Published in final edited form as:

J AAPOS. 2009 April ; 13(2): 215–217. doi:10.1016/j.jaapos.2008.11.005.

Genetic and clinical evaluation of juvenile retinoschisis

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Abstract

Juvenile retinoschisis is a rare retinal dystrophy caused by RS1 gene mutations.¹ Clinical examinations and molecular testing definitively diagnosed juvenile retinoschisis in 2 male infants, one of whom had a novel mutation not previously reported in the United States. Genetic testing may be the simplest way to confirm this diagnosis in infants.

Case Reports

Patient 1

A 6-month-old boy was examined for frequent turning-in of his left eye, a symptom that began at 2 months of age. Prenatal, perinatal, and developmental history was unremarkable. On examination, he was found to have 30^Δ of esotropia and a preference for the right eye. Anterior segment examination was unremarkable. Dilated fundus examination under anesthesia of the right eye revealed normal disk and retinal vessels, but retinal pigment epithelial mottling was identified in the macula (Figure 1A). A retinoschisis cavity, extending up to the inferior arcade, was noted inferiorly. At the 7 o'clock position, there was a large ellipse-shaped inner-layer hole with an adjacent area of tortuous vessels near the ora serrata. Scattered vitreous hemorrhages were present in the midvitreal cavity, and punctate retinal hemorrhages were noted in the inferior periphery. No obvious retinal detachment was noted. In the left eye, the disk and vessels were normal, but the foveal reflex was blunted. A large, highly elevated dome-shaped retinoschisis cavity was draping over the macula (Figure 1B). Optical coherence tomography of the right eye showed a lamellar schisis; the left eye showed a large, highly elevated schisis cavity (Figure 2). Dilated fundus examination of the mother was unremarkable. There was no family history of retinal diseases or visual impairment.

Patient 2

A 9-month-old boy was examined for exotropia. He had noncentral and unsteady fixation with his right eye and central and steady fixation with the left eye. Prenatal, perinatal, and developmental history was unremarkable. Right exotropia was 25^Δ. An afferent pupillary defect was noted in the right eye. An examination under anesthesia demonstrated that the anterior segment examination of both eyes was normal except for mild posterior subcapsular

lens changes in the right eye. Intraocular pressures were normal. Funduscopy examination of the right eye showed a chronic, combined traction and rhegmatogenous retinal detachment of the temporal retina and the macula (Figure 3A). The detached retina was gathered into a tight fold extending from 4 o'clock to 11 o'clock position. A pigmented demarcation line was present. The nasal retina was attached. The left fundus showed mild pigmentary mottling in the macula. There was an area of vitreous condensation but no evidence of retinal detachment (Figure 3B). The child's family history was significant for four maternal great-uncles having visual impairment from presumed X-linked retinoschisis.

Genetic Analysis

Sequence analysis of the *RS1* gene² in Patient 1 identified a hemizygous 371A>G missense mutation in exon 5. The patient's mother was heterozygous 371A/G, whereas an unaffected brother and sister were both negative for this mutation. The mutation resulted in the loss of the *TatI* enzymatic site in the PCR product for exon 5, allowing for the creation of a genetic test. Seventy-five unaffected controls were evaluated and were negative for this mutation.

Sequence analysis of the *RS1* gene in patient 2 identified a hemizygous 214G>A missense mutation in exon 5 resulting in a Glu72Lys substitution. The patient's mother was heterozygous 214G/A.

Discussion

X-linked retinoschisis (XLRs) is a vitreoretinal dystrophy with an estimated prevalence of 1:5,000 to 1:25,000.^{1,3} It is most frequently diagnosed in school-age children but can manifest early in life.⁴ The hallmark feature of the disease is foveal retinoschisis, but approximately half of patients also have peripheral retinoschisis.⁴ The differential diagnosis of retinal elevation in infancy, in addition to XLRs, includes retinoblastoma, Norrie disease, incontinentia pigmenti, autosomal-recessive vitreoretinal dysplasia, familial exudative vitreoretinopathy, Goldman-Favre disease, autosomal-dominant retinoschisis, and macular edema.^{1,4} A reduced b-wave with electroretinography can be helpful in confirming the diagnosis of XLRs in a male infant with foveal schisis, but this finding also can be observed with X-linked congenital stationary night blindness.¹ The characteristic retinal splitting in the fovea seen with OCT can also help confirm the diagnosis of XLRs. In comparison with electroretinography, this test has the advantage of being widely available and not requiring general anesthesia for infants.⁵ Genetic testing, however, is emerging as the preferred way to confirm the diagnosis of XLRs, particularly in patients without a family history suggestive of hereditary disease. A clinical test is now widely available and, as elaborated by Koenekoop and colleagues,⁶ has the ability to improve diagnostic accuracy and provide prognostic information by correlating genotype and phenotype.

The 371G>A mutation identified in patient 1 leads to an Arg156Gly substitution in the discoidin domain of the RS1 protein. This mutation has been reported in a Chinese family but has not been previously reported in the United States.⁷ The Arg156 is an evolutionarily conserved amino acid, likely playing an essential role for the function of RS1. It has been previously shown that the RS1 protein is secreted from photoreceptors and bipolar cells as a homo-oligomeric protein complex.⁸ Functional analysis of missense *RS1* mutations established 3 disease mechanisms: (1) mutations interfering with retinoschisin secretion; (2) mutations interfering with retinoschisin octamerisation; (3) mutations that allow secretion and octamerisation, but interfere with protein function.⁹ Our hypothesis, based on the fact that Arg156 is within the discoidin domain, is that the Arg156Gly mutation interferes with the function of the RS1 protein. It has been shown previously that many RS1 discoidin mutations lead to intracellular retention and degradation of mutant protein.⁸ However, in

vitro expression studies are needed to functionally establish the molecular fate of the Arg156Gly mutant.

Literature Search

MEDLINE was searched (1950 to 2008) using the following terms: x-linked retinoschisis, RS1 gene, retinal dystrophies, infant, and optical coherence tomography.

Acknowledgments

We thank Dr. Kimberly Drenser of Oakland University, Michigan, for providing OCT of Patient 1.

This work was funded by the Core Grant for Vision Research (P30 EY01931), an unrestricted grant from Research to Prevent Blindness, and a Milwaukee donor fund supporting Macular Degeneration.

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FIG. 1. Fundus photograph of the right eye (A) revealing RPE mottling in the macula with scattered vitreous hemorrhage; a retinoschisis cavity was noted inferiorly extending up to the inferior arcade. Fundus photograph of the left eye (B) showing a highly elevated dome shaped retinoschisis cavity draping over the macula.

FIG. 2.
OCT of the right eye (A) showing a lamellar schisis. OCT of the left eye (B) showing a large, highly elevated schisis cavity.

FIG. 3. Fundus photograph of the right eye (A) showing a chronic, traction/rhegmatogenous retinal detachment of the temporal retina and the macula along with a pigmented demarcation line. Fundus photograph of the left eye (B) showing mild pigmentary changes at the macula.