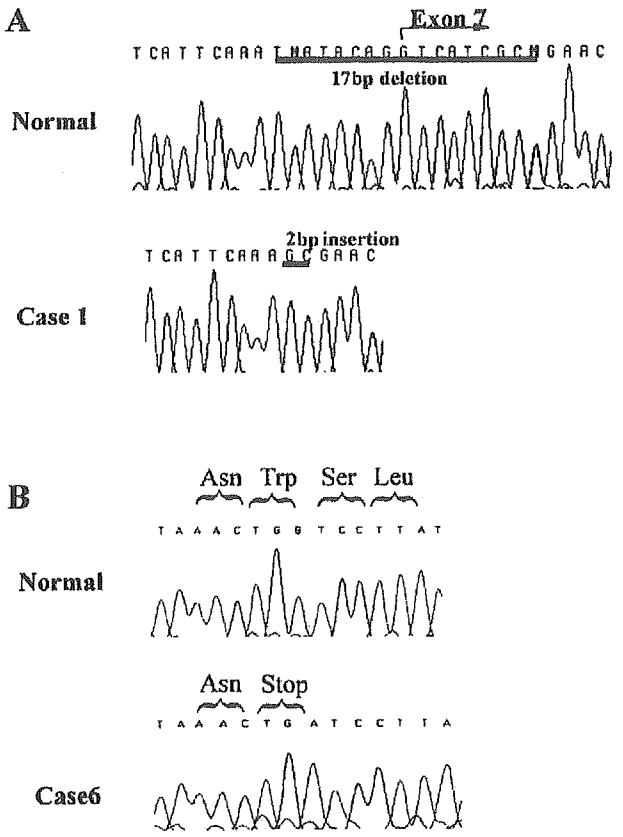

FIGURE 2. Results of DNA sequencing of cases 1 and 6. (A) Top: Normal alleles from a healthy control. Bottom: Mutant alleles from case 1 showing the deletion of TCATACAGGTCATCGCG and the insertion of GC at 3′ splice site in exon 7. (B) Top: Normal alleles from a healthy control showing G in the third nucleotide at codon 340. Bottom: Mutant alleles from case 6 showing a homozygous transversion of guanine to adenine, which resulted in a stop codon at codon 340.

scotoma and constricted visual field in the right eye, and central scotoma in the right eye. Case 5 had a mildly constricted visual field and enlargement of the blind spot of Mariotte.

The scotopic single-flash, standard flash ERGs and 30-Hz flicker ERGs were nonrecordable in cases 1 and 6. In case 2, the a-wave of the standard flash ERG in the left eye and a-waves of photopic ERG in the both eyes were within the normal range. The other components of the ERGs were mildly reduced. In case 4, the a-wave of the standard flash ERG, the scotopic b-wave in the right eye, photopic a-wave in both eyes, photopic b-waves in the right eye, and 30-Hz flicker were mildly reduced. In case 3, all of the ERGs were within normal range, and in case 5, all ERGs were severely reduced (Table 2).

Crystalline deposits were detected at the superior limbus of the cornea in cases 2, 3, and 4 by specular microscopy (Figure 5).

DISCUSSION

IN 2004, LI AND ASSOCIATES[7] FIRST REPORTED THAT MUTATIONS of the *CYP4V2* gene caused BCD. To date, 13 mutations in the *CYP4V2* gene have been reported in European, Japanese, and Chinese patients.[7] It has been suggested that the *CYP4V2* gene might play a role in fatty acid and corticosteroid metabolism, because patients with BCD have abnormalities of lipid metabolism.[9] However, no previous report regarding genotype-phenotype correlation has been shown in Japanese patients with BCD.

Interestingly, molecular genetic analysis of the *CYP4V2* gene in the 6 Japanese patients demonstrated that 5 of the 6 patients had an identical IVS6 to 8delTCATACAGGTCATCGCG/insGC mutation, which resulted in skipping of exon 7. In 2004, Li and associates[7] reported that the IVS6 to 8delTCATACAGGTCATC mutation, which also resulted in skipping of exon 7, was detected in not only Japanese but also Chinese patients with BCD. If we consider that these two mutations were the same, our results would suggest that the IVS6 to 8delTCATACAGGTCATCGCG/insGC mutation is the most common mutation in the *CYP4V2* gene and extends to other races.

A comparison of the ophthalomologic examinations in patients aged in the 40s to 60s showed the natural course of the ophthalmologic characteristics and visual outcome in patients with BCD associated with mutations in the *CYP4V2* gene. Patients older than 50 years showed advanced choroidal sclerosis, decreased visual acuity, and attenuation of retinal vessel. These findings are compatible with the previous reports about the clinical characteristics of patients with BCD.[10]

Conversely, the clinical features, for example, the ERGs, kinetic visual fields, and fundus appearance produced by mutations in the *CYP4V2* gene, were variable. Case 4 had a demarcated choroidal sclerosis and retinal degeneration in the posterior pole, whereas other patients showed diffuse retinal degeneration. In addition, crystalline deposits were not apparent because of the severe choroidal sclerosis in case 1. For Goldmann kinetic visual fields, four patients showed paracentral scotoma, two had a central scotoma, and all patients had constricted visual fields.

It has been reported that the ERG findings in patients with BCD were markedly variable, even in patients with similar opthalmoscopic, fluorescein angiographic, and visual field findings.[11] The results of all the ERG tests in our patients were also variable; case 3 had an apparent retinal degeneration and abnormalities in fluorescein angiography; however, all ERGs were of normal amplitude. Conversely, all ERGs were nonrecordable in cases 1 and 6. We conclude that the mutation in the *CYP4V2* gene also causes clinical variability in functional manifestations among patients with BCD.

The patient with the novel Trp340X mutation was 46 years old, had the typical fundus of crystaline retinopathy,

TABLE 1. Ocular Findings Associated With the Mutations in the *CYP4V2* Gene

Patient	Age	Sex	Mutation	First Symptoms	Age at Onset of First Symptom	Biomicroscopic Findings	Fundus Finding	Fluorescein Angiography
1	61	F	IVS6-8delTCATACAGGTCATCGCG/insGC	DVA	46	PSC, NC	CS	NA
2	57	F	IVS6-8delTCATACAGGTCATCGCG/insGC	Night blindness	41	CC	CD, mild CS, BP	RSHypo F, DHyper F
3	43	F	IVS6-8delTCATACAGGTCATCGCG/insGC	Night blindness	43	CC	CD, mottled RPE, BP	RS Hypo F, DHyper F
4	63	F	IVS6-8delTCATACAGGTCATCGCG/insGC	DVA	49	mild PSC, NC	CD, CS*, BP	RSHypo F, DHyper F
5	48	F	IVS6-8delTCATACAGGTCATCGCG/insGC	Night blindness	43	Normal	CD, mottled RPE, BP, RSC**	RSHypo F, DHyper F
6	51	M	Trp340X	CVF	46	Normal	CD, mild CS, BP	Hypo F, DHyper F

BP = bone spicule pigmentation; CC = cortical cataract; CD = crystalline deposit; CS = choroidal sclerosis; CS* = sharply demarcated retinal degeneration with choroidal sclerosis; CVF = constricted visual field; DHyperF = diffuse hyperfluorescence; DVA = decrease of visual acuity; F = female; M = male; NA = not available; NC = nuclear cataract; PSC = posterior subcapsular cataract; RSC** = round-shaped choroidal atrophy in the mid-peripheral area, RSHypoF = round-shaped hypofluorescence.

TABLE 2. Ocular Functions With the Mutations in the *CYP4V2* Gene

Patient		Visual Acuity	Visual Field	Standard Flash		Scotopic	Photopic		30-Hz Flicker
				a-wave (μV)	b-wave (μV)	b-wave (μV)	a-wave (μV)	b-wave (μV)	b-wave (μV)
1	OD	0.03	CVF, CS	0	0	0	0	0	0
	OS	0.3	CVF, PCS	0	0	0	0	0	0
2	OD	1.0	CVF, PCS	271	400	135	42	100	57
	OS	1.0	CVF, PCS	357	485	171	35.7	71	78
3	OD	1.5	CVF	337	512	225	43.7	100	113
	OS	1.5	CVF	362	537	213	50	87.5	113
4	OD	0.1	PCS, CVF	350	467	200	50	87.5	84
	OS	0.02	CS, CVF	337	437	175	50	100	72
5	OD	0.9	CVF, EB	31	37.5	0	0	0	27.25
	OS	0.5	CVF, EB	25	37	0	0	0	27.25
6	OD	0.02	CVF, PCS	0	0	0	0	0	0
	OS	0.4	CVF, PCS	0	0	0	0	0	0

CS = central scotoma; CVF = constricted visual field; EB = enlargement of the blind spot of Mariotte; OD = right eye; OS = left eye; PCS = paracentral scotoma.
Normal: a-wave in standard flash ERG; 376.3 ± 49.4; b-wave in standard flash ERG; 560.2 ± 72.9.
Scotopic b-wave: 230.1 ± 51.2, a-wave in photopic ERG: 52.7 ± 17.1; b-wave in photopic ERG: 110.3 ± 22.6.
30-Hz flicker ERG: 127.5 ± 24.1.

and showed a clinical course similar to the patients with the IVS6 to 8delTCATACAGGTCATCGCG/insGC mutation.

According to previous reports, BCD patients developed decreased visual acuity, night blindness, and constriction of the visual field between the second and fourth decade of life; the marked visual impairment progressed to legal blindness by the fifth to sixth decade of life.[6,7] Although the initial symptoms were variable, our cases noted visual disturbances after age 40 years and had severe clinical features after age 50 years. These findings suggest that Japanese patients with BCD associated with mutations of the *CYP4V2* gene have a rapid and progressive decline in visual acuity after 50 years.

Additional molecular biologic analysis such as transgenic experiments or gene expression studies will augment our understandings of the mechanism of crystalline retinopathy.

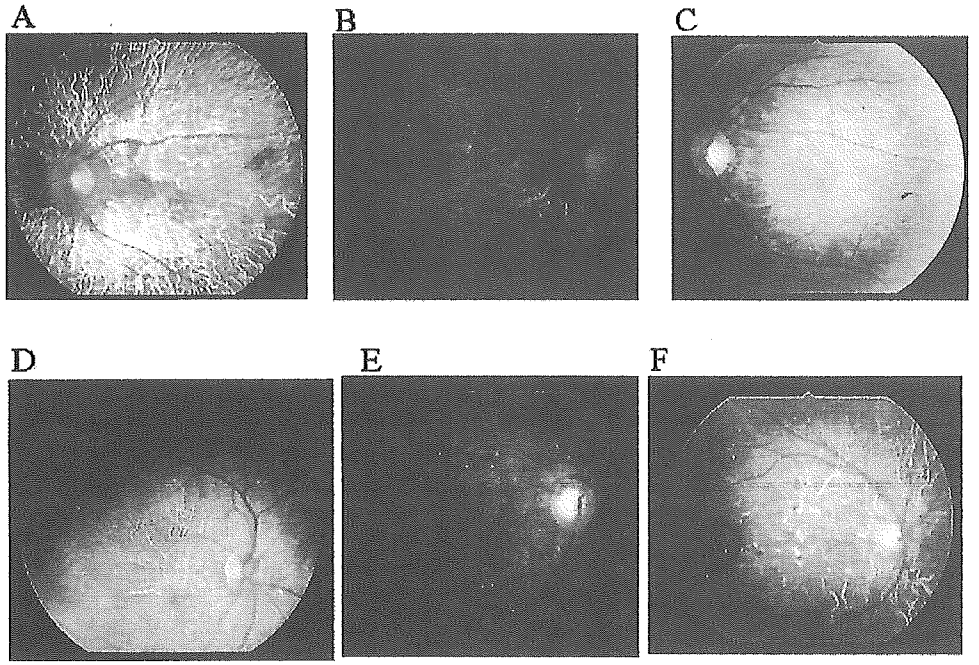

FIGURE 3. Fundus appearance of the six patients with Bietti's crystalline corneoretinal dystrophy. (A) Case 1 shows severe choroidal sclerosis without crystalline deposits. (B) Case 2 shows small yellowish-white sparkling spots distributed in the posterior pole. (C) Case 3 shows pigmentation and small yellowish-white sparkling spots distributed in the posterior pole. (D) Case 4 shows a few yellowish tiny deposits and demaracated chorioretinal degeneration. (E) Case 5 shows small yellowish-white sparkling spots distributed in the posterior pole. The pigmentation is seen around the macula and in the nasal area. (F) Case 6 shows small yellowish-white sparkling spots distributed in the posterior pole. The pigmentation is observed in the temporal area.

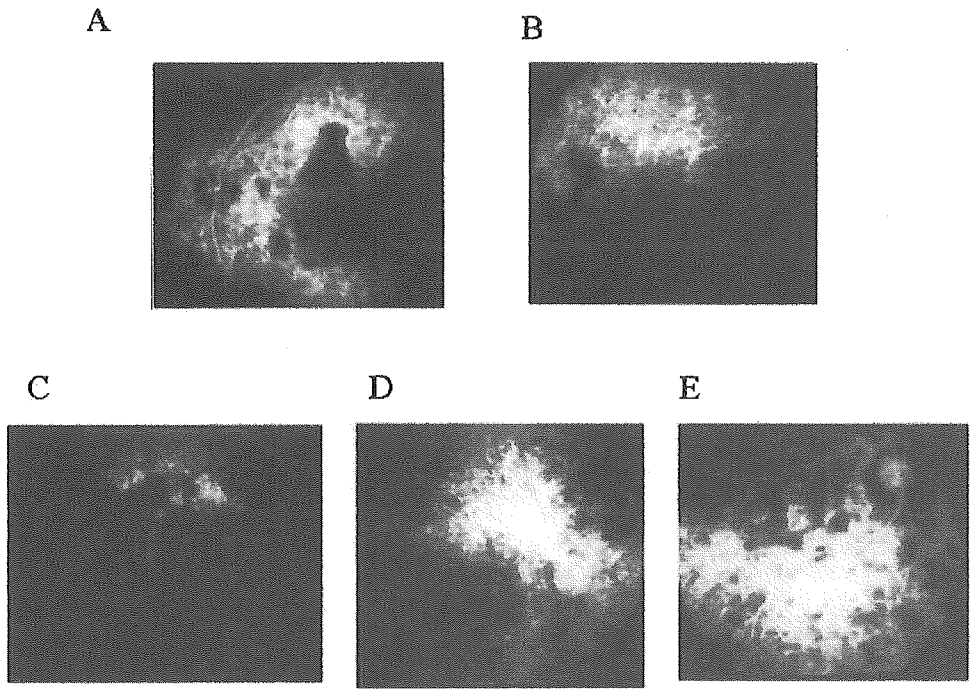

FIGURE 4. Fluorescein angiography of (A) case 2, (B) case 3, (C) case 4, (D) case 5, and (E) case 6. All patients show atrophy of retinal pigment epithelium and loss of choriocapillaris.

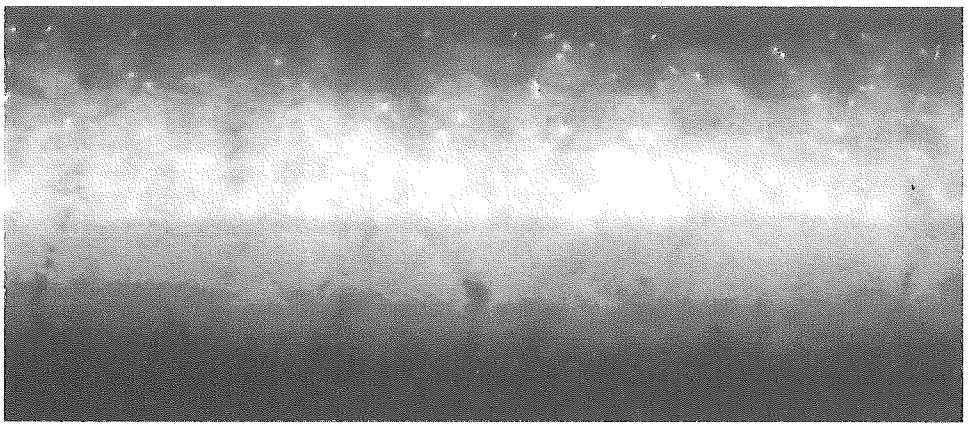

FIGURE 5. Specular microscopic findings in case 2. Many crystalline deposits can be seen at the limbus.

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3. 日本人常染色体劣性網膜変性疾患における ABCA4 遺伝子変異の解析

多田麻子、和田裕子、板橋俊隆、助川真里絵、今井詠子、佐藤　肇、西田幸二
(東北大)

研究要旨　ABCA4 遺伝子は Stargardt 病 (STGD)の原因遺伝子であるが、常染色体劣性網膜色素変性(ARRP)、常染色体劣性錐体桿体ジストロフィ (ARCRD) を起こすことが報告された。我々は、常染色体劣性の網膜変性疾患 (STGD、ARRP、ARCRD) における ABCA4 遺伝子異常と臨床像の関連について検討した。今回の研究で我々は STGD9 例に複合ヘテロ接合体のミスセンス変異を認めた。また STGD4 例に IVA12+2T>G 変異、STGD 5 例に His1838Asp 変異を認めた。IVA12+2T>G 変異を持つ Stargardt 病症例は黄斑部のみに萎縮巣をもつ症例から後極部全体の萎縮を認める症例まで多彩であった。

A. 研究目的

ABCA4 遺伝子は Stargardt 病 (STGD)の原因遺伝子であるが、常染色体劣性網膜色素変性(ARRP)、常染色体劣性錐体桿体ジストロフィ (ARCRD) を起こすことが報告された。今回我々は、常染色体劣性網膜変性疾患 (STGD、ARRP、ARCRD) の日本人患者における ABCA4 遺伝子異常と臨床像の関連について検討した。

B. 研究方法

遺伝子解析のインフォームドコンセントが得られた ARRP96 家系、CRD86 家系 STGD8 家系を対象とした。症例の末梢血から DNA を抽出し、エクソン 1 から 50 までの全翻訳領域に対して、51 種類のプライマーを作成し、PCR-Direct sequence 法による塩基配列の決定を行った。変異が認められた症例に対しては、矯正視力、細隙灯顕微鏡検査、眼底検査、蛍光眼底撮影、ゴールドマン動的量的視野検査、網膜電図を試行した。

C. 研究結果

ARRP18 例にミスセンス変異 (ヘテロ接合体 18 例)、CRD16 例にミスセンス変異 (ホモ接合体 1 例、複合ヘテロ接合体 2 例、ヘテロ接合体 13 例) を認めた。STGD 患者に IVA12+2T>G 変異、Thr106Phe 変異、

STGD

Pt.No	ALLELE1		ALLELE2	
#1358	IVS12+2T>G		Asn933Ile	exon19
#1	IVS12+2T>G		His1838Asp	exon39
#2	Arg537Cys	exon12	His1838Asp	exon39
#5	Thr106Phe	exon4	Asn933Ile	exon19
#694	Thr106Phe	exon4	Asn933Ile	exon19
#9	IVS12+2T>G		His1838Asp	exon39
#10	IVS12+2T>G		His1838Asp	exon39
#11	His1838Asp	exon39	Ser2255Ile	exon49
#12	Glu294ter	exon8	Thr1428Met	exon29

下線は新規変異

図 1　Stargardt 病解析結果

Glu294stop 変異、Arg537Cys 変異、Asn933Ile 変異、Thr1428Met 変異 His1838Asp 変異、Ser2255Ile 変異を認めた。CRD 患者に Thr1428Met 変異、His1838Asp 変異、Arg2149stop 変異を認めた。IVS12+2T>G を持つ症例は黄斑部のみに萎縮巣をもつ患者から後極部全体の萎縮を認める患者まで多彩であった。STGD10 例中 9 例に ABCA4 遺伝子変異を複合ヘテロ接合体で認めた (IVS12+2T>G/Asn933Ile、IVS12+2T>G/His1838Asp (3 例)、Arg537Cys/His1838Asp、Thr106Phe/Asn933Ile (2 例)、His1838Asp/Ser2255Ile、Glu294stop/Thr1428Met)。

D. 考察　E. 結論

Stargardt 病 10 例中 4 例に IVA12+2T>G 変異、5 例に His1838Asp 変異を認めた。IVS12+2T>G 変異、His1838Asp 変異は、日本人 Stargardt 病のホットスポットのひとつである可能性が考えられた。IVS12+2T>G 変異を持つ症例は黄斑部のみに萎縮巣をもつ症例から後極部全体の萎縮を認める症例まで多彩であった。

F. 健康危険情報

なし

G. 研究発表

1. 論文発表

なし

2. 学会発表

1. 多田麻子　他　「日本人常染色体劣性網膜変性疾患における ABCA4 遺伝子変異の解析」　第 59 回日本臨床眼科学会 (2005 年 10 月)
2. 多田麻子　他　「日本人常染色体劣性網膜変性疾患における ABCA4 遺伝子変異の解析」　第 108 回日本眼科学会総会 (2004 年 4 月)

H. 知的財産権の出願・登録状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

I. 参考文献

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Screening for Mutations in the IMPDH1 Gene in Japanese Patients With Autosomal Dominant Retinitis Pigmentosa

Yuko Wada, MD, Asako Tada, MD, Toshitaka Itabashi, MD, Miyuki Kawamura, MD, Hajime Sato, MD, and Makoto Tamai, MD

PURPOSE: To determine the presence and frequency of mutations in the IMPDH1 gene in Japanese patients with autosomal dominant retinitis pigmentosa (ADRP), and to characterize the clinical characteristics of patients with the Lys238Arg mutation in the IMPDH1 gene.

DESIGN: Case reports and results of DNA analysis.

METHODS: All 14 coding exons of the IMPDH1 gene were directly sequenced in 96 unrelated patients with ADRP. The clinical features were determined by visual acuity, slit-lamp biomicroscopy, and kinetic visual field tests.

RESULTS: Two novel mutations, a Leu227Pro and Lys238Arg, in the IMPDH1 gene were identified in two unrelated families with ADRP. The clinical features associated with the Lys238Arg mutation were an early-onset and severe retinal degeneration.

CONCLUSIONS: The most commonly reported Asp226Asn mutation was not found in the Japanese population, instead two novel mutations were found. These findings suggest that mutations of the IMPDH1 gene cause ADRP in the Japanese population. (Am J Ophthalmol 2005;140:163-165. © 2005 by Elsevier Inc. All rights reserved.)

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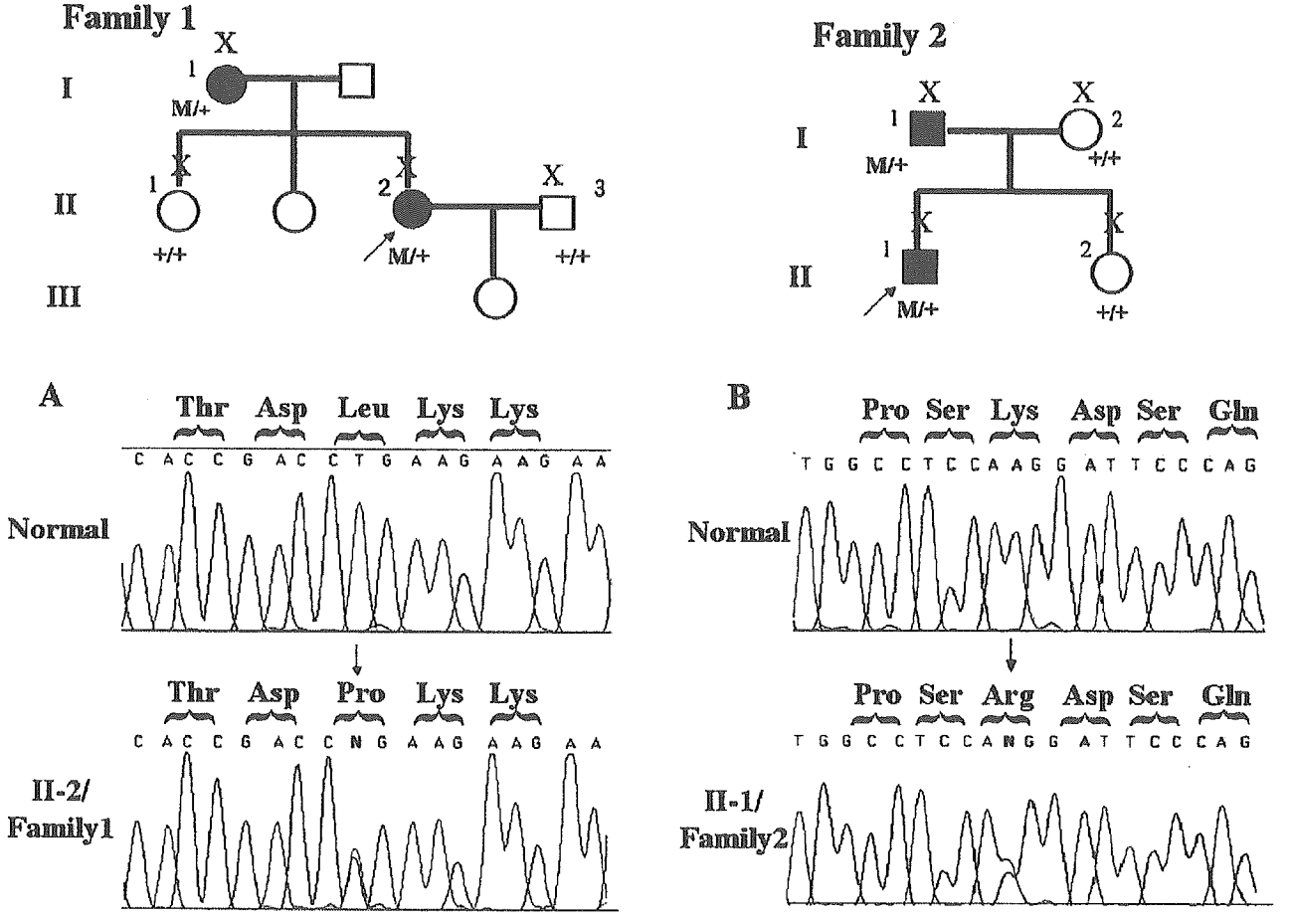

FIGURE 1. (Top) Pedigrees of two Japanese families with autosomal dominant retinitis pigmentosa associated with mutations in the IMPDH1 gene showing affected (solid symbols) and unaffected (open symbols) members. Squares, male members; circles, female members; X, individuals examined in this study; arrow, proband; M, mutant allele; plus, normal allele. (Bottom) (A) Results of nucleotide sequencing analysis. Family 1 has a Leu227Pro mutation. The upper sequence is that for normal individuals and the lower sequence is from patient II -2. (B) The abnormal nucleotide sequence of family 2 shows a Lys238Arg mutation. The upper sequence is that for normal individuals, and the lower sequence is from patient II -1.

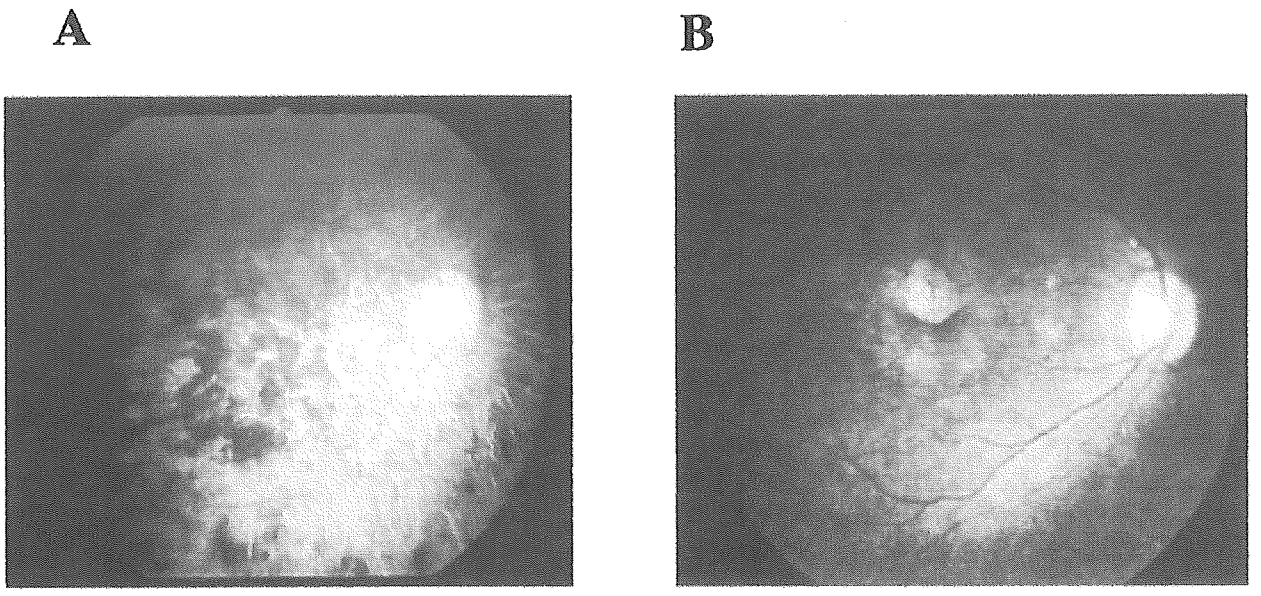

FIGURE 2. (A) Fundus photographs of patient I-1 of family 2 at age 54 showing severe retinal degeneration, attenuation of retinal vessels, and bone-spicule pigmentation. (B) Fundus photographs of patient II-1 of family 1 at age 19. Atrophic macular degeneration and mottled appearance of retinal pigment epithelium can be seen.

THE IMPDH1 GENE IS THE TENTH GENE TO HAVE A mutation in patients with autosomal dominant retinitis pigmentosa (ADRP). In 2002, it was reported that the IMPDH1 gene was a candidate gene in RP10 families, and this mutation may account for 5% to 10% of ADRP in the American and European population.[1,2] IMPDH1 is a ubiquitously expressed enzyme, functioning as a homotetramer that catalyzes the rate-limiting step in the de novo synthesis of guanine nucleotides. As such, it has been suggested that the IMPDH1 gene plays an important role in the metabolism of cyclic nucleosides in the photoreceptors. All of the reported mutations were in exon 7, and Asp226Asn was the most commonly reported mutation.[1–3]

The purpose of this study was to characterize the clinical features of patients with a newly identified mutation, Lys238Arg, in the IMPDH1 gene and to estimate the frequency of this mutation in the Japanese population.

Ninety-six genomic DNA samples from 96 unrelated families with ADRP were screened for mutations in the IMPDH1 gene. Informed consent was obtained from all subjects. The sequences from exons 1 to 14 were amplified by polymerase chain reaction (PCR). Nine sets of oligonucleotide primer pairs were used to amplify the entire coding region of the IMPDH1 gene.[1] Products of the PCR were directly sequenced on an ABI sequencer (Model 3100; Applied Biosystems; Foster City, California, USA).

The results demonstrated that Japanese patients do not have the most commonly reported Asp226Asn mutation but instead have two novel mutations, Lys238Arg and Leu227Pro. Although the number of families with the Lys238Arg mutation is small, this mutation cosegregated with the phenotype in this family (Figure 1). In addition, 50 normal controls did not have this mutation.

The visual acuity of the two affected members, a 19-year-old and a 54-year-old, ranged from no light perception to hand motions and progressed to legal blindness after 10 years-of-age. Fundus examination of II-1 of family 2 disclosed bilateral pigmentary retinal degeneration, attenuation of the retinal vessels, and tapetal reflex in the macula. I-1, father of II-1, showed diffuse atrophy of retinal pigment epithelium, bone spicule pigmentation, severe attenuation of the retinal vessels, and optic atrophy (Figure 2).

Two affected members in another family had a Leu227Pro mutation (Figure 1). The Leu227Pro mutation is within the CBS domain, a highly conserved residue and also was not detected in normal controls. These findings would suggest that the Leu227Pro mutation is probably a pathogenic mutation.

In 2003, the clinical feature of patients with the Arg231Pro mutation was an early onset of severe retinal degeneration. The authors reported that the presence of a severe form of ADRP might be a good sign of having mutations in the IMPDH1 gene.[3] The clinical feature of our patients with a Lys238Arg mutation in the IMPDH1 gene was also early onset of severe retinal degeneration, which supported their findings.

Furthermore, mutations in the IMPDH1 gene are relatively rare in Japanese patients with ADRP, as we have found this mutation in only 2% of unrelated patients with ADRP.

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Retinal Nerve Fiber Layer Thickness in the Fellow Eyes of Normal-tension Glaucoma Patients With Unilateral Visual Field Defect

Dong Myung Kim, MD, Uk Suk Hwang, MD, Ki Ho Park, MD, and Seok Hwan Kim, MD

PURPOSE: To quantitatively evaluate retinal nerve fiber layer (RNFL) thickness in the fellow eyes of normal-tension glaucoma (NTG) patients with unilateral visual field defect.

DESIGN: Observational case-control study.

METHODS: Twenty-nine NTG patients with unilateral visual field defect were enrolled in this study. All 29 fellow eyes showed normal visual field. Thirty-one normal eyes of 31 subjects served as controls. The RNFL thickness around the optic disk was determined using Fast RNFL thickness (3.4) of optical coherence tomography. Average and segmental (4 quadrants and 12 clock-hours) RNFL thickness measurements were compared among the three groups.

RESULTS: RNFL thicknesses were significantly different among the three groups in the average, superior quadrant (11 and 12 clock-hour segments), and inferior quadrant (6 clock-hour segment) ($P = .00$, one-way ANOVA and Tukey's tests).

CONCLUSIONS: RNFL thickness reductions are already present in the fellow eyes of NTG patients with unilateral visual field defect. (Am J Ophthalmol 2005;140: 165-166.

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NORMAL-TENSION GLAUCOMA (NTG) PATIENTS WITH unilateral visual field (VF) defect are likely to develop VF defect in both eyes with time.[1] However, whether fellow eyes with "normal" VF at the time of diagnosis, as determined by perimetry, are truly unaffected or not, is unknown because retinal nerve fiber layer (RNFL) changes have been known to precede VF change.[2] We used optical coherence tomography (OCT) to determine whether retinal nerve fiber layer thickness (RNFLT) changes are present in the fellow eyes of NTG patients with unilateral VF defect.

Twenty-nine NTG patients with VF defect in one eye (group A) and normal VF in the fellow eye (group B; n = 29) at the time of diagnosis, were selected for this study. The diagnostic criteria used for NTG were normal intraocular pressure (IOP), glaucomatous optic neuropathy, glaucomatous VF defects, open anterior chamber angle, and the absence of any contributing ocular or systemic disorders. Normal IOP was defined as a diurnal IOP of persistently <21 mm Hg without medication. Mean diurnal IOP was adapted to compare IOPs. VF was evaluated using the 30-2 program of the Humphrey Visual Field Analyzer Model 630 (Allergan Inc., San Leandro, California, USA). Only eyes with VFs available within three months of the OCT measurements were included. Eyes with spherical equivalent refractive error of ≥−6.00 diopters were excluded. Thirty-one eyes of 31 subjects matched for age and refraction were recruited as controls (group C). Informed consent was obtained from all subjects. Control subjects were required to have an IOP of <21 mm Hg, normal anterior and posterior segments, and normal VF in both eyes. One eye was randomly selected for inclusion. Fast RNFL thickness (3.4) of Stratus OCT (Carl Zeiss Meditec Inc., Dublin, California, USA) was used to measure the thickness of the peripapillary RNFL. Three measurements were performed for each eye. The following OCT parameters were used: average RNFLT, average RNFLT in each quadrant, and mean RNFLT in each of 12 30-degree clock-hour segments. Left eye data were converted into right eye format.

No significant differences were found in age, gender ratio, refraction, or IOP among the three groups (Table 1). RNFLTs were significantly different among the three groups in the average, superior quadrant (11 and 12 clock-hour segments), and inferior quadrant (6 clock-hour segment). In group B, RNFLT at the superior (11, 12, and 1 clock-hour segments), inferior (5 and 6 clock-hour segments), and nasal quadrants (2 and 4 clock-hour segments) were significantly lower than in group C. In group A, RNFLT at the superior (11 and 12 clock-hour segments) and inferior quadrants (6 and 7 clock-hour segments) were significantly lower than in group B (Table 2).

These findings suggested that RNFL changes are already present in group B and that the nasal side of the optic disk is affected earlier than what is currently considered.[3] It seems that preperimetric changes in the RNFL of group B are already present but have not yet reached a level that elicits changes in retinal sensitivity.

4. 日本人常染色体優性網膜色素変性患者における ROM1 遺伝子解析

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研究要旨　日本人常染色体優性網膜色素変性 150 家系において ROM1 遺伝子解析を行った結果、peripherin/RDS 遺伝子との二遺伝子性遺伝と考えられる新規遺伝子変異（ROM1: Leu141Ser 変異と peripherin/RDS: Asp186Val 変異）を 1 家系に認めた。また、別の新規遺伝子変異(ROM1: Pro332Thr 変異と peripherin/RDS: Ala339Thr 変異)を 1 家系に認めたが、この家系では二遺伝子性遺伝のほかにそれぞれの単一遺伝子性遺伝の可能性も考えられた。さらに ROM1 に Leu114insG 変異を 2 家系に認めたが、この変異のみでは常染色体優性網膜色素変性を呈さないと考えられた。本研究結果から日本人常染色体優性網膜色素変性患者の約 1 %に ROM1 遺伝子が責任遺伝子として関与していることが示唆されたが、ROM1 遺伝子のみの変異で網膜色素変性を生じるという明らかな家系は認められなかった。

A. 研究目的

ROM1 遺伝子は、peripherin/RDS 遺伝子との二遺伝子性遺伝で網膜色素変性を生じることが 1994 年に報告されている [1]。その後 ROM1 遺伝子の単独変異で常染色体優性遺伝や弧発型の網膜色素変性も生じることが海外で報告されているが、日本人での報告はまだない [2]。今回我々は、日本人常染色体優性網膜色素変性患者において ROM1 遺伝子解析を行い、臨床像と遺伝子変異の相関を検討することを目的とした。

B. 研究方法

常染色体優性網膜色素変性 150 家系を対象に、末梢血白血球から抽出した genome DNA を鋳型に、ROM1 遺伝子の全エクソンとその近傍のイントロンの塩基配列を PCR で増幅し、PCR 産物を用いて直接塩基配列を決定した。ROM1 遺伝子に塩基配列異常の認められた症例に対して、peripherin/RDS 遺伝子の塩基配列も同様に解析した。さらに ROM1 遺伝子と peripherin/RDS 遺伝子に同定した変異に関して正常人 96 人を対象にその頻度を解析した。また、対象患者に眼科的検査を施行した。

（倫理面への配慮）

本研究は、ヒトゲノム・遺伝子解析に関する倫理指針に従って、東北大学医学部倫理委員会の承認を得て、実施された。

C. 研究結果

150 家系中、ROM1 遺伝子に Leu141Ser 変異を 1 家系（家系 1)、Pro332Thr 変異を 1 家系（家系 2)、Leu114insG 変異を 2 家系（家系 3、4）に認めた。peripherin/RDS 遺伝子に家系 1 で Asp186Val 変異、家系 2 で Ala339Thr 変異を認めたが、家系 3、4 では調べた範囲で peripherin/RDS 遺伝子変異を同定できなかった（図 1)。これら 5 つの

変異は、正常人96人中、Leu141Ser変異が2人、Pro332Thr変異が0人、Leu114insG変異が1人、Asp186Val変異が0人、Ala339Thr変異が0人、いずれもヘテロ接合体で認められた。臨床像は、大半が定型網膜色素変性を呈していたが、家系2では血管アーケードに沿って軽度の変性を呈するものも見られ、表現型の多様性が認められた。

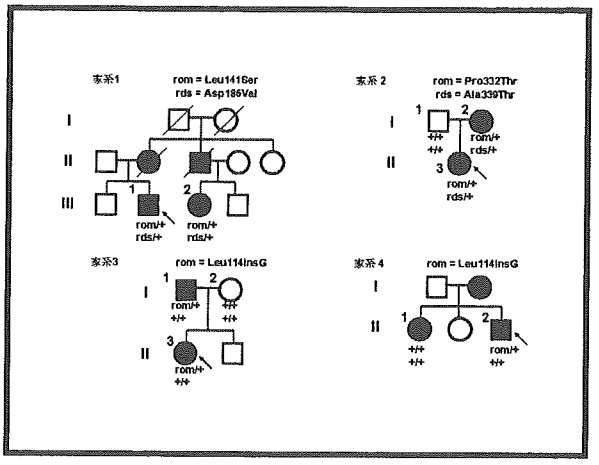

図1　4家系におけるROM1遺伝子およびperipherin/RDS遺伝子変異

D．考察

ROM1遺伝子Leu114insG変異のみでは網膜色素変性を呈さないと考えられた。家系1では二遺伝子性遺伝と考えられ、また家系2では二遺伝子性遺伝の可能性が高いが、単一遺伝子性遺伝の可能性も否定できないと考えられた。

E．結論

日本人常染色体優性網膜色素変性患者にもROM1遺伝子変異は存在する。その頻度は、米国での報告と同様に低く、約1％であった[3]。ROM1遺伝子変異のみで常染色体優性網膜色素変性を呈する家系を示すことはできなかったが、新規の二遺伝子性遺伝と考えられる遺伝子変異を同定した。

F．健康危険情報

なし

G．研究発表

1．論文発表

なし

2．学会発表

なし

H．知的財産権の出願・登録状況

1．特許取得

なし

2．実用新案登録

なし

3．その他

なし

I．参考文献

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TABLE 1B. Multivariate Analysis of Ocular Biometry and Refraction by Birth Parameters in the Year 1 Cohort of the Sydney Myopia Study

	Regression Coefficient (Adjusted for Age and Gender)	*P* Value	R^2	Regression Coefficient (Adjusted for Age, Gender, and Other Birth Parameters)	*P* Value	R^2
Birth weight (1000 g)						
Axial length (mm)	0.17 (0.10–0.24)	<.0001	0.19	0.10 (−0.01–0.21)	.0629	0.21
Corneal radius (mm)	0.07 (0.05–0.10)	<.0001	0.08	0.06 (0.02–0.09)	.0045	0.10
Spherical equivalent* (D)	0.05 (−0.06–0.16)	.3631	0.02	0.04 (−0.20–0.28)	.7306	0.02
Astigmatic power (D)	0.02 (−0.03–0.07)	.4247	0.00	0.00 (−0.08–0.09)	.9211	0.00
Birth length (1 cm)						
Axial length (mm)	0.02 (0.01–0.04)	.0023	0.19	0.02 (0.00–0.03)	.0472	0.21
Corneal radius (mm)	0.01 (0.006–0.02)	.0003	0.08	0.01 (0.00–0.01)	.1204	0.10
Spherical equivalent* (D)	0.00 (−0.03–0.02)	.8240	0.02	−0.01 (−0.05–0.02)	.4269	0.02
Astigmatic power (D)	0.00 (0.00–0.01)	.3473	0.00	0.00 (−0.01–0.01)	.5140	0.00
Head circumference (1 cm)						
Axial length (mm)	0.04 (0.02–0.07)	.0007	0.19	0.02 (−0.01–0.05)	.1226	0.21
Corneal radius (mm)	0.02 (0.01–0.03)	.0001	0.08	0.01 (0.00–0.02)	.1986	0.10
Spherical equivalent* (D)	0.03 (−0.01–0.07)	.1817	0.02	0.02 (−0.03–0.07)	.3637	0.02
Astigmatic power (D)	−0.01 (−0.02–0.01)	.3508	0.00	−0.01 (−0.03–0.01)	.4669	0.00

*Multivariate models of spherical equivalent also included parental myopia as an independent variable. Parental myopia (defined as either parent wearing glasses before age 30 years) was significantly correlated with spherical equivalent refraction only and not with ocular biometry. Parental myopia was therefore included in multivariate models of spherical equivalent refraction only.

Mutations in the Pre-mRNA Splicing Gene, *PRPF31*, in Japanese Families With Autosomal Dominant Retinitis Pigmentosa

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PURPOSE: To describe the clinical and genetic characteristics of three Japanese families with autosomal dominant retinitis pigmentosa (ADRP) associated with mutations in the PRPF31 gene.

DESIGN: Case reports and results of DNA analysis.

METHODS: Mutational screening of the PRPF31 gene was performed on 96 unrelated patients with ADRP by direct sequencing. The clinical features were characterized by complete ophthalmologic examinations.

RESULTS: Three mutations in the PRPF31 gene, designated as 1142delG, 1155–1159delGGACG/insAGGGATT, and IVS6 to 3 to -45del, were identified in three unrelated Japanese families with ADRP. The 1142delG and 1155–1159delGGACG/insAGGGATT mutations are novel. The phenotype of affected family members was typical of retinitis pigmentosa (RP). Additionally, we identified asymptomatic obligate carriers.

CONCLUSIONS: The 1142delG and 1155–1159delGGACG/insAGGGATT mutations in the PRPF31 gene cause RP. The prevalence of mutations in the PRPF31 gene in Japanese patients with ADRP is approximately 3%. However, it is important to note that there are asymptomatic obligate carriers. (Am J Ophthalmol 2005;140:537–540.

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IN 2001, THE *PRPF31* GENE, HOMOLOGOUS TO THE pre-mRNA splicing gene *PRP31* in *Saccharomyces cerevisiae*, was identified as the gene responsible for autosomal dominant retinitis pigmentosa (ADRP) linked to RP11.[1] The PRPF31 gene has 14 exons, encodes a protein of 499 amino acids, and is ubiquitously expressed. Protein 61K encoded by PRPF31 gene is required for U4/U6 · U5 tri-snRNP formation in each round of nuclear pre-mRNA splicing which is catalyzed by a large ribonucleoprotein complex, the spliceosome.[2] We screened 96 patients from unrelated Japanese families with ADRP to search for mutations in the PRPF31 gene.

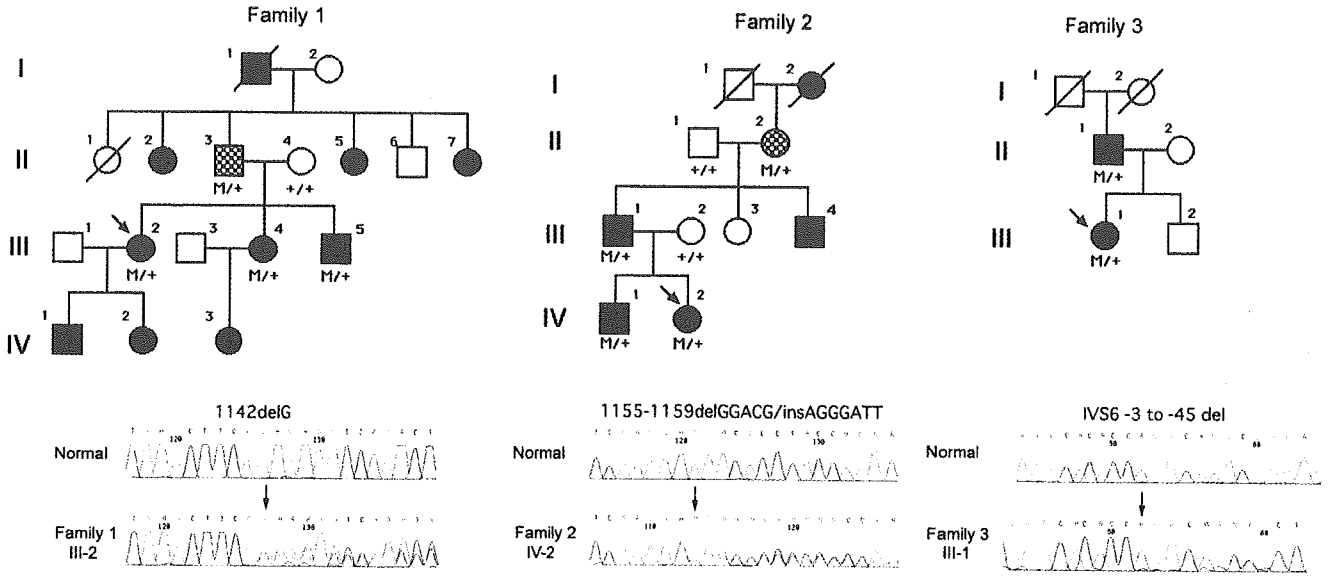

FIGURE 1. (Top) Pedigrees of three Japanese families with autosomal dominant retinitis pigmentosa associated with mutations in the *PRPF31* gene. Solid and open symbols represent affected and unaffected members, and check symbols represent asymptomatic carries. Genotypes are shown beneath the symbols. Squares = male; circles = female; Slash = deceased; arrow = proband; M = mutant allele; + = normal allelle. (Bottom) DNA sequences of the patients with the mutations in the *PRPF31* gene.

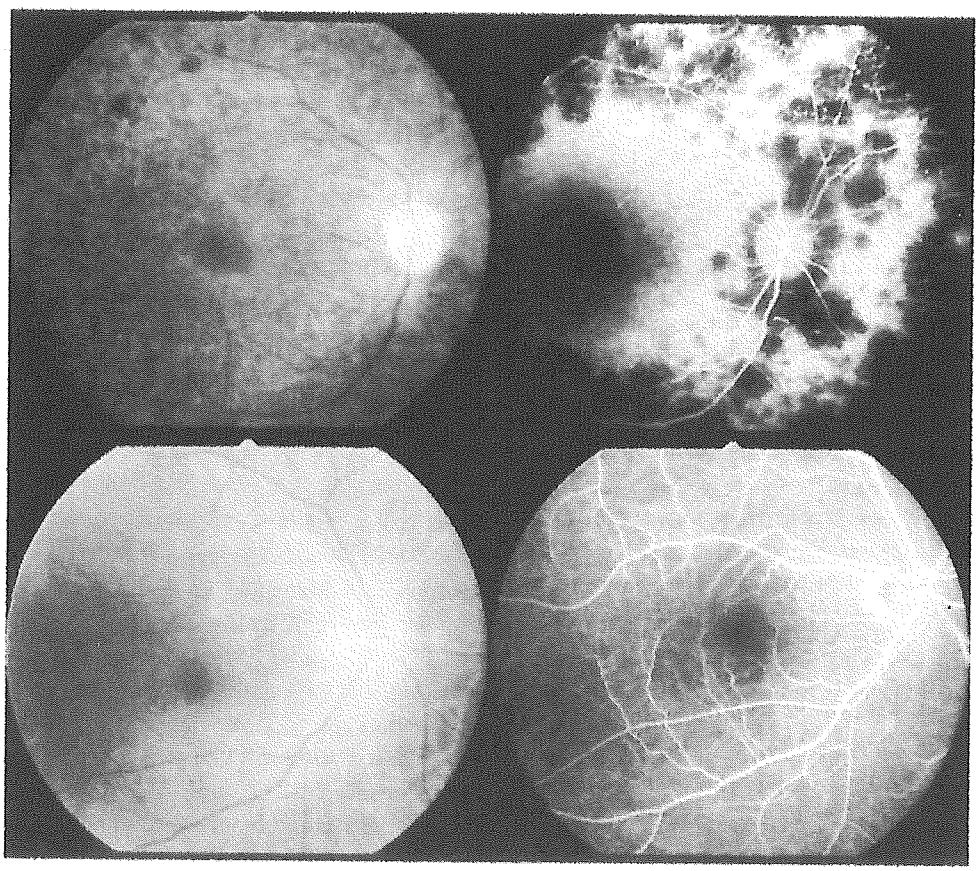

FIGURE 2. Fundus photographs and fluorescein angiograms of the cases with the mutations in the *PRPF31* gene. (Top left) Fundus photograph and (Top right) fluorescein angiogram of Case III-2 of family 1. Typical retinitis pigmentosa (RP) appearance of the fundus can be seen. (Bottom left) Fundus photograph and (Bottom right) fluorescein angiogram of Case II-3 of family 1. No signs of RP can be seen.

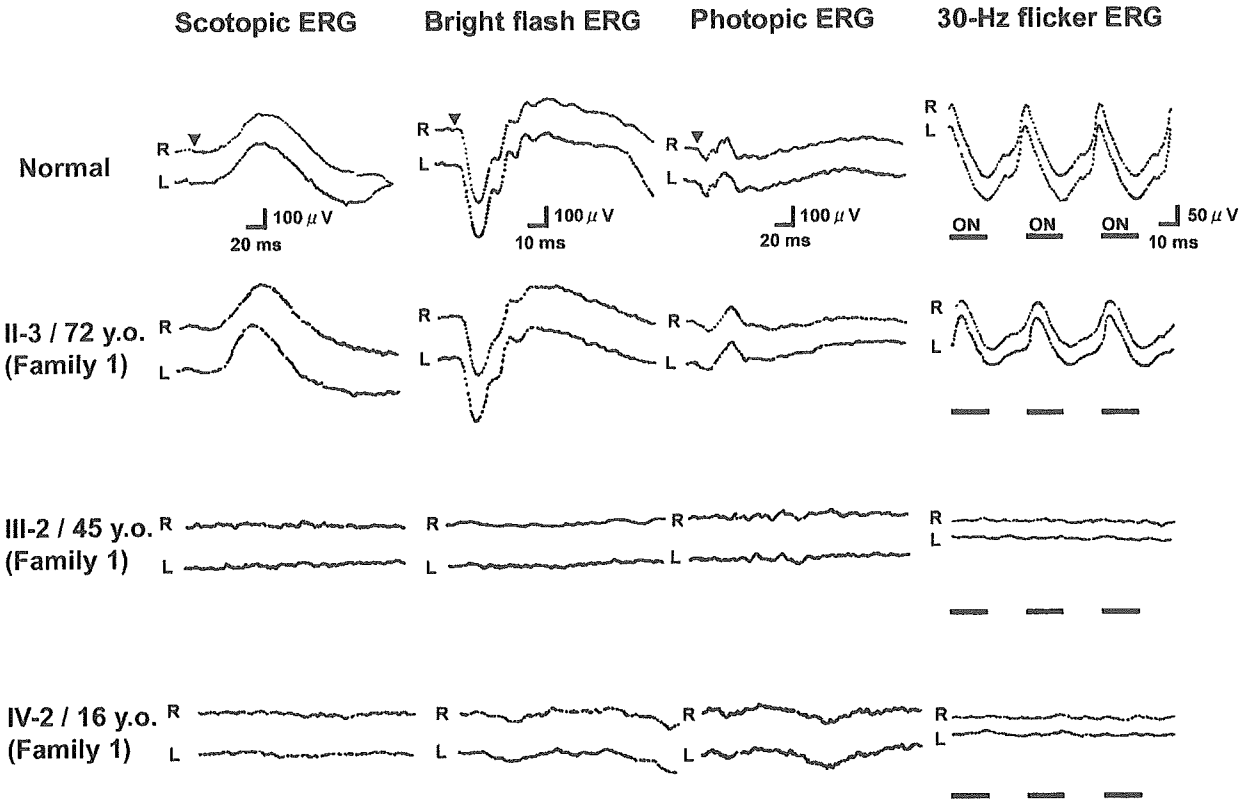

FIGURE 3. Electroretinograms (ERGs) of the Cases II-3, III-2, and IV-2 of family 1. Scotopic ERGs are non-recordable and other ERGs are severely reduced in Case IV-2. All ERGs are non-recordable in her mother (Case III-2). Although the amplitudes of a-waves and b-waves of bright flash ERGs are slightly reduced, the other ERGs are within normal range in the asymptomatic carrier II-3.

This study was approved by the Tohoku University Institutional Review Board, and written informed consent was obtained from all patients after an explanation of the purpose and procedures to be used. This study adhered to the tenets of the Declaration of Helsinki.

Genomic DNA samples were screened for mutations in the PRPF31 gene, and segregation studies were performed on family members of the patients who had a mutation. We also screened for other ADRP candidate genes, such as rhodopsin, peripherin/RDS, RP1, NRL, FSCN2, PRPC8, HPRP3, and IMPDH1, in these 96 patients.[3–5]

The DNA fragments of the complete coding and flanking intronic regions of the PRPF31 gene were amplified by polymerase chain reaction (PCR). The PCR products were directly sequenced in both the forward and reverse directions on an ABI sequencer (Model 3100; Applied Biosystems, Foster City, California).

Three kinds of mutations were identified in three unrelated families (Figure 1). Those were 1142delG, 1155 to 1159delGGACG/insAGGGATT, and IVS6 to 3 to -45del mutations (Figure 1). The 1142delG and 1155 to 1159delGGACG/insAGGGATT mutations were novel.

All of the symptomatic patients had night-blindness by the end of the first or second decade of life. The fundi of all the affected patients were typical of retinitis pigmentosa (RP)(Figure 2). Their visual acuities were preserved between 0.6 and 1.0 before age 45 unless there was cataract or cystoid macular edema. Goldmann kinetic visual field testing showed different degrees of constriction of the midperipheral and peripheral visual fields with relatively spared central fields dependent on the progression of RP.

A unique characteristic of these families was the presence of asymptomatic carriers who had mutations in the *PRPF31* gene. Case II-3 of family 1 was a 72-year-old man whose father, siblings, children, and grandchildren were symptomatic patients with RP. However, he had no disturbance of night vision, and ocular examination did not show any abnormality except for senile cataract. Fundus examination and fluorescein angiography disclosed no suspicious lesions suggesting the presence of RP (Figure 2). Goldmann kinetic visual fields were normal. The amplitudes of the a-waves and b-waves of the bright flash electroretinograms (ERGs) were slightly reduced, but the scotopic, photopic, and 30 Hz flicker ERGs were of normal amplitude (Figure 3).

Case II-2 of family 2 was a 90-year-old woman whose mother, children, and grandchildren were symptomatic patients with RP. She had no disturbance of night vision. Unfortunately, she could not visit our clinic to have a detailed assessment of her eyes.

The mutant mRNA was not expressed in the peripheral blood lymphocytes of Cases II-3, III-2, III-4, and III-5 in family 1. This finding suggested that the mutation induces functional loss of one allele resulting in haploinsufficiency.

The incomplete penetrance in RP11 could be attributable to the co-inheritance of a *PRPF31* gene defect and a low-expression of the wild-type allele.[6] Because a Chinese pedigree showed a high penetrance and a British family presented many asymptomatic carriers,[6,7] the expression of the wild-type allele of *PRPF31* gene may depend on the genetic background. To determine what genetic factors modulate the differential expression of the wild-type allele would be useful in the prognosis of family members with mutations.

In conclusion, we have identified two novel and one known mutations in three unrelated Japanese families with ADRP. This constitutes approximately 3% of the ADRP patients screened. There were also asymptomatic carriers in the Japanese population.

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Trans-Tenon Retrobulbar Triamcinolone Injection for Macular Edema Associated With Branch Retinal Vein Occlusion Remaining After Vitrectomy

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PURPOSE: To evaluate the effectiveness and safety of trans-Tenon retrobulbar triamcinolone injection for macular edema associated with branch retinal vein occlusion (BRVO) after vitrectomy.

DESIGN: Prospective interventional case series.

METHODS: The study included 20 eyes of 20 patients with BRVO, characterized by macular edema lasting more than 3 months after vitrectomy. Trans-Tenon retrobulbar injection of 40 mg triamcinolone was performed, and visual and anatomic responses were evaluated.

RESULTS: Mean foveal thickness was 499.4 ± 209.1 μm preoperatively, 281.8 ± 110.1 μm at 2-week follow-up, and 196.9 ± 92.1 μm at 6-month follow-up ($P < .0001$, at 2 weeks and 6 months, paired t test). Improvement of visual acuity by at least 0.2 logMAR (logarithm of the minimum angle of resolution) was seen in 14 (70%) of the 20 eyes.

CONCLUSIONS: Trans-Tenon retrobulbar injection of triamcinolone may be an alternative for additional treatment of eyes with BRVO that remains after vitrectomy.

RECENT INVESTIGATIONS HAVE DEMONSTRATED THE effectiveness of vitrectomy and its associated procedures for the decrease of macular edema in eyes with branch retinal vein occlusion (BRVO).[1] However, some cases of macular edema are resistant to vitrectomy. We evaluated the efficacy and safety of trans-Tenon retrobulbar triamcinolone injection for prolonged macular edema after vitrectomy in patients with BRVO.

Included in our study were 20 consecutive eyes of 20 patients with prolonged macular edema associated with BRVO lasting more than 3 months after vitrectomy.

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5. RDS遺伝子異常による黄斑変性にCNVを認めた症例

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（京都大）

研究要旨　黄斑部に網脈絡膜新生血管（CNV）を伴う非定型網膜変性を示し、遺伝子診断にて RDS 遺伝子に Gly167Ser の変異を認めた症例を経験した。今回の症例では網膜の変性は軽度で非定型の視野欠損を呈したが、網膜電図は平坦化していた。RDS 遺伝子異常による網膜変性は様々な病型を示す。特に CNV を伴う例では高度近視に伴う CNV や加齢黄斑変性と診断されている症例の中にも混在している可能性がある。これらを鑑別する為に遺伝子診断が有用であった。

A．研究目的

Peripherin/RDS の変異は網膜色素変性の原因遺伝子としてよく知られているが、その他にも黄斑変性など様々なバリエーションを持って視機能の異常を引き起こす。今回我々は黄斑部の脈絡膜新生血管（ＣＮＶ）を伴う非定型網膜色素変性の患者の遺伝子変異を検索し peripherin/RDS の遺伝子変異を認めたのでここに報告する。

B．研究方法

視力、ゴールドマン視野検査を施行し、眼底写真撮影、フルオレセイン蛍光眼底造影(FAG)、インドシアニングリーン眼底造影（ICG）、optical coherent tomography (OCT)を用いて眼底を観察した。網膜電図（ERG）で網膜機能を確認した。

患者および母親の静脈血を約 10ml 採血し、Transgenic 社の WAVE system を用いて変異のあるエクソンをスクリーニングし、ダイレクトシークエンスにて遺伝子変異を検出した。

（倫理面への配慮）

遺伝子診断についてはインフォームドコンセントを得て行った。京都大学医学部「医の倫理委員会」承認ずみ。

C．研究結果

症例は 47 歳女性。1997 年 9 月近医にて左眼の網膜裂孔に対して光凝固を施行。以後経過観察していたが周辺部の網脈絡膜萎縮巣や色素沈着を認め、ＧＰにて視野異常を認めたため、当院へ紹介受診となった。夜盲などに自覚症状は認めなかった。

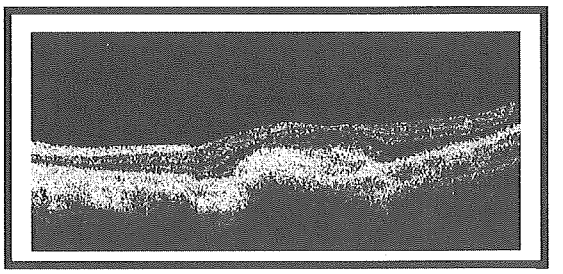

図１　左眼黄斑部 OCT。CNV を認める。

RV=(1.2xs-8.5Dcyl-1.25DAx20°)
LV=(1.0xs-9.0Dcyl-2.25DAx1000°)
両眼の周辺部に脈絡膜萎縮巣と動脈の狭窄、少量の色素沈着を認め、さらに両眼の黄斑

部に軽度の色素上皮萎縮を認めた。
2005年8月、再診時にはLV=(0.4x s-9.0D cyl-2.25D Ax160°)と左眼視力の低下を認め，黄斑部にＣＮＶを認めた。GPを施行したが、大きな視野の変化は認めなかった。FAGにて両眼の黄斑部にwindow defectを認めたが、蛍光漏出はあまり顕著ではなかった。ICGではCNVに一致して色素のpoolingを認めた。さらにOCTでは左眼にtype2 CNVを認めたが、網膜下液はわずかにしか認めなかった。
これらから、活動性の低いCNVであると考え、経過観察とした。
遺伝子診断では、患者母親ともにperipherin/RDSのGly167Serの遺伝子変異を認めた。現在に至るまで両眼に大きな変化は認めず、経過を観察中である。

Ｄ．考察

Peripherin/RDSの変異は網膜色素変性以外に蝶形黄斑ジストロフィーなどの様々な臨床像をとり、同一家系内においても異なる臨床像をとることが報告されている。
海外ではPeripherin/RDSの変異にＣＮＶをともなった症例が報告されているが、本邦ではまだ報告がない。Francisらは年齢が上がるとともにCNVをきたす率も上昇すると報告し、Limらは受診した常染色体優性型のFoveomacular dystrophyの患者のうち15%が前医にAMDと誤診されて紹介されていると述べている。
この症例の場合、患者には夜盲などの自覚症状はなく、眼底には周辺部に色素沈着が存在していたが少数であり、高度近視のＣＮＶト鑑別が難しい。
遺伝子診断を行うことにより、このような黄斑萎縮型の非定型網膜変性に対して確定診断が行うことができ、さらに将来CNVなどの合併症の危険性を考慮し経過を観察することによって早期に発見、対応することができると考えられる。

Ｅ．結論

ＣＮＶを伴った非定型網膜変性の診断に遺伝子診断が有用であった。

Ｆ．健康危険情報

なし

Ｇ．研究発表

１．論文発表

なし

２．学会発表

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Ｈ．知的財産権の出願・登録状況

１．特許取得

網膜の再生のための医薬（出願中）

２．実用新案登録

なし

３．その他

なし

Ｉ．参考文献

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Choroidal Neovascularization and Nonexudative Macular Associated with Mutation in the RDS gene. Invest Ophthalmol Vis Sci. 44: 3570-3577, 2003.

6. 名古屋大学における遺伝性網脈絡膜・視神経疾患の原因遺伝子検索の結果

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研究要旨　これまでに名古屋大学眼科で行った遺伝性眼疾患の原因遺伝子の検討の結果をまとめて報告した。平成11年9月から、平成17年10月までの6年間に、計452家系685症例について原因遺伝子を検索し、155家系で原因遺伝子を同定した。白点状眼底や不全型先天停止性夜盲、先天網膜分離症やスタルガルト病、クリスタリン網膜症などの単一遺伝子疾患では、ほとんどの症例で遺伝子診断可能だった。一方表現型が非典型的な症例では、遺伝子診断によってのみ、診断可能な場合があった。錐体（杆体）ジストロフィなど、多くの遺伝子が原因となる場合や、臨床所見からは診断不可能な症例では、原因遺伝子が同定できる場合はまだ多くなく、今後の課題である。

A．研究目的

これまでに名古屋大学眼科で行った遺伝性眼疾患の原因遺伝子の検討の結果をまとめ、疾患別の原因遺伝子の種類や頻度やphenotype、遺伝子検査によりわかったことについて報告した。

B．研究方法

平成11年9月から、平成17年10月までの6年間に、計452家系685症例の遺伝性眼疾患の症例から、インフォームドコンセントを得て静脈血を採取した。抹消白血球から染色体を抽出し、ダイレクトシークエンス法により各種遺伝子を検討した。対象としたのは、網膜色素変性症、錐体（杆体）ジストロフィ、黄斑変性症、オカルト黄斑変性症、白点状眼底、先天停止性夜盲（不全型、完全型)、小口病、若年網膜分離症、スタルガルト病、ベスト病、クリスタリン網膜症、レーバー先天盲、先天全色盲、青錐体増幅症候群、青錐体1色型色覚、優性遺伝視神経萎縮、レーベル病、などである。各症例について、視機能や形態などphenotypeについて詳細に検討した。

C．研究結果

452家系中155家系で原因遺伝子が同定できた。

家族歴から推定した遺伝形式は、常染色体優性遺伝、常染色体劣性性遺伝、X染色体劣性性遺伝、がそれぞれ約10%で、孤発例がほぼ3分の2だった。各遺伝形式で2分の1から3分の1の症例で、原因遺伝子が同定できた。

白点状眼底で黄斑変性を伴わないものでは16例全例[1)]、不全型先天停止性夜盲はほぼ全例[2)]、先天網膜分離症では15例中14例、スタルガルト病は6例全例、クリスタリン