



Case report

CRB1 related retinal degeneration with novel mutation

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ABSTRACT

Purpose: To describe novel and previously unreported genetic mutations in the CRB1 gene in a patient with retinal dystrophy. To increase the genotype-phenotype understanding of CRB1-related retinal degenerative diseases and describe patients' response to therapy.

Observations: Patient was evaluated for progressive loss of central and peripheral vision. Fundus photography, fundus autofluorescence (FAF), fluorescein angiography (FA), and ocular-coherence tomography (OCT) were used in the evaluation. Genetic screening was performed to explore underlying mutations. Genetics revealed a previously reported, pathogenic variant in the CRB1 gene (c.2842+5G > A), and a novel mutation (c.4014T > A) whose clinical significance is uncertain due to the absence of conclusive evidence. This case is phenotypically unique in that CME was refractory to therapy, while CME in CRB1 related maculopathy typically responds well to treatment.

Conclusions and importance: This study adds a breadth of phenotypic understanding to genetic analysis in CRB1 related retinal degenerative conditions. The newly described CRB1 variant mutation c.4014T > A may portend a poor prognosis for CME responsiveness to therapy. Genetic testing in an otherwise unexplained CME event may be useful to identify underlying CRB1 variants and reveal genotype-phenotype correlations, which may alter the treatment plan and prognosis.

1. Introduction

Variant mutations in the CRB1 gene (Crumbs homologue 1) have been reported in patients with a variety of phenotypes of retinal dystrophies.^{1–3} CRB1 associated retinopathies include Leber Congenital Amaurosis (LCA) and retinitis pigmentosa (RP), and are often accompanied by characteristic features, including preservation of the paraarteriolar retinal pigment epithelium (PPRPE), abnormal (often coarse) retinal lamination, retinal telangiectasia with exudation (or Coats-like vasculopathy), and early-onset maculopathy.² This case report reveals a rare, albeit previously reported, CRB1 mutation believed to alter splicing that is likely pathogenic (c.2842+5G > A), and an additional CRB1 mutation that has not been previously reported of unknown significance (c.4014T > A) in a patient with persistent non-leaking cystoid macular edema in both eyes refractory to local and topical therapy.

2. Case report

A twenty-one year old Caucasian female was referred for further

evaluation of progressive loss of central and peripheral vision for several years associated with cystoid macular edema of unknown etiology.

On examination, best-corrected visual acuity was 20/60 OD and 20/50 OS, with intraocular pressures within normal limits. Her pupillary and ocular motility exam was unremarkable. Confrontational visual fields showed temporal field loss OU. Her anterior segment examination revealed mild posterior subcapsular cataracts OU. The posterior segment examination in the right eye was significant for pigmentary changes in an annular pattern circumscribing the posterior pole (right eye greater than left eye) and cystoid macular edema both eyes (Fig. 1a and Fig. 1b).

Autofluorescence imaging revealed hypoautofluorescence in the macula with parafoveal petalloid hyperautofluorescence (Fig. 1c and d), and hypoautofluorescence in an annular pattern circumscribing the posterior pole, most prominent in the peripapillary area (right eye greater than left eye, Fig. 1c and d). Fluorescein Angiography (FA) showed window defects corresponding to the areas of annular hypoautofluorescence and the absence of any leakage in the macula OU (Fig. 1e and f). Optical coherence tomography (OCT) showed intraretinal cystoid changes in the fovea and parafoveal area with

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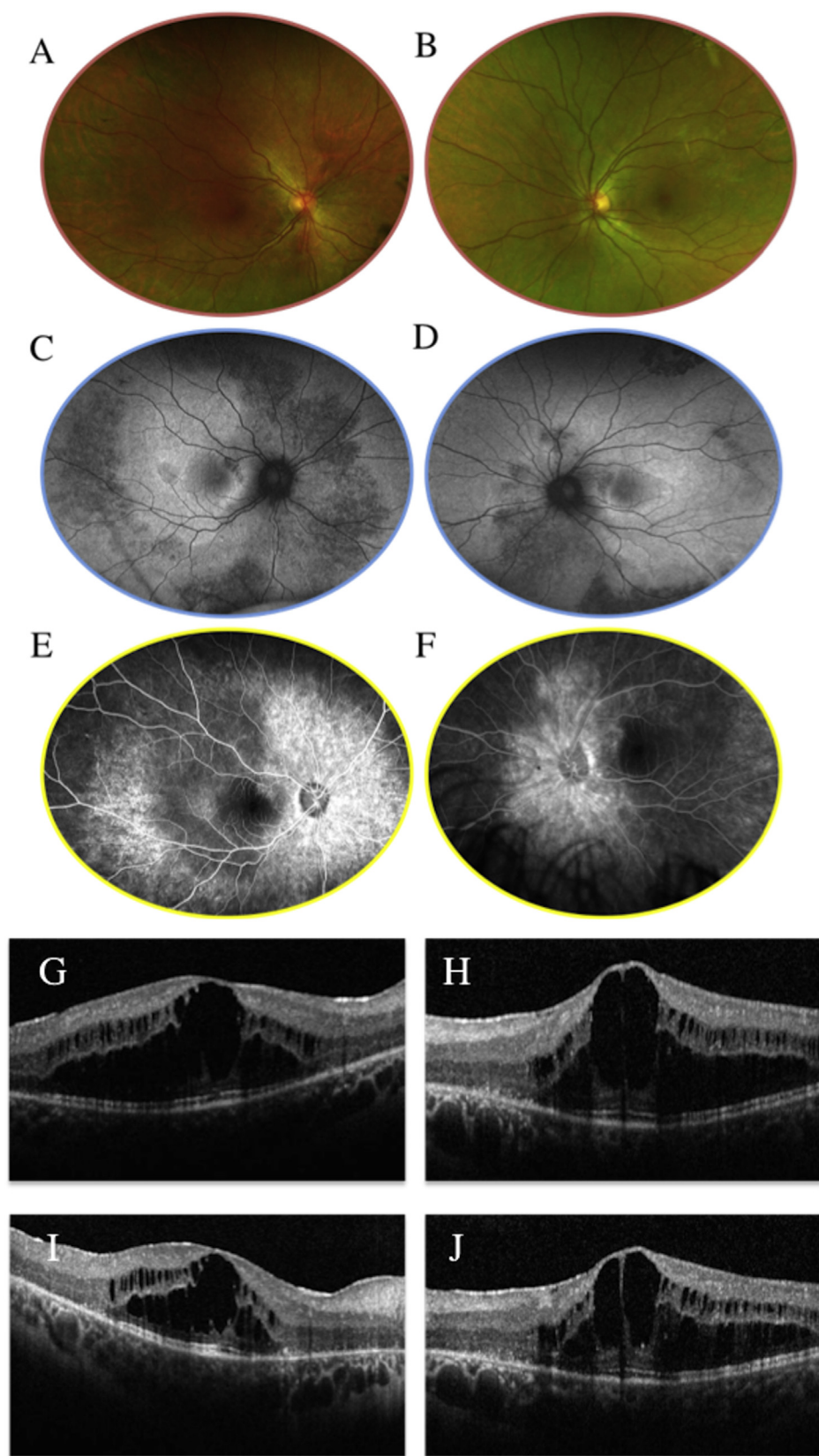


Fig. 1. Fundus Photography in both eyes showing pigmentary changes in an annular pattern circumscribing the posterior pole (right eye greater than left eye) (Fig. 1a and b). Wide field Optos fundus Autofluorescence showing hypoautofluorescence in the macula with parafoveal petalloid hyperautofluorescence and hypoautofluorescence in an annular pattern circumscribing the posterior pole (Fig. 1c and d). Fluorescein Angiography showed window defects corresponding to the areas of annular hypoautofluorescence and the absence of any leakage in the macula (Fig. 1e and f). Optical coherence tomography (OCT) showed intraretinal cystoid changes in the fovea and parafoveal area with surrounding disruption of the ellipsoid zone and outer nuclear layers both eyes, refractory to treatment (Fig. 1g–j).

surrounding disruption of the ellipsoid zone and outer nuclear layers both eyes. The cystoid changes persisted for 18 months to date despite treatment with sub-tenons triamcinolone and topical ketorolac 0.5% and dorzolamide 2% (Fig. 1g–j).

Full-field electroretinogram (ERG) revealed findings consistent with

cone-rod degeneration in both eyes, and 24-2 h Humphrey visual field showed temporal visual field loss in both eyes. Genetic screening using Inherited Retinal Disorders NextGen Sequencing Panel revealed a previously reported likely pathogenic, heterozygous variant in the CRB1 gene (c.2842+5G > A), as well as a previously unreported

heterozygous variant of uncertain significance in CRB1 (c.4014T > A).

3. Discussion

To our knowledge, this is the first report of a patient with retinal degeneration with CME associated with the c.4014T > A variant. The mutation is predicted to result in the amino acid substitution pAsp1338Glu and appears to be rare in the general population.

The AA substitution prediction programs PolyPhen-2, SIFT, and Mutation Taster predict the change to be benign. However, at this time its clinical significance is uncertain due to the absence of conclusive functional and genetic evidence, given this is the first documented report of this mutation (gnomAD). This case is phenotypically unique in that CME was refractory to therapy, while CME in CRB1 related maculopathy usually responds well to treatment including topical dorzolamide 2% and topical non-steroidals.¹

4. Conclusion

Our report further affirms that CRB1 mutations are a rare cause of maculopathy in patients with retinal dystrophies. While one mutation-case correlation does not provide conclusions regarding the mutation's effect on therapy response, it is not unreasonable to presume that given this mutation's rarity in the population, it is possible that the CRB1 variant c.4014T > A may portend a poor prognosis for CME responsiveness to therapy. Moreover, routine genetic testing in CRB1 associated CME patients are recommended by the authors to further reveal

the genotype-phenotype relationship, and gather evidence that may provide prognostic implications to various mutations.

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Patient consent

The patient consented to publication of the case orally.

Declaration of competing interest

The authors have not received grant support or research funding and do not have any proprietary interests in the materials described in the article. The manuscript has not been previously presented at a meeting or submitted to another journal.

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