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Electroretinographic Findings in Three Family Members with X-linked Juvenile Retinoschisis Associated with a Novel Pro192Thr Mutation of the *XLRS1* Gene

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Purpose: To present ocular findings in three family members with X-linked juvenile retinoschisis (XLRS) associated with a novel Pro192Thr mutation.

Cases: We examined 21- (Case 1), 17- (Case 2), and 10-year-old (Case 3) male patients who showed wheel-like cystic lesions in the macula and a silver-gray reflex in the peripheral retina. Case 2 was a cousin of Case 1. Case 3 was a brother of Case 2.

Methods: Scotopic electroretinogram (ERG) (dim and bright flash), oscillatory potentials, photopic ERG, and 30-Hz flicker responses were recorded in each patient. The *XLRS1* gene was analyzed in patient blood samples by a direct sequencing method.

Results: A novel missense mutation (Pro192Thr) was identified in the *XLRS1* gene in each patient. Variable b/a ratios upon scotopic bright flash stimulation were evident (Case 1: right 1.16, left 1.20; Case 2: right 0.98, left 1.01; Case 3: right 0.81, left 0.83). Only Case 3 showed the typical "negative" waveform. The amplitude of rod b-waves was significantly decreased in all patients.

Conclusions: Three cases with a novel Pro192Thr mutation showed the phenotypic variation in ERG, especially in b/a ratio, which has been considered an important diagnostic parameter. **Jpn J Ophthalmol 2002;46:568–576**

Key Words: Electroretinogram, retinoschisis, *XLRS1* gene.

Introduction

X-linked retinoschisis (XLRS) is characterized by splitting of the retinal nerve fiber layer in the macular area, causing a "spoke-wheel" pattern of macular cysts.[1,2] This condition may be clinically apparent at birth.[3–6] The inheritance of XLRS follows a recessive X-chromosomal pattern.[7] Under dark-adapted conditions, a negative electroretinogram (ERG), ie, reduced b-wave amplitude in spite of a normal a-wave, has been frequently described in XLRS patients.[8–13] The pathogenesis is not yet clear; however, electrophysiologic results have suggested an underlying defect in Müller cells[11] and in the proximal retina, postsynaptic to the photoreceptors,[14] and histopathologic studies also suggest this hypothesis.[1,2,15] XLRS is thought to be a progressive disease.[4]

The retinoschisis gene (*XLRS1*) has six exons that encode the 224-amino-acid protein. The predicted *XLRS1* protein contains a highly conserved motif implicated in cell–cell interaction, and this may be active in cell adhesion processes in retinal development.[16] Many types of mutations of *XLRS1* have been investigated.[17–22]

Received: August 15, 2001

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Published by Elsevier Science Inc.

0021-5155/02/$–see front matter
PII S0021-5155(02)00539-7

In this report, we present the ERG findings from a single family who showed the novel missense mutation, Pro192Thr.

Report of Cases

Case 1

Case 1 was a 21-year-old man. Poor corrected visual acuity in the right eye was found when he was 7 years old. He was first examined in our clinic when he was 11 years old. His corrected visual acuity was 0.6 in the right eye and 1.0 in the left. The cornea and lens were normal in both eyes. Both maculas showed radial retinal folds, ie, wheel-like cystic lesions. Goldmann kinetic perimetry showed no abnormal findings. Automatic static perimetry showed decreased sensitivity in the central retina bilaterally. His inferotemporal peripheral retina showed a silver-gray reflex in the right eye. There was no peripheral retinoschisis, retinal tear or retinal detachment in either eye.

Case 2

Case 2 was a 17-year-old man, who was the cousin of Case 1. Reduced corrected visual acuity in both eyes was found when he was 7 years old, and he was first examined in our clinic when he was 9 years old. His corrected visual acuity was 0.3 in the right eye and 0.2 in the left. However, his near visual acuity was 1.2 in both eyes. Wheel-like cystic lesions like those of Case 1 were found in both eyes. Silver-gray reflex was found in all the surrounding areas of the peripheral retina except the temporal quadrant. Peripheral retinoschisis, retinal tear, and retinal detachment were not evident. Goldmann kinetic perimetry was not examined.

Case 3

Case 3 was a 10-year-old boy who was a brother of Case 2. His corrected visual acuity was 1.0 in both eyes when he was 8 years old. He became aware of decreased corrected visual acuity at the age of 9 when he was first examined in our clinic. His corrected visual acuity was 0.4 in the right eye and 0.7 in the left. Wheel-like cystic lesions like those of Case 1 were found in both eyes. Color vision was normal (panel-D15). As in Case 2, silver-gray reflex was found in the peripheral retina of the inferior quadrant in both eyes, although peripheral retinoschisis, retinal tear and retinal detachment were not observed. Goldmann kinetic perimetry showed no abnormal findings.

The pedigree of these 3 cases is shown in Figure 1. A recessive X-chromosomal inheritance pattern was considered.

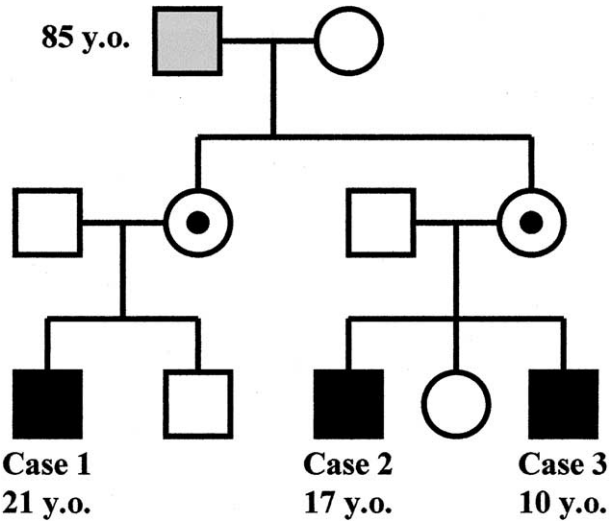

Figure 1. Pedigree of the family with X-linked juvenile retinoschisis (XLRS). □: male, ○: female, ■: affected, ·: obligate carrier. A recessive X-chromosomal inheritance pattern was considered. Macular degenerations without cystic changes were found in both eyes of 85-year-old grandfather (gray square). We could not confirm whether or not he had the mutation of *XLRS1*.

Macular degeneration without cystic lesions was found in both eyes of the 85-year-old grandfather (gray square in Figure 1). He told that his corrected visual acuity had been decreased since his childhood. Informed consent for further examination could not be obtained from him, so we could not confirm whether or not he had the mutation of *XLRS1*.

Materials and Methods

ERG Recording and Analysis

The ERG procedure complied with the International Society for Clinical Electrophysiology of Vision (ISCEV) standard protocol.[23] The methods were similar to those described in a previous study.[24] Both eyes were dilated with a mydriatic and subjects were dark-adapted for at least 45 minutes before testing. The responses were obtained from Burian-Allen bipolar electrodes (Hansen Ophthalmic Instruments, Iowa City, IA, USA). The stimulus was a 10-μs xenon flash (ERG Photic Stimulator, SLS-4100, Nihon Kohden, Tokyo) delivered by means of a Ganzfeld dome (Sanso, Tokyo). Stimulus intensity was controlled by means of neutral density filters (Fuji Film, Tokyo). Scotopic rod b-wave responses and scotopic bright flash ERGs were recorded with a 0.5 to 100 Hz filter setting. Oscillatory potentials (OPs) were recorded with a 50–500-Hz filter setting. The photopic ERGs and 30-Hz flicker responses were recorded

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Table 1. Electroretinogram Results of 3 Cases with X-linked Juvenile Retinoschisis and Normal Controls

	Normal		Case 1		Case 2		Case 3	
	Mean (SD)	Range	Right Eye	Left Eye	Right Eye	Left Eye	Right Eye	Left Eye
Scotopic bright flash a-wave amplitude (μV)	315.9 (51.3)	193.6–396.4	261.8	274.6	258.7	228.5	399.9	345.9
Implicit time (ms)	13.1 (0.8)	11.6–14.8	13.5	12.7	12.8	12.1	12.5	12.9
Scotopic bright flash b-wave amplitude (μV)	458.5 (84.8)	276.1–606.6	303.1	328.6	253.9*	231.7*	325.3	288.8
Implicit time (ms)	55.4 (3.3)	49.0–59.5	47.7*	47.5*	25.7*	26.7*	34.2*	57.3
b/a wave ratio	1.45 (0.15)	1.29–1.85	1.16*	1.20*	0.98*	1.01*	0.81*	0.83*
Rod b-wave amplitude (μV)	268.9 (59.3)	150.8–365.0	–	–	54.0*	33.3*	90.5*	133.3*
Photopic bright flash a-wave amplitude (μV)	61.3 (13.9)	38.7–82.2	60.7	46.7	50.3	44.6	47.7	52.7
Implicit time (ms)	14.6 (0.5)	13.4–15.5	14.9	13.7	14.9	14.7	15.5	15.8*
Photopic bright flash b-wave amplitude (μV)	133.1 (33.5)	71.9–184.4	69.2*	98.8	83.7	75.8	60.1*	70.8*
Implicit time (ms)	33.8 (1.2)	31.4–35.9	33.3	32.1	33.1	34.3	37.5*	37.7*
30-Hz flicker amplitude (μV)	83.2 (23.3)	47.5–133.0	5.0*	6.0*	49.8	58.2	81.2	63.1
Implicit time (ms)	14.5 (1.7)	11.6–17.4	24.4*	23.6*	14.2	14.4	12.8	12.8
Oscillatory potentials (O1+O2+O3) amplitude (μV)	186.8 (54.6)	108.0–275.8	92.3*	143.9	122.0	110.5	147.0	172.0
Rod log $\mid Rm_{p3} \mid$	2.39 (0.09)	2.18–2.51	2.31	2.36	2.32	2.27	2.54	2.47
Rod log S	1.02 (0.07)	0.90–1.11	1.04	1.02	1.22	1.20	1.18	1.08
Cone log $\mid Rm_{P3} \mid$	1.85 (0.09)	1.70–2.03	1.79	1.78	1.76	1.73	1.78	1.79
Cone log S	0.91 (0.09)	0.81–1.20	1.01	0.95	0.86	0.86	0.86	0.86

*Value outside normal range.

under 30 cd/m^2 background illumination after at least 15 minutes of light adaptation. Amplitudes and/or implicit times from the responses were calculated and compared with the values from 15 age-matched normal subjects aged 7–31 years (mean age = 21.3 years) (Table 1).

We analyzed rod and cone a-waves by fitting them to a model proposed by Hood and Birch.[25–27] Rod-only responses were obtained by computer subtraction of photopic ERGs from scotopic ERGs (flashes ranged from 3.0 to 3.6 log scot td-s in approximately 0.3 log unit steps). Rod-only responses and cone responses to all flash energies were fitted to the following equation by estimating one set of parameters: S, t_d and Rm_{p3} for rods and cones.[25–27]

$$P3(i,t) = \{1 - \exp[-i \cdot S \cdot (t - t_d)^2]\} \cdot Rm_{p3} \quad (\text{for } t > t_d)$$

where i = flash energy (log scot troland-s), t_d = time delay, t = time after flash onset, S = sensitivity, and Rm_{p3} = maximum response amplitude.

The means and standard deviations (SD) of the parameters (t_d, S, and Rm_{p3}) for 15 age-matched normal subjects aged 7–31 years were as follows: For the rod, t_d was 3.5 (SD = 0.3 ms); log S was 1.02 (0.07) ($s^{-2}(t_d\text{-}s)^{-1}$); log $\mid Rm_{p3}$ (μV) $\mid$ was 2.39 (0.09). For the cone, t_d was 2.4 (SD = 0.5); log S was 0.91 (0.09); log $\mid Rm_{p3} \mid$ was 1.85 (0.09). In this study, to compare the values of log S and log $\mid Rm_{p3}$ from patients with those from normal subjects, rod td and cone t_d were fixed at 3.5 and 2.4, respectively. Written informed consent was obtained from patients and normal subjects after explanation of our proposed clinical analysis.

DNA Analysis

About 10 mL of venous blood was drawn from each patient into a small volume of heparin solution. High-molecular-weight genomic DNA was extracted from leukocytes of each patient by a QIAamp® column (Qiagen GmbH, Hilden, Germany). All 6 exons of the *XLRS1* gene were amplified by polymerase chain reaction (PCR) with the use of the oligonucleotide primers and conditions described previously.[16] The PCR products were electrophoresed and visualized in 1.5% agarose gels. Nucleotide sequences of the PCR products were directly determined by the Dye Terminator Cycle Sequencing method (PE Applied Biosystems, Foster City, CA, USA) and an ABI Prism 310 Genetic Analyzer. For the molecular genetic study, proceedings followed the tenets of the Declaration of Helsinki and were approved by the Ethics Committee for Medical Research of Hirosaki University School of Medicine.

Results

ERG

In scotopic bright flash ERG, a-wave amplitudes were normal in all cases, and b-wave amplitudes were reduced in both eyes of Case 2. B/a ratios upon

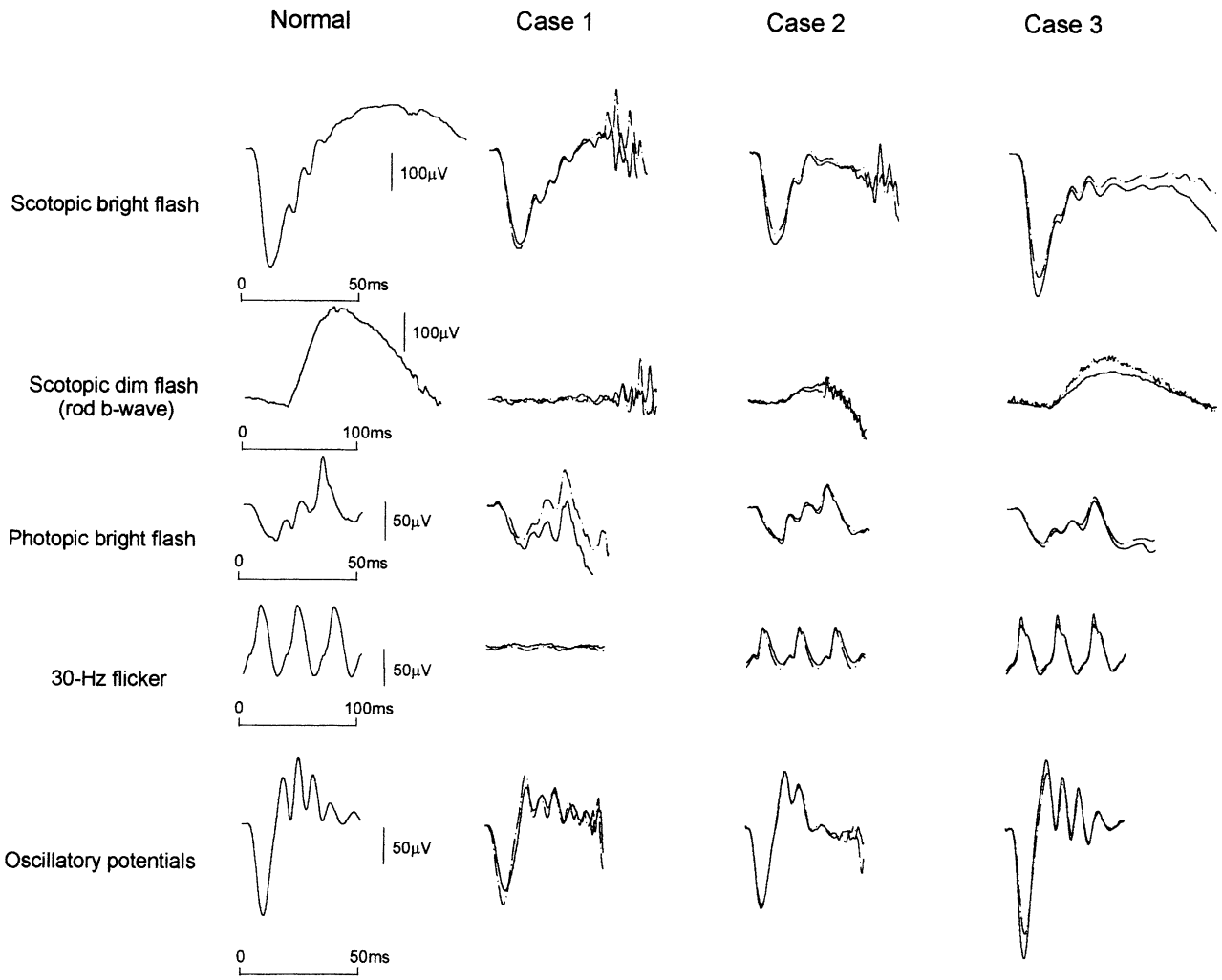

Figure 2. Electroretinogram findings in X-linked juvenile retinoschisis patients with Pro192Thr and in a normal subject. Solid curves are of right eyes, and dashed curves are of left eyes. Similar responses were obtained from both eyes in each of the three cases.

scotopic bright flash stimulation were decreased in all cases. The values were variable (Case 1: right 1.16, left 1.20; Case 2: right 0.98, left 1.01; Case 3: right 0.81, left 0.83) (Figure 2 and Table 1).

The amplitude of each OP (O1, O2, and O3) was measured from a baseline drawn as a first-order approximation between the troughs of successive wavelets. The sum of the amplitudes of the OPs (O1 + O2 + O3) was decreased in the right eye of Case 1.

The amplitudes of rod b-waves were decreased bilaterally in Cases 2 and 3, and were nonrecordable in Case 1.

In photopic bright flash ERG, the amplitudes of cone a-waves in all cases were within the normal range. The implicit time in the left eye of Case 3 was delayed. The amplitudes of cone b-waves were decreased in the right eye of Case 1 and in both eyes of Case 3. The implicit times of cone b-waves were delayed in both eyes of Case 3.

In 30-Hz flicker ERG, amplitudes were severely decreased in both eyes of Case 1. The implicit times were delayed only in Case 1.

Rod and cone functions were analyzed with fitting models (Figure 3). Log $|Rmp_3|$ and log S of both rod and cone were within the normal ranges in all 3 cases.

Table 1 shows a summary of ERG findings. The ERGs in Case 1 were most affected.

DNA Analysis

DNA analysis was performed after informed consent was obtained from the patients following a thorough explanation of this study.

Nucleotide sequencing analysis showed a novel hemizygous transversional change from a cytosine res-

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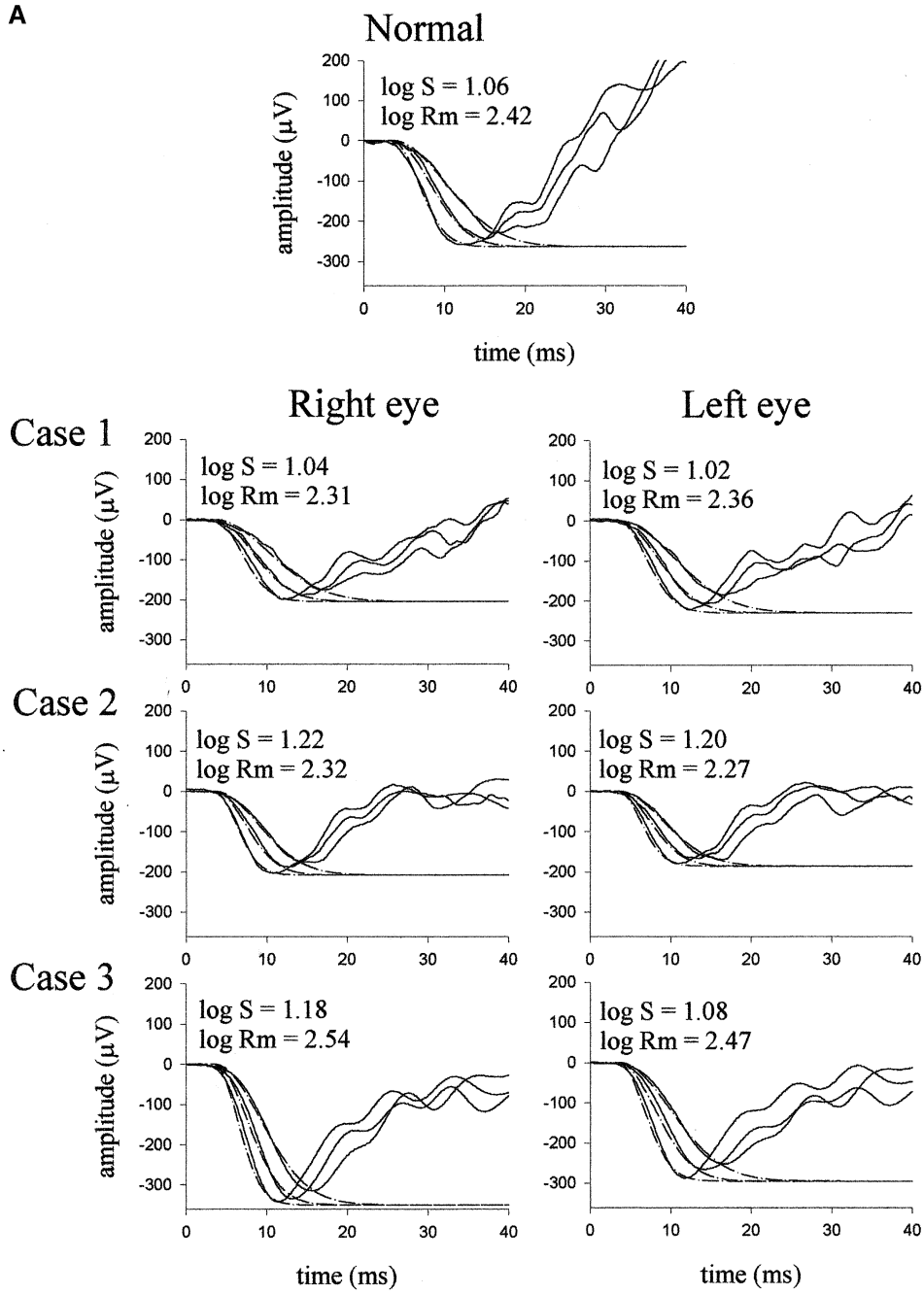

Figure 3. (**A**) Results of the rod a-wave fitted to a model proposed by Hood and Birch.[25] Solid curves are the raw data, and dashed curves are the models after fitting to the leading edge of the rod a-waves. *S* and Rm_{p3} values are given in the panel. (**B**) Results of the cone a-wave fitted to a model proposed by Hood and Birch.[34] Solid curves are the raw data, and dashed curves are the models after fitting to the leading edge of the cone a-waves. *S* and Rm_{p3} values are given in the panel.

idue to adenine at nucleotide 574 of the *XLRS1* gene in all 3 cases examined (Figure 4). This mutation predicts an amino acid substitution of threonine for proline at codon 192 in exon 6 (Pro192Thr) of the gene.

Discussion

The 3 cases in this report showed wheel-like cystic lesions in the macula, silver gray reflex in the peripheral retina, and the *XLRS1* mutation. These findings indicate XLRS.

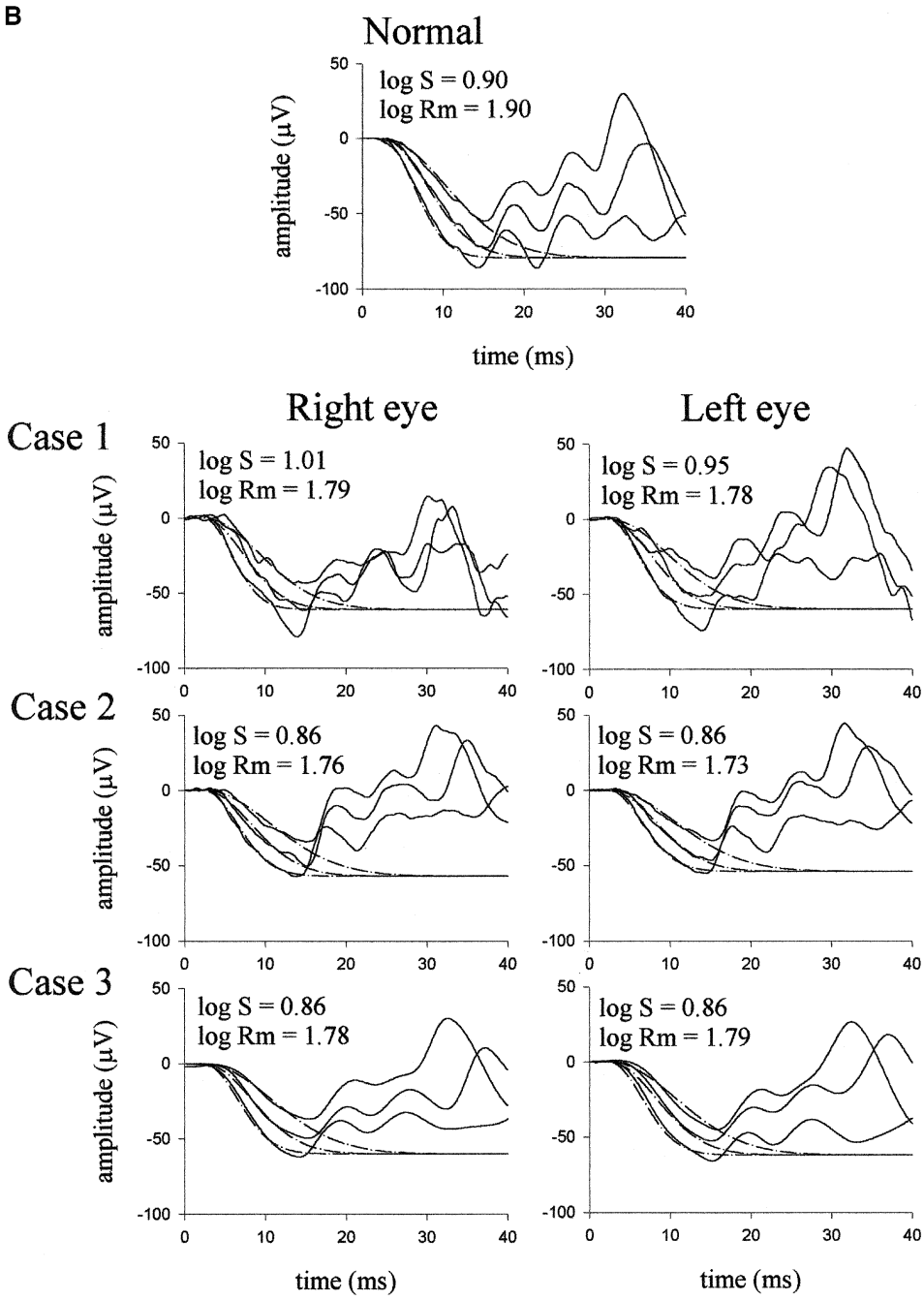

Figure 3. Continued

Electrophysiologic and histopathologic studies[1,2,11,14,15] have suggested an underlying defect in Müller cells and in the proximal retina, postsynaptic to the photoreceptors in XLRS. Recently, Grayson et al[28] reported that *XLRS1* mRNA was detected only in the photoreceptor layer, but the protein product of the gene, retinoschisin, was detected both in the photoreceptors and within the inner layer of the retina. Although the function of the retinoschisin, which contains a discoidin domain, is unknown, the protein might have effects not only on the inner layer of the retina but also on the photoreceptors. Some patients showed the ERG change in the outer retina.[10,11,18] It might be secondary in XLRS, as also proposed by

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Miyake et al.[29] Thus the state of photoreceptors is important for the interpretation of responses from the inner retina. The amplitude and latency of the trough of the a-wave are often used as parameters that represent photoreceptor function clinically. However, it should be noted that the peak a-wave amplitude does not represent the maximal receptor response. In addition, the response of the rod a-wave of the human ERG to moderately intense flashes is partially postreceptoral in origin,[30] as was originally shown for the cone.[31] Photoreceptor activity can be assessed by fitting the leading edge of the rod and cone a-waves to a model.[25–27] In our 3 cases, the left eye of Case 3 showed prolonged implicit times of photopic a-wave, although the functions of rods and cones were within the normal range.

Our results showed that the rod b-waves that might derive from bipolar cells[32] were reduced in all cases (nonrecordable in Case 1). Dysfunctions of bipolar cells might exist in all 3 cases in different degrees. The OPs that might derive from amacrine cells[33] were decreased only in the right eye of Case 1. In the right eye of Case 1, the damage might exist not only in bipolar cells but also in amacrine cells.

Only in both eyes of Case 1 the amplitudes of 30-Hz flicker response were diminished and the implicit times were delayed. Reduced 30-Hz flicker amplitude and delayed implicit times of 30-Hz flicker response have been typical findings in XLRS.[10,18,34] Recently, the on-pathway dominant impairment was described in XLRS using a sinusoidal flicker under photopic condition.[34] The authors suggested that the reduced amplitude and delayed implicit time of the 30-Hz flicker ERG were due, in part, to a relative reduction in an ERG ON response. The on-pathway dominant impairment was also described using a long flash under photopic conditions.[35] In our 3 cases, it is very interesting that 30-Hz flicker responses were different even though photopic bright flash responses were similar. Kondo and Sieving[36] reported on the characteristics of photopic sine wave flicker ERG in detail. They analyzed flicker response as the harmony of three vectors, the photoreceptor component, the ON-component and the OFF-component. The photoreceptor component becomes very small at flicker stimuli near 30-Hz, so 30-Hz flicker response is thought to be a result of the harmony of postreceptoral ON- and OFF-components. ON- and OFF-components depend on the function of photoreceptors. In our 3 cases, cone functions (cone log | Rm_{p3} | and cone log S) were within the normal range. The results of changes in the ON- and OFF-components at 32-Hz flicker ERG have been described.[36] Changes only in the ON-component do not result in a large reduction of flicker amplitudes. However, a mild OFF-component change (OFF-component delay) will result in reduced amplitudes and delayed

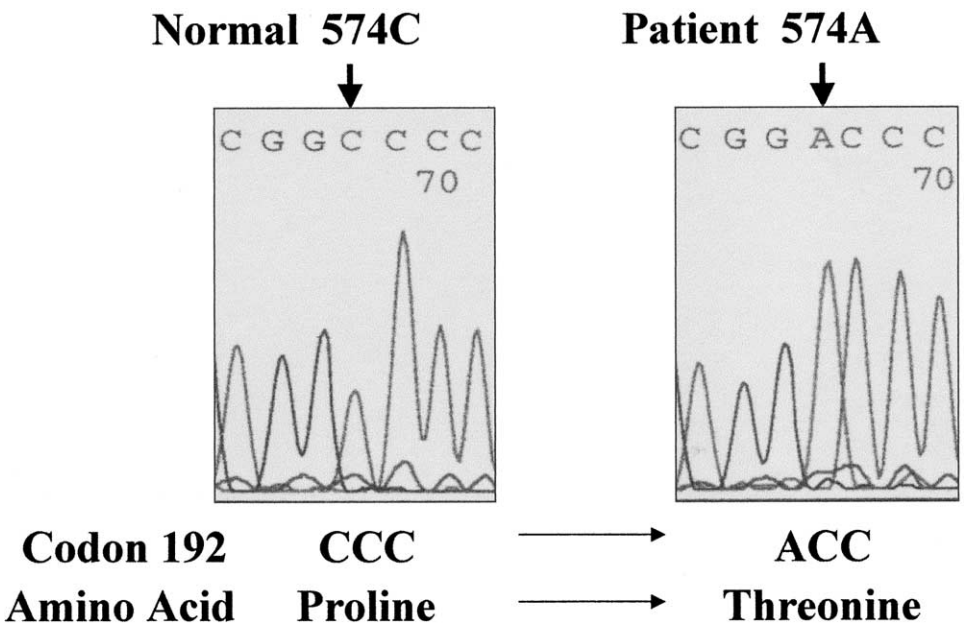

Figure 4. DNA analysis of the patients. One of representative nucleotide sequence data is shown. Identical hemizygous mutation was found in all affected patients examined. Arrows point to the nucleotide at position 574 of the *XLRS1* gene, which is a C (cytosine) in the normal subject but is altered to A (adenine) in the patients. This base change results in an amino acid substitution of threonine for proline at codon 192 (Pro192Thr).

implicit times of the flicker ERG. Therefore, the variability of 30-Hz flicker ERG in our cases might be influenced by the changes of not only ON- but also OFF-bipolar cells.

Under dark-adapted conditions, a negative ERG has frequently been described in XLRS.[8–13,18,20] Park et al[20] reported that three male siblings with a missense mutation, Arg141His, showed severely reduced scotopic b-waves (b/a ratio 0.77, 0.58, and 0.66, respectively). Bradshaw et al[18] reported that two cases with Arg141Cys showed reduced scotopic b-waves. B/a ratios were 0.57 in one case, about 0.7 in the other.

On the other hand, several cases of XLRS with mildly affected or normal ERG have been reported.[17,18,37] Sieving et al[37] reported a family with a missense mutation Arg213Trp. They described that a 54-year-old grandfather demonstrated typical "negative ERG" (b/a ratio 0.58), although a 13-year-old grandson showed a normal ERG (b/a ratio 1.62). Taketani et al[17] reported a 3-year-old boy with a missense mutation, Arg102Gln. The patient had a macular hole and retinal detachment in his left eye, and the lesion was treated surgically. At 8 years of age his ERG was recorded using conventional scotopic bright flash stimulation. His responses did not show the "negative" form bilaterally (b/a ratios > 1.0). Bradshaw et al[18] reported two patients in one pedigree with a missense mutation Gly109Arg. They did not show "negative ERG" (b/a ratio 1.23 and 1.31, respectively). They also described three patients with a missense mutation Arg200Cys and 2 patients with a missense mutation Cys219Gly. These two types of mutations showed variable b/a ratios; 1.01, 0.93, and 0.86 in Arg200Cys, 1.17, and 0.88 in Cys219Gly. Therefore, severely depressed b-waves, the so-called "negative ERG," are not uniformly common characteristics of this disease. In such cases, gene analysis is essential for the diagnosis of XLRS. In our 3 cases with the same *XLRS1* mutation, reduction of the b-wave was evident, but b/a ratios of Cases 1 and 2 showed only mild changes. These variable b/a ratios in the same family were found in previous reports (Arg200Cys, Cys219Gly[18]; Arg213Trp[37]).

It has been reported that the severity of the ERG abnormality in XLRS was variable, without clinical, genetic or age correlation.[18,19,38] We also found the phenotypic variation in a family with XLRS associated with a novel Pro192Thr mutation. The interest in a genotype-phenotype correlation has risen after *XLRS1* gene mutation was first reported.[16] Bradshaw et al[18] studied clinical findings in 19 patients with XLRS in 17 families and found significant variability across the patient population and no correlation between ERG changes, clinical features, and genetic mutation. As described above, we also found variable ERG findings, for example b/a ratio, even within a family. Further electrophysiological and genetic studies will be required to clarify the disease mechanisms in XLRS.

The rod and cone a-wave fitting programs were provided by Dr. Donald C. Hood.

This work was supported by a Grant-in-Aid for Scientific Research, Grant 13671828 (TU), (Ministry of Education, Culture, Sports, Science and Technology, Japan).

References

1. Haas J. Ueber das Zusammenvorkommen von Veränderungen der Retina und Choroidea. Arch Augenheilkd 1898; 37:343–348.
2. Yanoff M, Rahn EK, Zimmerman LE. Histopathology of juvenile retinoschisis. Arch Ophthalmol 1968;79:49–53.
3. Brockhurst RJ. Photocoagulation in congenital retinoschisis. Arch Ophthalmol 1970;84:158–165.
4. Deutman AF. Sex-linked juvenile retinoschisis. In: Deutman AF, eds. Hereditary dystrophies of the posterior pole of the eye. Springfield, MO: Charles C Thomas, 1971:48–99.
5. Prosperi L. Congenital hereditary sex-linked retinoschisis. J Pediatr Ophthalmol Strabismus 1978;15:26–30.
6. Sabates FN. Juvenile retinoschisis. Am J Ophthalmol 1966;62: 683–688.
7. Gieser EP, Falls HF. Hereditary retinoschisis. Am J Ophthalmol 1961;51:1193–1200.
8. George ND, Yates JR, Bradshaw K, Moore AT. Infantile presentation of X-linked retinoschisis. Br J Ophthalmol 1995;79: 653–657.
9. Hirose T, Wolf E, Hara A. Electrophysiological and psychophysical studies in congenital retinoschisis of X-linked recessive inheritance. Doc Ophthalmol Proc Ser 1977;13:173–184.
10. Kellner U, Brümmer S, Foerster MH, Wessing A. X-linked congenital retinoschisis. Graefes Arch Clin Exp Ophthalmol 1990;228:432–437.
11. Peachey NS, Fishman GA, Derlacki DJ, Brigell MG. Psychophysical and electroretinographic findings in X-linked juvenile retinoschisis. Arch Ophthalmol 1987;105:513–516.
12. Tanino T, Katsumi O, Hirose T. Electrophysiological similarities between two eyes with X-linked recessive retinoschisis. Doc Ophthalmol 1985;60:149–161.
13. Hotta Y, Fujiki K, Hayakawa M, et al. Japanese juvenile retinoschisis is caused by mutations of the *XLRS1* gene. Hum Genet 1998;103:142–144.
14. Murayama K, Kuo CY, Sieving PA. Abnormal threshold ERG response in X-linked retinoschisis. Evidence for a proximal retinal origin of the human STR. Clin Vis Sci 1991;6:317–322.
15. Condon GP, Brownstein S, Wang NS, Kearns AF, Ewing CC. Congenital hereditary (juvenile X-linked) retinoschisis. Histopathologic and ultrastructural findings in three eyes. Arch Ophthalmol 1986;104:576–583.
16. Sauer CG, Gehrig A, Warneke-Wittstock R, et al. Positional cloning of the gene associated with X-linked juvenile retinoschisis. Nat Genet 1997;17:164–170.

Jpn J Ophthalmol
Vol 46: 568–576, 2002

17. Taketani R, Yokoyama T, Hotta Y, et al. A case of juvenile retinoschisis diagnosed by analysis of the *XLRS1* gene. Nippon Ganka Gakkai Zasshi (J Jpn Ophthalmol Soc) 1999;103: 817–820.
18. Bradshaw K, George N, Moore A, Trump D. Mutations of the *XLRS1* gene cause abnormalities of photoreceptor as well as inner retinal responses of the ERG. Doc Ophthalmol 1999;98: 153–173.
19. Inoue Y, Yamamoto S, Okada M, et al. X-linked retinoschisis with point mutations in the *XLRS1* gene. Arch Ophthalmol 2000;118:93–96.
20. Park JHC, Ott SH, Wang X, et al. Clinical phenotype associated with the Arg141His mutation in the X-linked retinoschisis gene. Arch Ophthalmol 2000;118:127–129.
21. The Retinoschisis Consortium. Functional implications of the spectrum of mutations found in 234 cases with X-linked juvenile retinoschisis (XLRS). Hum Mol Genet 1998;7:1185–1192.
22. Rodriguez IR, Mazuruk K, Jaworski C, Iwata F, Moreira EF, Kaiser-Kupfer MI. Novel mutations in the XLRS1 gene may be caused by early Okazaki fragment sequence replacement. Invest Ophthalmol Vis Sci 1998;39:1736–1739.
23. Marmor MF, Arden GB, Nilsson SEG, Zrenner E. Standard for clinical electroretinography. Arch Ophthalmol 1989;107: 816–819.
24. Usui T, Tanimoto N, Takagi M, Hasegawa S, Abe H. Rod and cone a-waves in three cases of Bietti crystalline chorioretinal dystrophy. Am J Ophthalmol 2001;132:395–402.
25. Hood DC, Birch DG. Rod phototransduction in retinitis pigmentosa: estimation and interpretation of parameters derived from the rod a-wave. Invest Ophthalmol Vis Sci 1994;35: 2948–2961.
26. Hood DC, Birch DG. Assessing abnormal rod photoreceptor activity with the a-wave of the electroretinogram: applications and methods. Doc Ophthalmol 1997;92:253–267.
27. Hood DC, Birch DG. Phototransduction in human cones measured using the a-wave of the ERG. Vision Res 1995;35: 2801–2810.
28. Grayson C, Reid SNM, Ellis JA, et al. Retinoschisin, the X-linked retinoschisis protein, is a secreted photoreceptor protein, and is expressed and released by Weri-Rb1 cells. Hum Mol Genet 2000;9:1873–1879.
29. Miyake Y, Shiroyama N, Ota I, Horiguchi M. Focal macular electroretinogram in X-linked retinoschisis. Invest Ophthalmol Vis Sci 1993;34:512–515.
30. Hood DC, Birch DG. The b-wave of the scotopic (rod) ERG as a measure of the activity of human on-bipolar cells. J Opt Soc Am 1996;13:623–633.
31. Bush RA, Sieving PA. A proximal retinal component in the primate photopic ERG a-wave. Invest Ophthalmol Vis Sci 1994;35:635–644.
32. Kofuji P, Ceelen P, Zahs KR, Surbeck LW, Lester HA, Newman EA. Genetic inactivation of an inwardly rectifying potassium channel (Kir4.1 subunit) in mice: phenotypic impact in retina. J Neurosci 2000;20:5733–5740.
33. Korol S, Leuenberger PM, Englert U, Babel J. In vivo effects of glycine on retinal ultrastructure and averaged electroretinogram. Brain Res 1975;97:235–251.
34. Alexander KR, Fishman GA, Grover S. Temporal frequency deficits in the electroretinogram of the cone system in X-linked retinoschisis. Vision Res 2000;40:2861–2868.
35. Shinoda K, Ohde H, Mashima Y, et al. On- and off-responses of the photopic electroretinograms in X-linked juvenile retinoschisis. Am J Ophthalmol 2001;131:489–494.
36. Kondo M, Sieving PA. Primate photopic sine-wave flicker ERG: vector modeling analysis of component origins using glutamate analogs. Invest Ophthalmol Vis Sci 2001;42:305–312.
37. Sieving PA, Bingham EL, Kemp J, Richards J, Hiriyanna K. Juvenile X-linked retinoschisis from *XLRS1* Arg213Trp mutation with preservation of the electroretinogram scotopic b-wave. Am J Ophthalmol 1999;128:179–184.
38. George NDL, Yates JRW, Moore AT. Clinical features in affected males with X-linked retinoschisis. Arch Ophthalmol 1996;114:274–280.