

Unusual Manifestations of X-Linked Retinoschisis: Clinical Profile and Diagnostic Evaluation

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- **PURPOSE:** To describe the unusual clinical manifestations and diagnostic evaluation of X-linked retinoschisis (XLR).
- **DESIGN:** Prospective, observational case series.
- **METHODS:** Eight patients with subnormal vision seeking treatment at a tertiary eye care center were evaluated clinically by optical coherence tomography (OCT) and electroretinography (ERG) in this prospective, noncomparative case series. Mutational screening was performed for the retinoschisin gene (*RS1*) by direct deoxyribonucleic acid (DNA) sequencing. The primary outcome measures were the clinical fundus findings and genetic results.
- **RESULTS:** The mean patient age was 16.4 years (range, two to 33 years). Family history was positive in seven patients. Four demonstrated atypical fundus findings of XLR bilaterally. Atypical features included macular dragging and distortion (seven eyes, five patients), macular pigmentary changes or scarring (five eyes; three patients), and bilateral exudative detachments (one patient). One patient had macular dragging and pigmentary changes bilaterally. ERG aided diagnosis in five patients: selective B-wave suppression was observed in all. OCT demonstrated typical retinal schitic cavities universally, including the eyes with macular dragging and scarring. Genetic studies confirmed the clinical diagnosis in all patients; two revealed novel mutations.
- **CONCLUSIONS:** We identified unusual presentations of XLR with the help of ERG, OCT, family screening, and genetic analysis; OCT seems to be a consistent diagnostic aid across the clinical spectrum of XLR. (Am J Ophthalmol 2007;144:419–423. © 2007 by Elsevier Inc. All rights reserved.)

X-LINKED RETINOSCHISIS (XLR) IS ONE OF THE LEADING causes of macular degeneration in male children. Bilateral stellate foveal schisis is the hallmark feature, with a peripheral retinoschisis in half of the cases. Clinical diagnosis sometimes is difficult because of a high

degree of phenotypic variability¹: the described noncystic appearances of posterior pole include pigment mottling, atrophic lesions, retinal dragging, and exudative maculopathy.^{2,3} The diagnosis is established classically by X-linked inheritance and negative electroretinogram (ERG) results.^{1–3} More recently, optical coherence tomography (OCT)^{4–8} and genetic studies¹ have been used to establish the diagnosis. The latter methods assume greater significance when the disease is at an early stage,⁵ manifests in an atypical manner, or is fairly advanced with complications like retinal detachment (RD), which alter the typical ERG pattern.² We identified patients with unusual presentations of XLR by clinical examination and the aforementioned investigations and corroborated the clinical findings with results of mutation screening for the retinoschisin (*RS1*) gene.

METHODS

THIS OBSERVATIONAL STUDY INCLUDED EIGHT MALE PATIENTS with poor vision from early childhood. They were evaluated in a detailed manner and were diagnosed as having XLR on the basis of clinical examination, OCT, ERG, and genetic analysis. The patients were evaluated clinically at the Retina-Vitreous Service, Aravind Eye Hospital & Postgraduate Institute of Ophthalmology, Madurai, India. The deoxyribonucleic acid (DNA) sequencing was performed at the Department of Genetics, Aravind Eye Hospital, as well as at the Department of Ophthalmology and Visual Sciences, Eccles Institute of Human Genetics, University of Utah Health Sciences Center, Salt Lake City, Utah, USA.

A detailed family history was elicited and pedigree charts were constructed. The family members, when available, were evaluated in a similar manner. The patients were followed up for 19 to 60 months (mean, 34 months). Patients' blood samples were collected, and genomic DNA was extracted using the Puregene DNA isolation kit (Qiagen Incorp, Valencia, California, USA). Polymerase chain reaction (PCR) was performed to amplify six exons of the *RS1* gene. Sequencing reactions were performed on the PCR products with BigDye Terminator version 3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, California, USA), according to the manufacturers' instructions. Samples were sequenced directly by loading the sequencing reaction product onto an Applied Biosystems 3130xl Genetic An-

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TABLE. Atypical X-Linked Retinoschisis: Demographic and Clinical Features

| Patient No. | Age (yrs) | BCVA | | Atypical Features | |
|-------------|-----------|-----------|----------|--|---------------------------------------|
| | | Right Eye | Left Eye | Right Eye | Left Eye |
| 1 | 20 | 20/120 | 20/50 | Inferotemporal dragging of the optic disk and macula | — |
| 2 | 10 | 20/300 | 20/300 | RPE atrophy; pigmented scar | RPE atrophy; pigmented scar |
| 3 | 12 | 20/300 | 20/200 | — | RPE atrophy and scarring |
| 4 | 5 | CF | 20/30 | Supranasal dragging of macula | — |
| 5 | 8 | 20/300 | 20/200 | Nasal dragging of macula; RPE atrophy | Nasal dragging of macula; RPE atrophy |
| 6 | 33 | 20/60 | 20/80 | Inferotemporal dragging of macula | Inferotemporal dragging of macula |
| 7 | 31 | No LP | LP | Total exudative retinal detachment; band keratopathy | Subtotal exudative retinal detachment |
| 8* | 2 | 20/200 | 20/100 | Nasal dragging of macula | — |

BCVA = best-corrected visual acuity; CF = counting fingers; LP = light perception; RPE = retinal pigment epithelium. The typical fundus features of X-linked retinoschisis (foveal schisis with or without peripheral schisis), where present, are indicated by an em-dash (—).
*No family members affected.

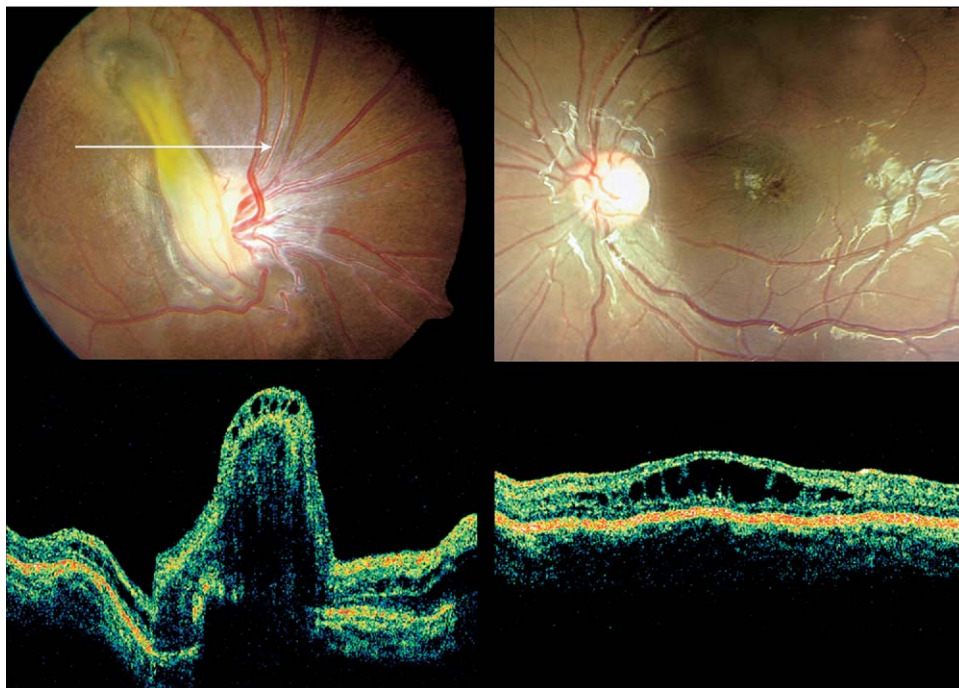


FIGURE 1. Patient 4 (X-linked retinoschisis and macular dragging). Best-corrected visual acuity was counting fingers in the right eye and 20/30 in the left eye. (Top left) Right fundus photograph showing macular retina dragged up supranasally into a curvilinear vertical fold. The arrow indicates the direction of the optical coherence tomography (OCT) scan. (Top right) Fundus photograph of the left eye showing a classic foveal schisis. (Bottom left) OCT image of the right eye showing an elevated fold lined by schitic cavities, which extend on either side of the fold. (Bottom right) OCT image of the left eye revealing the classic pattern of multi-layered schisis cavities bridged by vertical hyper-reflective columns. Family examination revealed an affected elder brother who had classic foveal schisis bilaterally.

alyzer (Applied Biosystems, Foster City, California, USA). The patients' DNA sequences were compared with the normal sequence in unaffected controls and then were analyzed for variations.

RESULTS

- **CLINICAL FINDINGS:** Clinical findings are summarized in the [Table](#). The age ranged from two to 33 years (mean,

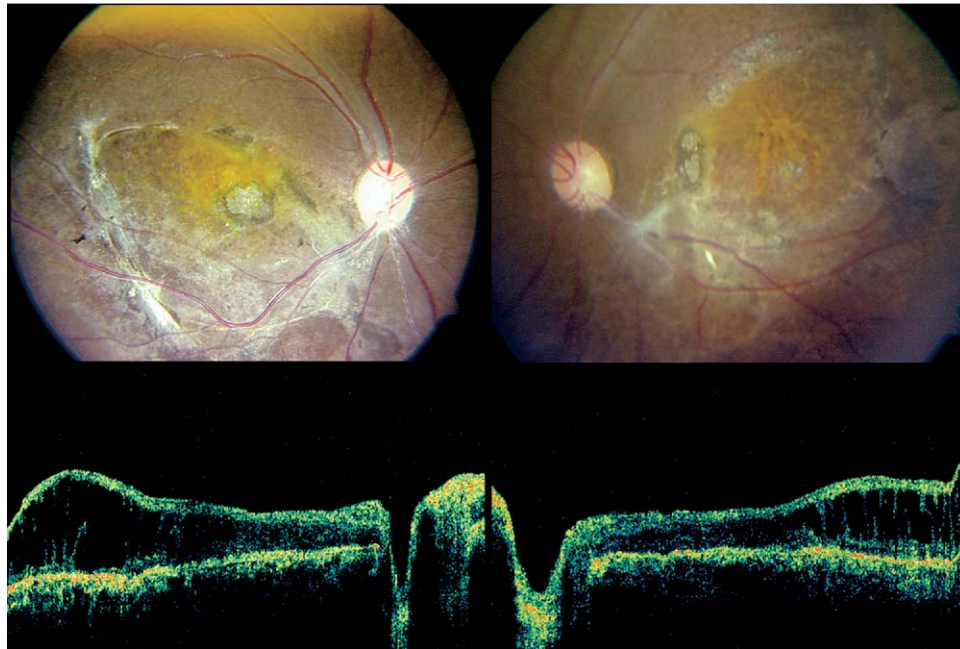


FIGURE 2. Patient 2 (X-linked retinoschisis with macular scarring). Best-corrected visual acuity was 20/300 bilaterally. (Top left) Fundus photograph of the right eye showing a central pigmented macular scar bordered by an oval pattern of subretinal fibrosis and pigment mottling. (Top right) Fundus photograph of the left eye showing a similar appearance, except in the central fovea, which shows a typical schisis in stead of a scar. (Bottom left and right) Horizontal optical coherence tomography (OCT) scan (10 mm) through the fovea demonstrating similar retinal schitic cavities, lined by vertical palisades in both the eyes, notwithstanding the atrophic clinical appearance in the right eye. Retinal thickness and differentiation was reduced in the papillomacular bundle. The elder brother (Patient 3) was similarly affected.

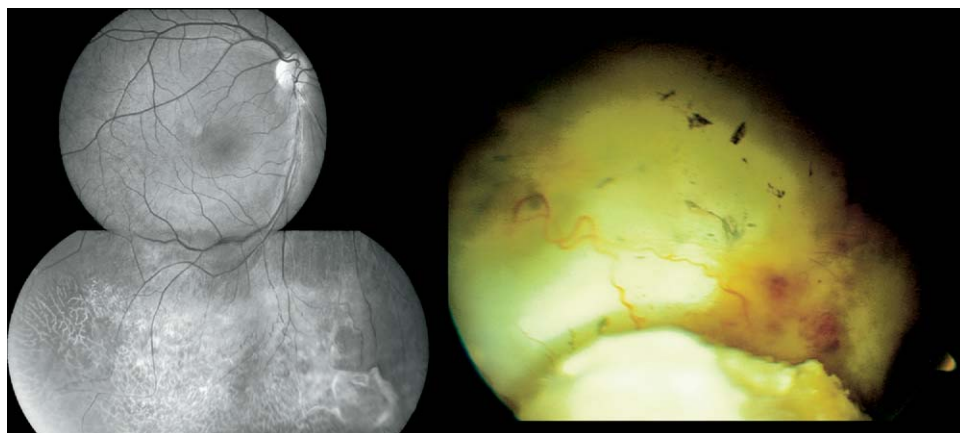


FIGURE 3. Fundus photographs from two maternal uncles (Patients 6 and 7) of Patient 5 (atypical X-linked retinoschisis). (Left) Right eye of Patient 6 showing inferotemporal dragging of the macula with peripheral dendritiform figures. A tuft of superficial fibroglial tissue is visible at the 6 o'clock meridian. (Right) Left eye of Patient 7 showing a subtotal exudative detachment with massive subretinal lumps of exudates, partly undergoing fibrous organization.

16.4 years). In the 12 eyes with atypical features of XLR, best-corrected visual acuity ranged from 20/60 to no light perception (measured with Cardiff acuity cards in Patient 8). The family history was positive in seven patients: Patient 1 had an affected maternal uncle and a younger brother. Patients 2 and 3 were brothers; the younger

brother of Patient 4 had typical features of XLR in both eyes; Patients 6 and 7 were maternal uncles of Patient 5. None of the patients had any remarkable perinatal history.

Of the eight patients, four (Patients 2, 5, 6, and 7) demonstrated atypical manifestations of XLR bilaterally. The fellow eye revealed classic foveal schisis in four

patients (Patients 1, 3, 4, and 8). The atypical features included macular dragging and distortion (seven eyes; five patients), chorioretinal atrophy, pigmentation and scarring of the macula (five eyes; three patients), and massive exudative RDs (one patient). Patients 4, 5, and 8 had maculae dragged nasally toward the optic nerve (Figure 1, Top left); the dragging was inferotemporal in Patients 1 and 6. The chorioretinal changes were particularly severe in two brothers (Patients 2 and 3; Figure 2, Top left and right). Patient 5 displayed macular dragging as well as pigmentary changes bilaterally. Both of his maternal uncles also showed atypical manifestations bilaterally: inferotemporally dragged macula and exudative RD (Patients 6 and 7; Figure 3). The exudative detachments were longstanding and inoperable: the right eye had a total detachment with bullous keratopathy, and the left detachment was subtotal, with a nasal segment spontaneously reattached.

Electroretinography was performed in five patients (Patients 1, 2, 3, 5, and 6) under dark-adapted conditions. Classic negative electroretinogram results with suppression of the B-wave and a relative sparing of A-wave were obtained with a single-flash stimulus in all patients. Reduced flicker response and oscillatory potentials also were recorded in Patients 2 and 5.

OCT (StratusOCT 3; Carl Zeiss Meditec, Dublin, California, USA) was performed on all eyes except those with extensive RDs (Patient 7). Cross-sectional images of the fovea in six meridians were obtained. Additional scans were performed to highlight atypical features. OCT demonstrated spaces resembling cysts in multiple schitic planes in all the affected eyes, including those with atypical fundus findings (Figures 1 and 2, Bottom left and right).

• **GENETIC RESULTS:** Sequencing results indicated five nucleotide changes in nine affected individuals within the five families. A novel missense mutation c.618G→C in the *RS1* gene was found in exon 6 of Patient 1, resulting in an amino acid change at position 206 (Trp206Cys; Gene bank accession no. GenBank EF036314).

A c.422G→A known missense mutation was identified in exon 5 of Patients 2 and 3 (brothers). This nucleotide variation led to the replacement of amino acid arginine at position 141 by histidine (Arg141His).

A known missense mutation was observed at G590A in exon 6 in Patient 4 and his affected brother, with bilateral classic foveal schisis.^{9,10} A third unaffected brother was negative for the mutation, as was the father. The mother was heterozygous for the mutation. G590A resulted in an amino acid change at position 197 (Arg→His).

A reported missense mutation was observed at c.598C→T in exon 6 of Patient 5. The mother was heterozygous for the mutation. His two affected maternal uncles also showed the same mutation. This nucleotide change caused a change of amino acid arginine at position 200 by cysteine (Arg200Cys).

A novel *RS1* mutation in exon 4 of Patient 8 was observed at nucleotide 215 (A→G). This nucleotide change caused an amino acid change at position 72 (Glu→Gly). The patient's mother was heterozygous for the mutation. No other family members were affected. This mutation was not found in the patient's unaffected father or maternal uncle. Neither of the two novel mutations identified in this study were found in 125 normal controls tested using restriction endonuclease *Ple1*.

DISCUSSION

THE MOST STRIKING CLINICAL FINDING IN THIS SERIES WAS severe dragging of the macula (nasally in Patients 4, 5, and 8 and inferotemporally in Patients 1 and 6), which was heaped over the optic nerve head in three of the eyes. Only Greven and associates previously reported the nasal dragging of retina in XLR.² They hypothesized that the bullous temporal dehiscence allowed the adherent cortical vitreous to drag the nerve fiber layer and vascular arcades toward the broader vitreous base on the nasal side. When severe, this retinal dragging may distort the foveal schisis, making clinical diagnosis difficult. When less severe, it may resemble *situs inversus*, recently described as an additional feature of XLR by Apushkin and associates.³ Hirose and Schepens described inferotemporal dragging of the macula toward the retinal hole in a detached retina.¹¹ A previous episode of intravitreal or intraschisis hemorrhage resulting from torn vitreous veils similarly may incite surface contraction of vitreoretinal membranes inferotemporally,² dragging down the macula in our cases. Three patients (Patients 2, 3, and 5) demonstrated the other unusual presentation of this series: extensive mottling and atrophy of the retinal pigment epithelium at the posterior pole. Although these findings have been described before,^{1,3,4} the severity observed in our patients was not noted previously. Patient 7 had bilateral, massive exudative RDs resembling a bilateral Coats'-like response. Subretinal exudation in XLR is likely to result from incompetence of retinal vessels under traction. Although peripheral exudative detachments have been described previously,^{2,12} we are unaware of any description of total exudative detachments secondary to XLR in the literature.

Differential diagnosis for such cases includes both infectious and noninfectious conditions like toxocariasis, retinopathy of prematurity, and familial exudative vitreoretinopathy (for dragged macula); toxoplasmosis, tuberculosis, etc. (for macular chorioretinal scarring); and also conditions like Coats disease (for exudative RD). Proactive suspicion and search for clinical clues can help to avoid unnecessary investigations and misdirected treatment. The foveal schisis and peripheral bullous schisis in the fellow eye and affected eye were important diagnostic clues in some patients; others

had affected family members. ERG contributed to diagnosis in five of eight cases. OCT has been described as a useful diagnostic adjuvant in typical cases.^{1,4-8} To the best of our knowledge, its usefulness has not been tested in atypical presentations of XLR. With the help of OCT, the schitic retinal splitting has been shown to occur not only in the nerve fiber layer, as previously believed, but also (and more prominently) in the outer retinal layers, housing the pathologic Müller cells and their synaptic connections.^{4-6,8} OCT was helpful and remarkably consistent in our cases, despite their varied presentation. Not only were we able to demonstrate schitic retinal splitting by OCT, but we also found its extension beyond the arcades into the nasal retina in four of the eyes with nasal retinal dragging. Although schitic changes seen on OCT are reported to extend beyond the visible foveal schisis,⁶ we are not aware of any report of extension of schisis into the nasal retina.

Greven and associates confirmed the diagnosis of XLR by family history, ERG, and the finding of typical foveal

schisis in family members or fellow eyes of the patients. However, they conceded that ERG may not help in advanced, bilateral cases, because both A- and B-wave amplitudes are suppressed.² However, ERG results may be normal in early stages of the disease. Further, family history may be negative in some cases.¹³ We found OCT to be a useful diagnostic tool across the entire clinical spectrum of classic and atypical XLR in this series. Genetic confirmation, however, is the most definitive evidence for diagnosis of XLR, especially in the presence of atypical clinical features and in view of the inconsistency of ERG findings, familial association, as well as wide phenotypic variability within families.¹⁴ Mutational analysis was confirmatory in all the cases; two novel mutations also were discovered during this study. In view of the protean manifestations of XLR, knowledge of its unusual clinical features is essential for prognostic and therapeutic considerations, proper familial evaluation, and genetic counseling, and also to avoid misdirected investigations and interventions for mimicking diseases.

THE AUTHORS INDICATE NO FINANCIAL SUPPORT OR FINANCIAL CONFLICT OF INTEREST. INVOLVED IN CONCEPTION AND design (D.S., A.R.); analysis and interpretation (D.S., A.R., D.G., B.S., K.Z., P.S.); writing (D.S., A.R., D.G., B.S., K.Z.); critical revision (D.S., A.R., D.G., B.S., K.Z., P.S.); final approval (D.S., A.R., D.G., B.S., K.Z.); data collection (D.S., A.R., B.S.); provision of materials (D.S., A.R., K.Z., P.S.); statistical expertise (D.S., A.R.); obtaining funding (D.S., K.Z., P.S.); literature search (D.S., A.R.); and administration (D.S.). Appropriate approval was obtained from the Institutional Review Board, Aravind Eye Hospital, Madurai, India. Signed informed consent was obtained from each patient. The study was approved by the Institutional Review Board of Aravind Eye Hospital, Madurai, India.

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Biosketch

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Biosketch

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