Conflict of interest

The authors declare no conflict of interest.

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Sir,

Outer retinal structural anomaly due to frameshift mutation in *CACNA1F* gene

X-linked congenital stationary night blindness (CSNB) is associated with mutations in nyctalopin[1] (*NYX*;CSNB1A) or in the α1 subunit of L-type voltage-gated Ca^{2+} channel[2] (*CACNA1F*;CSNB2A). We report for the first time, optical coherence tomography (OCT) features consistent with abnormal synapses in the outer nuclear layer (ONL) in a molecularly confirmed case of CSNB2A.

Case report

A 15-year-old-male presented with history of nonprogressive nyctalopia and diminution of distance vision since childhood. Nystagmus was first noted in infancy, but it gradually improved. On examination, he had no nystagmus. The best-corrected visual acuity was 20/40 and 20/30 in the right and left eyes, respectively; he had mild red–green color deficit. Fundus evaluation

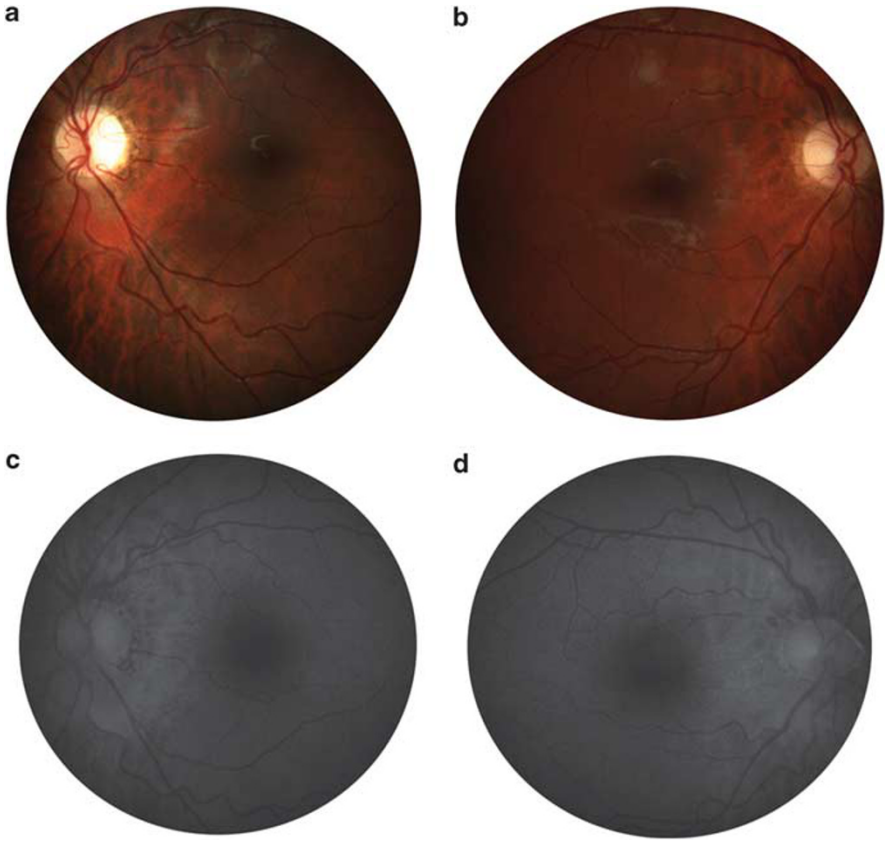

Figure 1 Fundus photographs (a, b) and fundus autofluorescence images (c, d) from either eye of the patient was normal.

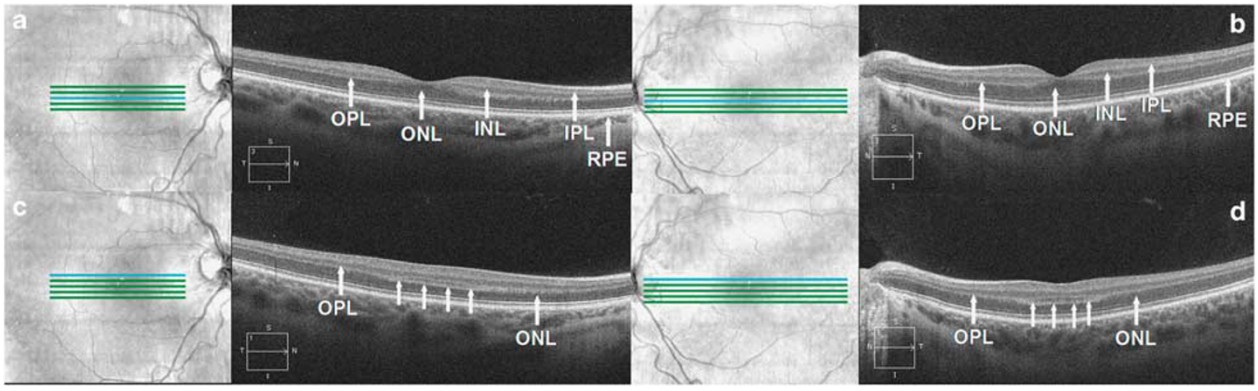

Figure 2 Cirrus OCT images from the right (a, c) and left eyes (b, d), respectively. The high definition raster scans through the foveola showed normal retinal layering in the right (a) and left eyes (b), respectively. The raster scans 500 μm above the foveola showed evidence of bipolar cell synapses in both outer plexiform (normal) and outer nuclear (abnormal) layers in both eyes (see series of white arrows in c and d). In Figures 2c and d note the appearance of splitting of the OPL in the affected regions. There is no abnormality noted in the inner retinal layers. The relevant layers of the retina are labeled: RPE, retinal pigment epithelium; ONL, outer nuclear layer; OPL, outer plexiform layer; INL, inner nuclear layer; IPL, inner plexiform layer.

and autofluorescence were normal (Figure 1). Cirrus OCT showed normal central retinal thickness (Figures 2a and b). Raster scans 500 μm superior to foveola consistently showed areas of splitting of the outer plexiform layer (OPL) suggesting bipolar cell synapses in OPL and ONL in either eye; synapses in the ONL are abnormal (Figures 2c and d). Electroretinogram results were characteristic of incomplete CSNB. Genetic testing identified a previously reported hemizygous frameshifting insertion in exon 27 of *CACNA1F* that caused premature protein truncation(c.3166insC/p.Leu1056Profs $\times$ 11).[2]

Comment

This is the first case report describing outer retinal structural anomaly consistent with abnormal bipolar cell synapses in *CACNA1F*-related disease. Immunocytochemical analysis of various mouse models of *Cacna1f* have shown abnormality in retinal synapses wherein bipolar cells partly synapse in ONL and retinal pigment epithelium instead of the OPL.[3–5] The mouse models studied carried null, nonsense, or loss of function *Cacna1f* mutations suggesting a severe disease model. The subject described here has a frameshifting mutation that produces truncated protein that is unlikely to survive nonsense-mediated decay, likely to cause a severe phenotype. The abnormal synapses were noted superior to foveola where both photoreceptors exist.[6] Macular OCTs on few CSNB2A cases due to other mutations[7,8] report no abnormality in retinal synapses. Hence, abnormal synapses may not be visualized in all cases of CSNB2A. Currently, electroretinogram is used to differentiate between *NYX*- and *CACNA1F*-related CSNB. The OCT structural abnormality when present could serve as a useful phenotypic marker of *CACNA1F*-related disease in X-linked CSNB patients because unlike *Cacna1f* models, *Nyx* mouse models[9] show normal retinal synapses.

Conflict of interest

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