherin repeats form the longest part of the protein, they are the most conserved, suggesting an important biological function [3]. Ultrastructural analysis with immunogold labelling of CDHR1 in murine retinae identified that evaginating, nascent discs at the base of the photoreceptor outer segments form CDHR1-based connections with the inner segments [4]. Formed from the ectodomains of CDHR1, the contacts are lost as outer segment discs mature. This physical separation occurs through proteolytic cleavage of the CDHR1 ectodomain [3]. Non-truncating *CDHR1* variants affecting the ectodomain may interfere with its proteolytic cleavage, or attachments to the inner segment, thereby resulting in dystrophic outer segments without widespread photoreceptor degeneration seen with biallelic truncating variants.

c.783G>A$_{CDHR1}$ appears to be the most common *CDHR1* variant associated with late-onset macular dystrophy, based on mean allele frequency [1, 5]. Indeed, when hypomorphic variants are included, *CDHR1* was amongst the more common causes of macular and cone- or cone-rod dystrophy in one large series [6]. Although isolated macular dystrophy appears to be the most common phenotype in c.783G>A$_{CDHR1}$ homozygotes [5], peripheral retinal degeneration has been reported [7], suggesting the influence of unknown modifiers which may result in rod photoreceptor degeneration instead of only macular involvement. The identification the inner segment binding partner of CDHR1 and the enzyme catalysing the cleavage of the CDHR1 ectodomain may help to explain the macular-predominant dystrophy in this cohort. Variants in these unknown genes may themselves act as potential disease modifiers, or even be disease causing in their own right.

Similar phenotypes are found in association with *CDHR1*, *PROM1* and *PRPH2* variants—all of which encode proteins supporting photoreceptor outer segment structure. It remains to be determined why cones, or macular photoreceptors in general, appear to be more susceptible to the effects of specific variants in these genes.

Funding IHY is funded by MRC and REM is funded by NIHR and MRC.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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