PRPH2 mutation update: In silico assessment of 245 reported and 7 novel variants in patients with retinal disease

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Abstract

Mutations in PRPH2, encoding peripherin-2, are associated with the development of a wide variety of inherited retinal diseases (IRDs). To determine the causality of the many PRPH2 variants that have been discovered over the last decades, we surveyed all published PRPH2 variants up to July 2020, describing 720 index patients that in total carried 245 unique variants. In addition, we identified seven novel PRPH2 variants in eight additional index patients. The pathogenicity of all variants was determined using the ACMG guidelines. With this, 107 variants were classified as pathogenic, 92 as likely pathogenic, one as benign, and two as likely benign. The remaining 50 variants were classified as variants of uncertain significance. Interestingly, of the in total 252 PRPH2 variants, more than half (n=137) were missense variants. All variants were uploaded into the Leiden Open source Variation Database. Our study underscores the need of experimental assays for variants of unknown significance to improve pathogenicity classification, which is needed to better understand genotype-phenotype correlations, and in the long-term, hopefully also support the development of therapeutic strategies for patients with PRPH2-associated IRD.

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