Novel Mutation in BEST1 Associated With Retinoschisis

Best vitelliform macular dystrophy (BVMD) is caused by mutations in BEST1 (also known as VMD2; OMIM 153700) on the long arm of chromosome 11. An array of BEST1 phenotypes have now been characterized, including microcornea, rod-cone dystrophy, early-onset cataract, posterior staphyloma syndrome, vitreoretinchoroidopathy, and adult-onset foveomacular vitelliform dystrophy. BEST1 encodes bestrophin, a 585–amino acid protein with more than 120 described mutations. We herein present 2 siblings with bilateral retinoschisis and electroretinography (ERG) consistent with BVMD associated with a novel mutation in BEST1.

Report of Cases. Case 1. An 8-year-old Jamaican girl presented with a several-week history of blurry vision in both eyes. Best-corrected visual acuity (BCVA) at presentation was 20/40 OD and 20/60 OS. Fundus examination of the right (Figure 1A) and left (Figure 1B) eyes was significant for bilateral macular retinoschisis and serous retinal detachments. Ocular coherence tomography demonstrated central macular thickness to be 381 μm OD (Figure 2A) and 430 μm OS (Figure 2B). Fluorescein angiography demonstrated multiple hyperfluorescent spots in the periphery with central leakage in both eyes (Figure 3). Indocyanine green angiography revealed multiple hypo-fluorescent spots in the periphery with hyperfluorescence centrally. Electroretinography demonstrated normal rod, rod-cone, high-A
intensity rod-cone, oscillatory, cone, and cone flicker responses in the patient’s right and left eyes (Figure 4). Multifocal ERG demonstrated severely impaired central macular function in the right eye (Figure 5A and B) and left eye (Figure 5C and D). An electrooculogram demonstrated severely subnormal light response of the standing potential in both eyes, with an Arden ratio of 1.27 and 1.26 in the right and left eyes, respectively (Figure 6). The patient’s blood was sent for genetic analysis (the John and Marcia Carver Nonprofit Genetic Testing Laboratory, University of Iowa) and direct genetic sequencing of the entire coding region of Best1 revealed a novel mutation with probable high penetrance. Specifically, a heterozygous GAG to AAG nucleotide substitution in the coding sequence of Best1 was identified. Notably, sequencing of the entire coding region of Xlrs1 demonstrated no disease-causing variations. Follow-up at 2 years demonstrated stable visual acuity, fundus examination, and ocular coherence tomography findings.

Case 2. The brother of case 1, a 12-year-old Jamaican boy, reported difficulty reading for 3 years. His BCVA at presentation was 20/80 OD and 20/40 OS. Fundus examination was significant for vessel sheathing in both eyes (though most prominent at the superior arcuate fibers in his left eye), central retinal pigment epithelial (RPE) changes, bilateral macular retinoschisis, and serous retinal detachments. Fluorescein angiography demonstrated multiple hyperfluorescent spots in the periphery with central leakage while indocyanine green angiography yielded significant multiple hypofluorescent spots in the periphery with hyperfluorescence centrally. Genotypic analysis of the patient’s blood revealed the same mutation in Best1 demonstrated in his sister. Also like his sister, sequencing of the entire coding region of Xlrs1 in this patient also demonstrated no disease-causing variations. Follow-up at 2 years demonstrated stable visual acuity, fundus examination, and ocular coherence tomography findings of the right eye and worsening visual acuity (20/100 BCVA) with a new full-thickness macular hole in the left eye (Figure 7).

Comment. These 2 cases exhibit clinical findings consistent with BVMD: bilateral symmetric multifocal macular lesions, suggestions of a central vitelliform lesion on fluorescein angiography, and a normal full-field ERG with an abnormal electrooculogram. The unusual aspect of the cases is the presence of subretinal fluid and retinoschisis associated with a novel mutation in Best1.

Fluorescein angiography in BVMD varies by stage but classically demonstrates early hyperfluorescence (from RPE atrophy) with late pooling. This is demonstrated in the central macula in our patients (Figure 3), with fluorescein angiography of the left eye of case 1 consistent with a pseudohypopyon lesion.

Full-field photopic and scotopic ERG responses in BVMD are usually normal in a-wave and b-wave amplitude, dark adaption, and recovery time, reflecting mostly extramacular photoreceptor function. Multifocal ERG, however, may demonstrate variable central loss (depending on the stage of the vitelliform lesion) generally believed to be a reflection of abnormal macular cone and bipolar cell function. In the case of the first sibling, the severity of her phenotype expectedly produced this central attenuation on multifocal ERG (Figure 5), with no abnormalities on full-field ERG. The characteristic electrooculogram finding in BVMD is a decreased Arden ratio, noted even in asymptomatic carriers. The electrooculogram in case 1 demonstrated a reduction in the Arden ratio to a level consistent with BVMD (Figure 6).

Wild-type Best1 encodes a transmembrane protein localized to the basolateral plasma membrane of the RPE cell, which probably functions as a Ca2+-sensitive chloride channel. In our siblings, 6 separate polymorphisms were identified in sequencing Best1. Only 2 of these were deemed phenotypically significant:

Figure 3. Fluorescein angiography of case 1. Fluorescein angiography of the right (A) and left (B) eyes demonstrates bilateral, heterogeneous, central fluorescein staining that mimics a fluid level. Late hyperfluorescence peripherally, corresponding to vitelliform lesions seen in Figure 1, is also noted.
Figure 4. Electroretinogram of case 1. Scotopic electroretinogram responses of the right (OD) (A) and left (OS) (B) eyes demonstrate a-wave amplitudes of −9.36 and −8.70 µV, b-wave amplitudes of 213.7 and 209 µV, and implicit times of 28 and 27 and 115 and 119 milliseconds, respectively. Maximal combined response of the right and left eyes demonstrates a-wave amplitudes of −123 and −117 µV, b-wave amplitudes of 318 and 276 µV, and implicit times of 18 and 18 and 63 and 64 milliseconds, respectively. Oscillatory potentials of the right and left eyes are 38.8 and 43.5 µV, respectively. Photopic responses of the right and left eyes demonstrate a-wave amplitudes of −25.7 and −33.3 µV, b-wave amplitudes of 145 and 143 µV, and implicit times of 15 and 16 and 34 and 34 milliseconds, respectively. The 30-Hz flicker responses of the right and left eyes demonstrate b-wave amplitudes of 130 and 128 µV with implicit times of 30 and 30 milliseconds, respectively. Div indicates division; F, flicker; and OP, oscillatory potential.
Figure 5. Multifocal electroretinogram of case 1. Multifocal electroretinogram of the control right eye (A), the patient’s right eye (B), the control left eye (C), and the patient’s left eye (D) demonstrates severe macular dysfunction in both eyes. Both eyes demonstrate central depression of cone responses with P1 amplitudes reduced by approximately 71% of reference values in both eyes.

Figure 6. Electrooculogram of case 1. Electrooculogram of the right (A) and left (B) eyes demonstrates an attenuated light response of the standing potential in both eyes, with an Arden ratio of 1.27 and 1.26 in the right and left eyes, respectively. Downward arrowheads indicate a dark trough and upward arrowheads, a light peak.

Figure 7. Optical coherence tomography of case 2. Optical coherence tomography of the left eye with foveal sectioning reveals retinoschisis with an extensive serous retinal detachment. Also seen is a full-thickness macula hole at the fovea.
a single guanine to adenosine substitution resulting in a Glu213Lys amino acid change and a frameshift mutation at amino acid position 404 (Pro404del1ctc). The exact effect of the amino acid substitution, from glutamic acid (which has a negative charge at physiologic pH) to lysine (which has a positive charge), is unclear. However, a similar missense mutation in hemoglobin (specifically a glutamic acid to valine substitution) retards ionic cross-linking and results in altered tertiary protein structure to yield, most famously, the “sickling” of erythrocytes characteristic of sickle cell anemia.

Dysfunction of bestrophin likely indirectly impairs apical fluid transport. This then indirectly impairs RPE phagocytosis of photoreceptor outer segments, lysosomal function, and regulation of subretinal fluid, yielding the characteristic vitelliform lesions and serous retinal detachments characteristic of BVMD.6 Similarly, the phenotypic severity of the siblings we describe, particularly serous retinal detachments and retinoschisis, suggests the mutation they harbor grossly affects chloride transport and Ca ++ signaling, both thought to underlie RPE ionic transport and fluid homeostasis.

In summary, we herein present 2 siblings with BVMD, both exhibiting a previously unreported missense mutation in BEST1 as well as the novel findings of retinoschisis and a full-thickness macular hole.

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Congenital Bilateral Aplasia of Medial Recti in a Family

A 50-year-old male patient from a nonconsanguineous marriage (case 1) was seen with outward deviation of both eyes since birth. He and his 2 sons (case 2, 24 years old, and case 3, 21 years old) had similar concerns of outward deviation of eyes. There was no history of any orthoptic treatment like occlusion, prism, or convergence exercises. There was no other medical or surgical ailment in either the father or the sons. Pedigree analysis revealed no similar ailment in any family member other than the father and his 2 sons; the only other issue was a stillbirth.

Report of Cases. Case 1. On ocular examination of the father, visual acuity was 6/6 OD with −1.0 diopter sphere and −3.5 diopters cylinder, axis 80°, and 6/9 OS with −1.0 diopter sphere and −3.0 diopters cylinder, axis 80°. Examination of the anterior and posterior segments was normal and unremarkable. He had gross limitation of adduction (−3) in both eyes, 80–prism diopter exotropia at distance, and 85–prism diopter exotropia at near (Figure 1A). There was no limitation of vertical eye movements. The forced duction test revealed only a tight lateral rectus on both sides. An intraoperative forced duction test confirmed a mildly tight lateral rectus, and a thin empty sheath of medial rectus (MR) was found in both eyes (Figure 2A). A decision was made to do split vertical rectus transposition and Foster augmentation (Figure 2B) with lateral rectus recession of 10 mm on each side. Magnetic resonance imaging of the patient showed thin MR muscle on both sides (Figure 3). Postoperative recovery was uneventful. His deviations measured 25 prism diopters exotropia at distance and he had limited adduction (−1) after 4 weeks (Figure 1B). Subsequent follow-up after 3 months and 6 months did not show any further change.

Cases 2 and 3. Both his sons had similar large exodeviations. Magnetic resonance imaging in both cases revealed thin MR on both sides while intraoperatively, only an empty muscle sheath was seen. They were managed similarly with good postoperative results. Follow-up of both cases was satisfactory with minimal (<20–prism diopter exotropia) deviation.

Comment. Agenesis or hypoplasia of the extraocular muscles have been grouped as congenital cranial dysinnervation disorders with absent muscle development or abnormal innervation of the target muscle. Magnetic resonance imaging may show affected muscles and cranial nerves to be normal, hypoplastic, or absent.2-4 There is only 1 reported case of unilateral agenesis of MR muscle by Girard and Neely5 in 1958 and another case of bilateral agenesis of MR muscle by Houtman et al6 in 2009. However, familial occurrence of this anomaly has never been reported, to the best of our knowledge.

Our case appears to be a very rare case of autosomal dominant aplasia of MR seen in a male patient and his 2 sons. In all 3 cases, MR was not absent on the magnetic resonance image, which only showed mild hypoplasia; however, the intraoperative findings showed only a thin sheath of muscle capsule. As pointed out by Demer et al,3 the orbital and global fibers have differences in