Incomplete Congenital Stationary Night Blindness Associated with a Novel Mutation in the *CACNA1F* Gene

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Introduction

- Congenital stationary night blindness (CSNB) refers to a group of inherited, non- progressive retinal diseases, each with varying genetic causes, clinical findings and electroretinography (ERG) results. A subtype is incomplete CSNB (iCSNB). Most cases of iCSNB result from mutations in the X-linked gene *CACNA1F* (1).

- We describe two cases of iCSNB in male siblings, both carrying a novel mutation c.4041+5G>T in the *CACNA1F* gene, inherited from their mother, which has not been previously reported in the literature.

Description of Cases

Case 1

- A 3-year-old male (Patient A) had high myopia in both eyes (right -4.50/-1.50 x 10, left -3.50/-1.25 x 175) and reduced visual acuities (0.9 logMAR at 2 metres for both eyes). Fundoscopy was normal (Figure 1) and orthoptic examination revealed exophoria in both eyes.

- ERG testing demonstrated findings resembling that of iCSNB, i.e. markedly reduced amplitude to dim flashes and an electronegative waveform to bright flashes under dark-adapted conditions, and markedly reduced light-adapted ERGs (Figure 4), leading to the diagnosis.

- Next generation sequencing of genes identified a novel hemizygous c.4041+5G>T variant in the *CACNA1F* gene. Functional analyses were unable to definitively confirm pathogenicity and the variant was classified as a variant of unknown significance. In-silico tools predicted that it would disrupt normal splicing of *CACNA1F*, leading to a null effect.

- The patient reported night blindness. Follow-up at seven years demonstrated stable visual acuities of 0.40 logMAR in the right eye and 0.38 logMAR in the left eye.

Case 2

- Patient A's younger brother (Patient B) had reduced visual acuities of 0.475 logMAR in the right eye and 0.450 logMAR in the left eye. He also had myopia in both eyes (right -1.75/+2.75x118 and left -2.00/+2.75x70). Orthoptic examination demonstrated a slight well compensated exophoria.

- ERGs showed that both light and dark-adapted ERGs were affected, and b-waves were more affected than a-waves with an electronegative DA3 ERG, resembling that of the iCSNB phenotype (Figure 4). Genetic testing identified the same c.4041+5G>T variant in *CACNA1F*.

- Follow-up at 3 years demonstrated improved visual acuities of 0.200 logMAR in the right eye and 0.175 logMAR in the left eye, with fundal photographs demonstrating peripapillary atrophy and increased visibility of the choroidal vasculature (Figure 2), consistent with myopia.

Mother

- Their mother was asymptomatic apart from being very photophobic with dilated pupils. She had visual acuities of 85 letters in both eyes at 40 years. Wide field colour and autofluorescence imaging were normal (Figure 3). She had almost entirely normal ERGs; however, there was subtle delay of her light-adapted ERG b-waves and she was found to have the same variant.

Description of Cases

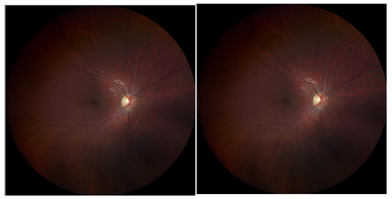


Figure 1: Wide field fundus photographs, case 1

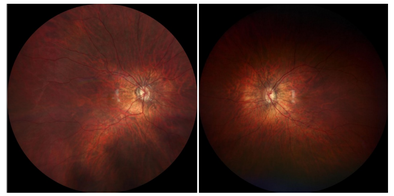


Figure 2: Wide field fundus photographs, case 2

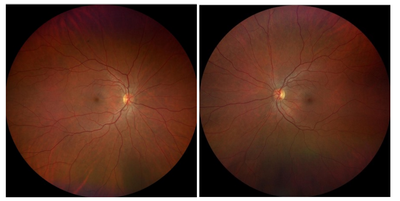


Figure 3: Wide field fundus photographs, case 3

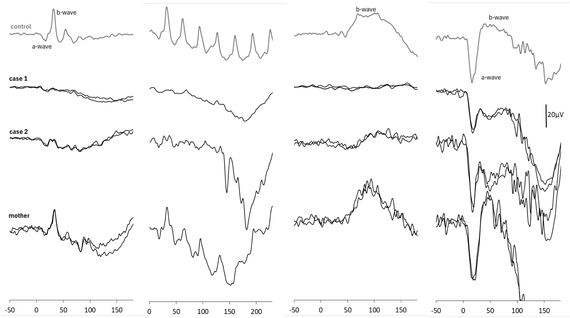


Figure 4: ERGs. From left to right, panels show light-adapted single flash ERGs (LA3); light-adapted 30 Hz flicker ERGs; dark-adapted dim flash ERGs (DA0.01) and dark-adapted strong flash ERGs (DA3). Top, grey traces are example ERGs from a healthy individual. The DA3 ERGs are electronegative in case 1 and 2.

Discussion

- Clinical features of CSNB may include reduced visual acuity, myopia, strabismus, nystagmus, poor night or dim-light vision, photophobia, tonic downgaze and upward saccades (1,2). Both male patients presented with decreased visual acuities, an unusually high myopia for their age and exophoria. Patients with iCSNB have normal fundi as seen in our patients. Follow-up after five and two years in patients A and B respectively demonstrated no progression of symptoms, in keeping with the non-progressive nature of iCSNB.

- ERGs are very important for making the diagnosis. Characteristic findings include an extant but reduced b-wave of the dark-adapted dim flash ERG and classical electronegative waveform, with reduced b-waves but relatively preserved a-wave of the dark-adapted strong flash ERG, and reduced light-adapted ERGs often with a bifid peak.

- The hemizygous c.4041+5G>T variant in the *CACNA1F* gene (OMIM *300110) is a novel mutation not previously reported in the literature. Although functional analysis with RNA was unable to confirm pathogenicity of this variant, it was predicted to lead to a null effect, thus disrupting normal Cav1.4 function and affecting neurotransmission to bipolar cells (3). Given the consistency of these findings with the pathogenicity of iCSNB, this novel mutation is likely to be disease-causing in both male patients. Reporting of this family further widens the genotypic spectrum of iCSNB.

References

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