Novel De Novo Mutation in a Patient With Best Macular Dystrophy

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Objective: To report a novel de novo vitelliform macular dystrophy (VMD2) mutation in a patient with Best macular dystrophy.

Methods: Best-corrected visual acuity, dilated fundus examination, and electro-oculography were performed in a patient with Best macular dystrophy and his parents. Both the patient and his parents also had blood samples drawn, and their DNA was analyzed by direct genomic sequencing.

Results: A heterozygous VMD2 gene missense mutation in exon 2 (Thr6Ala [ACA>GCA]) was identified in the proband. This mutation was not present in his clinically unaffected parents.

Conclusions: A novel de novo mutation in the VMD2 gene was found in a patient whose phenotype and electro-oculographic findings were characteristic of Best macular dystrophy, whereas both parents were phenotypically and genetically unaffected. The findings in this family document that a de novo mutation needs to be considered when an isolated family member is found to have a Best disease phenotype.

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Best macular dystrophy was initially described in 1905 and was subsequently recognized to have an autosomal dominant inheritance. It is characterized by a vitelliform-appearing lesion generally observed initially between 3 and 15 years of age. A distinctive feature of this disease is an abnormal light-peak to dark-trough ratio observed on electro-oculography, not only in affected individuals but also in clinically unaffected carriers.

A mutation in the Best vitelliform macular dystrophy (VMD2) gene has been reported in patients affected with this disease. The gene produces a protein that has been termed bestrophin. This protein has been localized predominantly to the plasma membrane of the retinal pigment epithelium.

To our knowledge, only 1 spontaneous VMD2 gene mutation has been reported previously (exon 6, C221W). This mutation was observed in a 4-year-old girl whose parents did not show any evidence of a carrier state on funduscoppy or genetically. Electrophysiologic findings were not reported for either of the 2 parents. We report a second de novo and novel mutation in the VMD2 gene in a patient with Best disease whose parents were clinically and electrophysiologically unaffected in addition to not showing the same VMD2 gene mutation.

Methods

An 8-year-old patient was diagnosed as having Best macular dystrophy on the basis of characteristic fundus changes and an abnormal Arden ratio on electro-oculography. Blood samples were obtained from both the patient and his parents for DNA analysis.

Best-corrected visual acuity was determined for the patient and his parents with Snellen acuity charts. Slitlamp biomicroscopy of the anterior segment was performed, and intraocular pressure was measured by applanation tonometry. Detailed fundus examination was performed by direct and indirect ophthalmoscopy. An electro-oculographic measurement was obtained using a protocol described previously.

Genomic DNA was extracted from peripheral blood of the patient and his parents and screened for sequence changes in exons 2 through 8 of the VMD2 gene using fluorescent deoxynucleotides on an automated sequencer (model 377; Applied Biosystems, Fos...
ter City, Calif]. Mutations were identified by the approximately equal peak intensity of 2 fluorescent dyes at the mutant base. All sequencing was bidirectional. Short tandem repeat polymorphism analysis was used to analyze segregation of alleles and parental identity.

Informed consent was obtained from all study participants. This project was approved by the institutional review board at the University of Illinois Medical Center at Chicago.

RESULTS

CASE REPORT

The 8-year-old proband was of English, German, and Polish ancestry. He was referred for the evaluation of possible Best macular dystrophy. He had no subjective visual complaints. A general review of systems showed no known systemic disorders. A review of the family pedigree disclosed that the patient had a maternal aunt with retinitis pigmentosa.

His visual acuity was correctable to 20/20−1 OD with −2.00 + 0.50 × 90 diopters and 20/20−1 OS with −0.50 + 0.25 × 95 diopters. He read Jaeger 1 for near. The results of color vision screening with the Ishihara plates were normal. Intraocular pressure was 10 mm Hg and 11 mm Hg in the right and left eye, respectively. The anterior segment was normal. Fundus examination showed normal-appearing optic discs with normal retinal vessels. Each eye showed a vitelliform-appearing lesion within the fovea (Figure).

The patient’s electro-oculographic results showed a light-peak to dark-trough ratio of 1.33 OD and 1.20 OS. Both were well below the lower normal limit of 1.75.

The patient’s parents had visual acuity that was correctable to 20/20 OU. Each had normal ocular examination results with no evidence of a retinal lesion. Electro-oculography was performed on the patient’s mother on 2 separate occasions within a period of 3 weeks. She showed light-peak to dark-trough ratios of 3.00 OD or greater on both visits. His father’s electro-oculographic ratio was 3.35 OD and 2.69 OS. All values were well above the lower limit of normal.

GENETIC ANALYSIS

A heterozygous VMD2 gene missense mutation in exon 2, nucleotide 16 (Thr6Ala [ACA>GCA], was identified in the proband, whereas this mutation was not present in either of his clinically unaffected parents. Additional non–disease-causing polymorphisms were also identified. The proband and his father were heterozygous for the Leu37Leu, Ile73Ile, and C>T 24-base pair 5’ exon 5 variations, whereas his mother showed Leu37Leu and C>T 24-base pair 5’ variants. Parental identity studies were performed using a short tandem repeat polymorphism analysis. We used 3 markers, D4S2367, D5S820, and D11S956, that are present on 3 different chromosomes. The analysis showed that the designated parents were the biological mother and father.

COMMENT

Previous observations have supported the contention that patients with Best macular dystrophy manifest abnormal electro-oculographic light-peak and dark-trough ratios. In addition, it has been assumed that such individuals will show a mutation in the VMD2 gene. We observed a novel de novo mutation in a single member of a family whose parents were both clinically and electrophysiologically unaffected and did not show a mutation in the VMD2 gene. Our findings, in addition to those of one other report, have implications for the diagnosis and genetic counseling of an isolated member of a family with a vitelliform-like macular lesion. These results also suggest that de novo mutations in the VMD2 gene may occur more frequently than might previously have been anticipated.
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REFERENCES


From the Archives of the Archives

The Bacillus subtilis was found to be the cause of acute conjunctivitis in 17 patients who had got earth into their eyes. It was not found alone but associated with staphylococci and pneumococci. Its virulence was variable.