Case report

Pseudodominance in two families with KCNV2 related retinopathy

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ARTICLE INFO

Keywords:
- Cone dystrophy
- Electrophysiology
- Genetics
- KCNV2
- Mutation

ABSTRACT

Purpose: To describe the phenotypic and genotypic characteristics of two families with cone dystrophy with supernormal rod responses (CDSRR) presenting with a pseudodominant inheritance of disease.

Observations: Three affected members from each family were ascertained. Family 1 of Egyptian ancestry showed consanguinity, and Family 2 was of Northern Iraqi ancestry. Both families showed pseudodominance in their pedigrees.

Individuals presented with reduced visual acuity and nyctalopia. Macular disturbances were present in all, varying from a decreased foveal reflex to geographic atrophy. Electrophysiology showed reduced scotopic b-wave amplitudes and prolonged implicit times, and characteristic elevated b-wave amplitudes with high intensity flashes in all individuals.

Genetic analysis of Family 1 identified a complete homozygous deletion of the KCNV2 gene, and in Family 2 a homozygous missense variation of c.562T > A: p.(Trp188Arg).

Conclusions and importance: To our knowledge this is the first report of pseudodominance of CDSRR, with a novel pathogenic KCNV2 variant present in the second family. Clinicians evaluating these individuals should consider autosomal recessive disease manifesting as pseudodominant inheritance. In such cases, electrophysiology remains essential for making a definitive diagnosis.

1. Introduction

Cone dystrophy with supernormal rod responses (CDSRR) is a rare form of progressive autosomal recessive retinal dystrophy, first reported by Gouras et al. in 1983, with characteristic electrophysiology findings of unique rod dysfunction. This dystrophy is associated with pathogenic variants in the KCNV2 gene, which is expressed in retinal photoreceptors and encodes a modulatory subunit of the Kv8.2 voltage gated potassium channel protein (OMIM #610356). The phenotypic characteristics and mutation spectrum are further expanded in later studies, with all cases presenting in an autosomal recessive or sporadic manner.

Affected individuals with CDSRR typically present with reduced visual acuity, dyschromatopsia, photophobia, and central scotoma in the first two decades of life. Other associated features include nyctalopia, nystagmus and myopia. A spectrum of fundus appearances is described ranging from normal in the early stages, a variety of macular changes from mild retinal pigment epithelium (RPE) changes, to bull’s eye maculopathy, and a hyperautofluorescent perifoveal ring on fundus autofluorescence (FAF).

The characteristic electrophysiological features of KCNV2 retinopathy permit a possible early diagnosis of this disorder. The photopic responses are reduced and delayed, representing global cone dysfunction. Scotopic responses are subnormal to dim flashes, but increasing flash intensity results in an exaggerated response of the b-wave amplitude. Another diagnostic feature is the “squared a-wave” pattern in dark adapted ERG traces with bright flashes.

We describe two families, originating from Egypt and Northern Iraq, with KCNV2 associated CDSRR presenting with a pseudodominant inheritance of disease.

2. Findings

2.1. Methods

Patients with genetically proven KCNV2 were identified from the...
3. Results

3.1. Family 1

In family 1 of Egyptian ancestry, the parents were consanguineous (Fig. 1), with 3 children, and one parent affected. High to moderate myopic refractive error was noted in two cases. BCVA ranged from 6/18 to 6/45 (median = 6/30). IV:1 described poor vision since childhood which deteriorated over time, as well as night blindness and poor colour vision. His children (V:1 and V:3) were had reduced near and distance vision but didn’t complain of nyctalopia, and none had nystagmus.

Sequencing and subsequent qPCR identified a homozygous deletion of the 2 exon KCNV2 gene, present in all affected individuals, and present in the heterozygous state in the unaffected mother and sister (IV:2; V:2).

3.2. Family 2

Family 2 were Northern Iraqi Christians, and denied any consanguinity. All three affected individuals had diminished vision from childhood, and night blindness (Fig. 1). IV:4 and IV:7 complained of photophobia and photopsia, with nystagmus. BCVA ranged from 6/45 to 6/120 (median = 6/60).

A homozygous missense variation in exon 1 of KCNV2, c.562T > A; p.(Trp188Arg), was present in all three affected individuals. This variant is absent in databases of human variation, predicted to be probably damaging by PolyPhen-2 with the highest score of 1.0, and a SIFT score of 0.0. Additionally, a heterozygous missense variation was identified in IV:7 in the RP1L1 gene namely c.2814G > T p.(Glu938Asp), predicted to be probably damaging by PolyPhen-2 with a score of 0.996, but was not present in IV:4 or III:3.

Retinal examination findings of two families are demonstrated in Fig. 2a–f. ERG recordings from all patients are represented in Fig. 2g. 30 Hz and light adapted 3.0 amplitudes as well as scotopic b-wave amplitudes with low intensity flashes were considerably reduced and delayed in all individuals. Cone mediated function was abnormal with increased implicit time and significantly reduced amplitude to at least 10% of normal values for age-matched protocol in all three patients in Family 1. All affected individuals in both families showed a characteristic excessive increase in b wave amplitude, and squaring of the a-wave in dark adapted high intensity flash ERG recordings.

4. Discussion

307 retinal genes and loci are known (https://sph.uth.edu/retnet/disease.htm), with all inheritance patterns observed - autosomal dominant, recessive, and X-linked, compounded by reduced penetrance, variable expressivity, and unfavourable lyonisation. Next generation sequencing retinal disease panels may not identify the underlying causative gene in up to 30%, identify multiple pathogenic variants, or variants of unknown significance. Therefore it is the comprehensive clinical history and phenotyping, careful pedigree, examination of family members, and electrophysiology which are required to make a likely diagnosis, before and in conjunction with genetic testing.

This paper demonstrates these principles in two families with CDSRR which presented with apparent dominant inheritance. Electrophysiology identified CDSRR features, associated with complete homozygous deletion of KCNV2 in Family 1, and a novel missense variant in Family 2. CDSRR is reported in association with mutations in the KCNV2 (potassium channel, subfamily V, member 2) gene which
encodes a member of the family of voltage-gated potassium channels.\(^3\) It congregates with other channel subunits forming functional heteromeric channels that preserves an outward flow of potassium in dark conditions.\(^19,20\) Reported pathogenic variants of the \textit{KCNV2} gene include point mutations with amino acid substitutions, small or large insertion and deletion changes that causes stop codons, deletion of exons or deletion of one allele.\(^2,4,5,7,8\) Grigg et al.\(^21\) previously reported one case of a 6-year-old boy with CDSRR with both \textit{KCNV2} alleles deleted. Their case showed highly abnormal cone mediated function compared to other patients with \textit{KCNV2} mutations. In Family 1, affected individuals with the homozygous deletion of \textit{KCNV2} also demonstrated poor cone responses with reduced amplitudes of at least 10% of normal values on 30 Hz flicker and photopic potentials. In one study, 15.5% of mutations were large deletions,\(^2\) but no specific reference is made to the specific cone functioning in these patients, compared to other \textit{KCNV2} variants.

No characteristic symptom indicating CDSRR was present in our patients. Nyctalopia was relatively common in the adults, following dyschromatopsia, photophobia and photopsia in our case series as previously reported\(^9,10,12\) although nyctalopia is often a delayed presentation of this disorder. Abnormal head shaking and nystagmus is common in children with CDSRR and can show spontaneous resolution.\(^9\) One of the children in our series presented with moderate myopia with reduced vision and the other with exotropia showing no history of nystagmus or head shaking which may be due to relatively well preserved BCVA.

Macular changes described in CDSRR range from inconspicuous changes to more pronounced macular atrophic areas.\(^3,11,22\) Our cases exhibited this spectrum, from very subtle macular changes including accentuation of the foveal reflexes in children, to altered macular pigmentation, and geographic atrophy found in older patients. Individual IV:1 from Family 1 had minimal RPE changes without atrophic areas, demonstrating the utility of autofluorescence imaging in subtle fundus findings. A parafoveal hyperAF ring has been described in older patients encircling RPE atrophy if present.\(^23\) In younger patients diminished macular hypoAF has been reported,\(^9,11\) consistent with our case.
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series. SD-OCT demonstrated diffuse outer retinal atrophy and reduced central macular thickness with photoreceptor loss in affected patients, in keeping with the literature demonstrating varying levels of discontinuity and disruption of the retinal layers.\(^{11,12}\)

5. Conclusion

To the best of our knowledge this is the first report of pseudodominance of KCNV2-associated CDSRR, associated with a homozygous deletion in one pedigree and a novel pathogenic variant in the other. Pseudodominance may be encountered with consanguinity in multiple generations, as in Family 1. However, in Family 2 consanguinity was denied, and is possible this pathogenic variant has a higher frequency within the Northern Iraqi Christian community, representing a founder effect. These patterns may be seen in small ethnic groups living in isolated geographic areas, as well as in the presence of consanguinity. When faced with apparent dominant inheritance, particularly in endogamous pedigrees, or small isolate populations, comprehensive phenotyping and electrophysiology gains paramount importance in determining the correct diagnosis.

Patient consent

Patients and family members were recruited into the New Zealand Database of Inherited Retinal and Optic Nerve Disease, following written informed consent from patients or legal guardian. This study followed the tenants of the Declaration of Helsinki, with institutional ethics approval (Northern X Regional Ethics Committee, Ministry of Health, New Zealand (NTX/08/12/123/AM02), and Auckland District Health Board (ADHB, A+4290)). The patients consented to the publication of the cases orally.

Funding

Retina New Zealand, Omlber Trust, Cure Kids.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The following authors have no financial disclosures (GK, MR, DS, ALV).

Acknowledgements

John Chiang, Molecular Vision Laboratory, Portland, Oregon for genetic sequencing.