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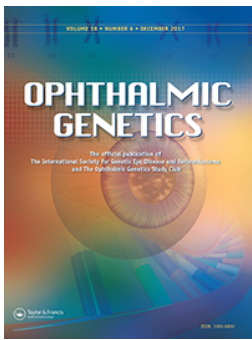
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CASE REPORT

Inner retinal dystrophy in a patient with biallelic sequence variants in *BRAT1*

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ABSTRACT

Background: Mutations in the *BRCA1*-associated protein required for the ataxia telangiectasia mutated (ATM) activation-1 (*BRAT1*) gene cause lethal neonatal rigidity and multifocal seizure syndrome characterized by rigidity and intractable seizures and a milder phenotype with intellectual disability, seizures, nonprogressive cerebellar ataxia or dyspraxia, and cerebellar atrophy. To date, nystagmus, cortical visual impairment, impairment of central vision, optic nerve hypoplasia, and optic atrophy have been described in this condition. This article describes the retinal findings in a patient with biallelic deleterious sequence variants in *BRAT1*.

Materials and methods: Case report of a child with biallelic sequence variants in the *BRAT1* gene.

Results: This patient had developmental delay, microcephaly, nystagmus, and esotropia, and full-field electroretinography (ERG) revealed an inner retinal dystrophy. She was found on exome sequencing to have compound heterozygous sequence variants in the *BRAT1* gene: one maternally inherited frameshift variant (c.294dupA, predicting p.Leu99Thrfs*92), which has previously been reported, and one paternally inherited novel missense variant (c.803G>A, p.Arg268His), which is likely to affect protein function.

Conclusions: Biallelic sequence variants in *BRAT1* have been reported to cause a variety of ocular and systemic manifestations, but to our knowledge, this is the first report of inner retinal dysfunction manifest as selective loss of full-field ERG scotopic and photopic b-wave amplitudes.

ARTICLE HISTORY

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KEYWORDS

BRAT1; electroretinography; retinal dystrophy

Introduction

Mutations in the *BRCA1*-associated protein required for the ataxia telangiectasia mutated (ATM) activation-1 (*BRAT1*) gene are associated with lethal neonatal rigidity and multifocal seizure syndrome (RMFSL, OMIM# 614506). This is an autosomal recessive epileptic encephalopathy in which patients develop rigidity and seizures in the first weeks of life.¹ Patients typically demonstrate intractable myoclonic seizures, hypertonia, arrested head growth, and episodes of apnea-bradycardia which lead to cardiac arrest and death usually within the first months or years of life.² Recently, several reports have characterized a milder phenotype, comprising ataxia, intellectual disability, and cerebellar atrophy (sometimes with microcephaly and epilepsy).^{3–5} To date, there have been no reports of retinal abnormalities in patients with *BRAT1* sequence variants. Here, we describe the first case of inner retinal dystrophy in a patient who is compound heterozygous for two deleterious sequence variants in *BRAT1*.

Case report

During the pregnancy, the mother was treated with lovenox and aspirin because of a history of asymptomatic factor V Leiden disorder. Prenatal ultrasound was unremarkable. The

patient was born at term by induced vaginal delivery. At 6 weeks of age, she was noted to have delayed growth, with weight and occipitofrontal circumference values below the 5th percentile. She was noted to have nystagmus and to display reduced responses to visual stimuli at 6 weeks of age. Between 6 and 24 months of age, she had multiple short seizures lasting 10–15 seconds which were associated with fevers. She was diagnosed with febrile seizures and has not been treated with antiepileptic agents. She had no episodes of apnea. By 20 months of age, her weight had normalized to the 60th percentile for age but her head size remained small for age at the 10th percentile. Her motor development remained delayed, but she was able to sit without support and made movements to stand with her knees. A cranial magnetic resonance imaging scan has not been performed.

Her maternal grandfather had strabismus and her maternal grandfather's sister had oculocutaneous albinism, but family history was otherwise unremarkable. She has a sister who is 3 years older and developing normally. There is no known parental consanguinity or history of retinal disease. When first reviewed at 2 months of age, she had large amplitude nystagmus, but no strabismus. Ocular movements were full. Anterior segment examination was normal and dilated fundus examination showed a blonde fundus (as shown in Figure 1A, acquired at 19 months of age). At 9 months of age, she had

developed a large esotropia. Cycloplegic refraction was +1.75 diopters sphere in each eye. The patient was prescribed full hyperopic correction, which did not significantly change the esotropia. A DNA sample of the patient underwent single-nucleotide polymorphism array which revealed a ~420 kb interstitial duplication within 22q11.1 (genomic coordinates: 17,026,095-17,446, and 157) which is maternally inherited. This is likely benign. Whole exome sequencing (WES, GeneDx Laboratory, Gaithersburg, MD, USA) was then carried out. Exon regions were targeted with the Agilent SureSelect XT2 All Exon V4 kit. Targeted regions were sequenced using the Illumina HiSeq 2000 sequencing system (Illumina Inc., San Diego, CA). Samples from the patient's parents were both submitted for variant segregation analysis. Two variants in a *BRAT1* were identified: a maternally inherited variant, c.294dupA (p.Leu99ThrfsX92), is a frameshift, and a paternally inherited variant, c.803G>A (p.Arg268His), is a missense substitution. This latter variant has not previously been reported in normal controls in the ExAC browser or 1000 Genomes databases. The nucleotide substitution occurs at the last base pair of exon 5 and is predicted to result in loss of the donor splice site; *in silico* analyses predict that it likely damages protein structure and function (PolyPhen-2 score 1.0, probably damaging and MutationTaster—disease causing, $p = 0.999$). No other plausible causative variants were identified.

At 19 months of age, she underwent strabismus surgery with bilateral medial rectus muscle recessions of 5.5 mm. An electroretinogram (ERG) was also performed under anesthesia at the time of surgery. The ERG responses were recorded using a portable full-field ERG system (Espion, Diagnosys LLC, Lowell, MA) with pediatric Burian-Allen contact lens electrodes (Hansen Ophthalmic Development Laboratory, Coralville, IA). Normal ERG responses were measured from six healthy subjects aged 11–38 months (mean age 19.3 months, standard deviation 10.0 months) under the same anesthetic conditions. The ERG showed severely reduced rod-mediated responses to a dim flash and a negative response to the scotopic bright flash with b-wave amplitudes reduced by more than two standard deviations below the normal mean, but a-wave amplitudes within normal limits. The photopic single-flash b-wave and 30 Hz flicker amplitudes were reduced by more than two standard deviations below the normal mean with normal implicit times and the 30 Hz flicker responses showed an abnormal waveform (Figure 2). The findings were consistent with inner retinal dysfunction with reduced on-bipolar responses. Fundus examination was unremarkable (Figure 1A). Optic coherence tomography (OCT) examination performed using the handheld OCT (Envisu, BiopTigen, Inc., Morrisville, NC) revealed a normal foveal contour with intact-appearing inner and outer retinal layers (Figure 1B).

When last seen at 20 months of age, she was able to fix and follow targets with each eye. Her nystagmus was unchanged. There was a residual small-angle alternating esotropia with a left eye fixation preference. Spectacle correction had been discontinued, but she continued with occlusion therapy for the right amblyopia. She continues to be developmentally delayed and to have mild generalized hypertonia, but has not had any further seizures.

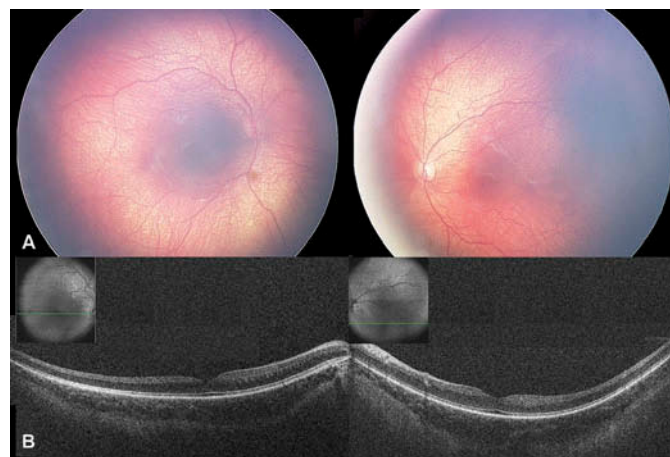


Figure 1. Fundus photographs (Retcam, Clarity Medical Systems, Pleasanton, CA) (A) and handheld optical coherence tomography (OCT, Envisu, BiopTigen, Inc., Morrisville, NC) images (B) of patient at 19 months of age. Fundus photographs demonstrate slightly pale retinal periphery with no bone spicule pigmentary changes and mild retinal pigment epithelial mottling in the macula bilaterally. OCT images through the fovea revealed a good foveal contour with normal inner and outer retinal layers and no intraretinal fluid.

Discussion

The *BRAT1* gene, also known as *BAATI*, encodes the BRAT1 protein which interacts with *BRCA1* (a tumor suppressor) responsible for cell-cycle signaling pathways, particularly in response to DNA damage.⁶ *BRAT1* has also been reported in pathways controlling cell proliferation and mitochondrial function.⁷

Biallelic mutations in this gene can cause lethal neonatal rigidity and multifocal seizure syndrome, but milder phenotypes have been reported. Our patient was found to have two *BRAT1* sequence variants that were predicted to be deleterious. The first was a maternally inherited heterozygous variant, c.294dupA, predicting p.Leu99Thrfs*92 and a premature stop codon with likely loss of function, either through premature protein truncation or through nonsense-mediated decay. This variant has previously been reported in a child with neonatal onset of hypertonia and seizures.³ The second variant was a paternally inherited missense variant, c.803G>A, predicting p.Arg268His. This variant has not previously been reported in normal controls in the ExAC browser or 1000 Genomes databases. The nucleotide substitution occurs at the last base pair of exon 5 and is predicted to result in loss of the donor splice site; *in silico* analyses predict that it likely damages protein structure and function. However, functional studies to demonstrate the deleterious nature of this variant have not been performed, and the effects of this variant on protein function are unknown.

All patients with lethal neonatal rigidity and multifocal seizure syndrome reported to date have shared similar clinical features including microcephaly, developmental delay, seizures, and apneic episodes. Srivastava et al.⁴ review all currently reported *BRAT1* variants which include four homozygous frameshift variants,^{1,2,5,8,9} one compound heterozygous change causing an alteration of exon splice pattern,⁵ and two compound heterozygous changes with a frameshift mutation combined with a missense variant.^{1,3}

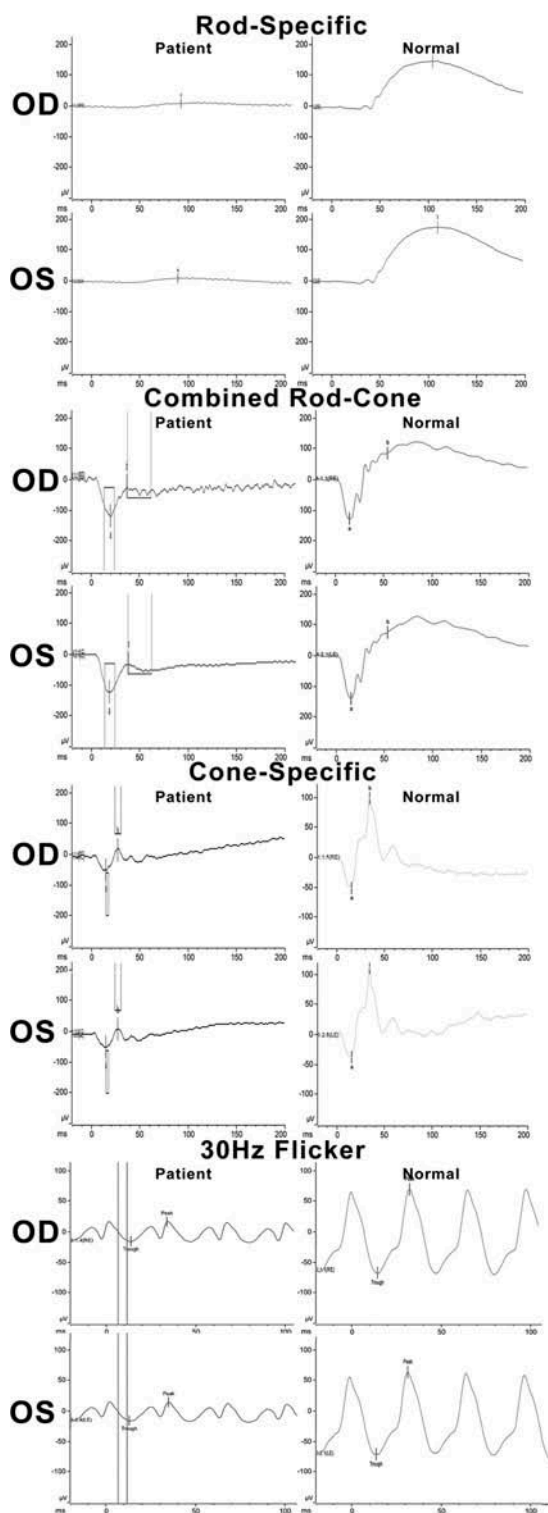


Figure 2. Full-field electroretinogram (ERG) of patient compared to age-controlled normal patient tested under the same anesthetic conditions as the patient. The patient had severely reduced rod-mediated b-wave responses and a negative response to the scotopic bright flash. The photopic single-flash responses were reduced in amplitude with normal implicit time. The 30 Hz flicker responses were reduced and showed a notched waveform.

Here, we report a patient with compound heterozygous mutations in the *BRAT1* gene: one previously reported frame-shift mutation and one novel missense mutation. She demonstrated features consistent with lethal neonatal rigidity and multifocal seizure syndrome, including microcephaly, developmental delay, seizures, and hypertonia. Unlike many cases in the literature, this patient did not demonstrate intractable seizures and continued to make progress at 20 months of age. She was also found to have nystagmus and esotropia (both of which have been previously described)⁴ and an inner retinal dystrophy, yet to be associated with mutations in *BRAT1*. It is unclear how mutations in this gene may affect bipolar cell function, but detailed ocular phenotyping including ERG recording in other cases may help to characterize the ocular phenotype better and improve understanding of *BRAT1* in retinal function.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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