Letter to the Editor

No strong evidence to date for an association between *RIMS1* and retinal dystrophy

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Dear Editor,

Weston *et al*. report the case of a child with a retinopathy in whom variants were found in the genes *CACNA1F* and *RIMS1* [1]. *CACNA1F* is associated with congenital stationary night blindness 2 (CSNB2), also known as cone-rod synaptic disorder. The phenotype in the patient is largely consistent with *CACNA1F*-associated disease, and we agree with the authors' conclusion that this is the gene relevant to this patient's retinopathy. *RIMS1* has been previously associated with cone-rod dystrophy 7 (CORD7), and it is that association, reported in a four-generation non-consanguineous family [2], that has prompted the authors, and others, to take particular notice of variants in this gene in the context of retinal disease. We have very recently published our reassessment of the original family in whom *RIMS1*-associated disease was reported: the autosomal dominant cone-rod dystrophy is in fact attributable to a well-characterised pathogenic variant in the *PROM1* gene (c.1118C>T, p.Arg373Cys) [3]. The phenotypes (ranging from macular, to cone-, or cone-rod, dystrophy) in the affected family members were in keeping with those reported for the *PROM1* variant, and one member of that family was found to be affected despite not harbouring the *RIMS1* variant.

Since the original CORD7 family, and prompted by that study, other reports have been published implicating *RIMS1* variants in retinal disease [4-7]; however, in all of these publications, the evidence was not as strong, and the phenotypes were quite different. The same *RIMS1* variant as in the original CORD7 family was reported in a simplex case of retinitis pigmentosa (RP) [4]. A different variant was reported in a family with likely autosomal dominant RP [5], and two further variants were reported in infants with more severe eye disease: in both of these studies, the authors themselves concluded that there was insufficient evidence to implicate *RIMS1* as the causative gene [6,7]. The population frequencies of the variants reported in those studies (as well as in the original CORD7 family) can now be checked in large databases (such as the Genome Aggregation Database available at https://gnomad.broadinstitute.org/), and appear too high for a fully penetrant dominant rare condition. The purpose of our letter is thus to highlight that, to date, there is no strong evidence of an association between *RIMS1* and retinal dystrophy.

References

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