Rod-cone dystrophy associated with the Gly167Asp variant in *PRPH2*

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Peripherin *2*-associated retinopathies are phenotypically heterogenous and can present as autosomal dominant retinitis pigmentosa, cone-rod dystrophy, various forms of macular and pattern dystrophy, or recessive retinopathy[1,2]. We report a case of rod-cone dystrophy associated with the variant c.500G>A, p.(Gly167Asp) in *PRPH2* (OMIM 179605), which was previously reported to cause autosomal dominant butterfly-shaped pigment dystrophy of the fovea in a three-generation pedigree (MIM 169150)[3].

A 66-year old British woman of European ancestry was referred to the inherited retinal disorders clinic with bilateral pigmentary retinopathy, and a 5-year history of nyctalopia. There were no knowingly affected family members; her late father and mother had normal vision in their sixties and eighties respectively, and the patient's two children had no symptoms in their third decade of life. Previously, she underwent laser refractive surgery for myopia, bilateral cataract extraction and laser posterior capsulotomy.

On examination, the Snellen visual acuity was 20/30 in the right eye, and 20/80 in the left eye; and color vision (Ishihara plates) was normal bilaterally. Color fundus imaging showed bilateral peripapillary atrophy in keeping with myopia, and peripheral patches of pigment epithelial atrophy and some intra-retinal pigmentation. Fundus autofluorescence imaging showed symmetrical hypo-autofluorescent spots distributed along the major vascular arcades with peripapillary sparing, anterior to the myopic crescent. A macular hyper-autofluorescent ring, often seen in retinitis pigmentosa[4], was absent (Figure 1). Spectral-domain optical coherence tomography on the right showed intact retinal layers at the macular center, but with small peri-foveal cysts in the inner-nuclear layer. There was a defect in the ellipsoid zone at the left fovea, and a lamellar hole (Figure 1). Full-field and pattern electroretinography (ERG; PERG-Figure 1) were consistent with rod-cone dystrophy

and normal central macular function. Genetic testing using next generation sequencing of exons and splice-site regions of a panel of 176 genes associated with retinal disorders, showed the patient to be heterozygous for the variant c.500G>A, p.(Gly167Asp) in *PRPH2* (NM_000322). There were no likely pathogenic rare variants in other candidate genes, and no family members were available for segregation analysis.

In this case, the absence of family history of retinopathy, late onset of symptoms and subtle retinal changes, confounded early diagnosis of a hereditary retinopathy. However, fundus autofluorescence images revealed a symmetrical pattern of retinal pigment epithelial disturbance, suggesting a genetic cause. The phenotypic features are unusual and differ from other retinal disorders and other *PRPH2*-related retinopathies so far reported.

There are 177 variants in *PRPH2* that have been associated with different macular and retinal dystrophies, with a range of phenotypes relating to the relative involvement of macular and peripheral cones and rods (The Human Gene Mutation Database http://www.hgmd.cf.ac.uk/ac/gene.php?gene=PRPH2, accessed December 2018). Moreover, carriers of the deletion of codon 153 or 154 of *PRPH2* in one family have been shown to manifest with different phenotypes including retinitis pigmentosa, pattern dystrophy and fundus flavimaculatus[5].

This case demonstrates the utility of non-biased genetic testing using large gene panels or whole genome sequencing, which has the potential to expand the phenotypic spectrum associated with any known gene. Establishing a genetic diagnosis in an apparently sporadic case has implications for family counselling and potential eligibility for future therapeutic trials.

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Figure legends:

Figure 1: Fundus images, right eye images in the left panel and left eye images on the right panel. (*A*) Widefield pseudo-color fundus images of both eyes showing peripapillary atrophy, with unremarkable maculae, and small patches of outer retinal changes with intra-retinal pigmentation temporal to the macula. (*B*) Fundus autofluorescence (FAF) showing bilateral peri-macular stippling, sparing the peri-papillary region. The peripheral FAF is relatively attenuated with patchy loss of signal, not apparent on color images. (*C*) Spectral-domain optical coherence tomography (SD-OCT) and the corresponding FAF image (insets). OCT scan of the right eye shows cystic changes and attenuation of the ellipsoid zone temporally. The left OCT shows a lamellar hole, with cystic changes and disruption of the ellipsoid zone at the fovea. The increased FAF signal in the left is likely caused by the loss of the outer segments of the foveal photoreceptors. (*D*) Full field electroretinogram (ERG) and pattern ERG (PERG) for the right (RE) and left eye (LE) of the patient and a representative normal control (N) for comparison. The dark-adapted (DA) rod specific (DA 0.01) ERG is severely reduced and the bright flash (DA 10.0) ERG a- and b-waves are markedly subnormal. The light-adapted (LA) 30Hz flicker ERG and the single flash cone (LA 3.0) ERG are markedly subnormal. The PERG P50 and N95 components are normal bilaterally. Note the 20ms pre-stimulus delay in single flash ERG responses and the increased scale compared with control recordings (N), used to better illustrate the patient full-field ERG data. All patient recordings are superimposed to demonstrate reproducibility. (*E*) Kinetic visual fields of the left (left panel) and right (right panel) eye showing greater constriction of the three isopters I4e, III4e, and V4e in the right visual field compared to the left, in keeping with the larger area of reduced AF signal.