ELSEVIER

Analysis of Peripherin/*RDS* Gene for Japanese Retinal Dystrophies

Keiko Fujiki,* Yoshihiro Hotta,* Mutsuko Hayakawa,* Takuro Fujimaki,* Misako Takeda,* Yasushi Isashiki,†‡ Norio Ohba‡ and Atsushi Kanai*

**Department of Ophthalmology, Juntendo University School of Medicine, Tokyo, Japan; †Division of Molecular Pathology and Genetic Epidemiology, Center for Chronic Viral Diseases and ‡Department of Ophthalmology, Kagoshima University Faculty of Medicine, Kagoshima City, Japan*

Abstract: We studied 133 Japanese patients with retinal dystrophies to detect peripherin/*RDS* (retinal degeneration slow) gene defects. The patients analyzed included 52 with autosomal dominant retinitis pigmentosa, 36 with autosomal recessive retinitis pigmentosa, 3 with simplex retinitis pigmentosa, 12 with cone-rod dystrophy, 5 with rod-cone dystrophy, 3 with vitelliform macular dystrophy (Best's disease), 4 with macular dystrophy, 2 with cone dystrophy, 2 with fundus flavimaculatus, 2 with fundus albipunctatus, and 12 with retinitis pigmentosa with macular degeneration as well as 40 unrelated normal persons. Three exons of the peripherin/*RDS* gene cut into 150–200 base-pair fragments were amplified by polymerase chain reaction and screened by single-strand conformation polymorphism. The DNA fragments with any suspected variations were directly sequenced. Eight point mutations were detected. Among them, two missense mutations at codons 304 and 338 result in an amino acid substitution of glutamine for glutamic acid and aspartic acid for glycine, respectively. However, they were not cosegregated with the diseases, and these mutations were also commonly found in normal controls. For these controls, the proportion of transversion from G to C at codon 304 (GAG→CAG) and transition from G to A at codon 338 (GGC→GAC) were 0.192 ± 0.045 and 0.173 ± 0.053, respectively. Our results suggest that a peripherin/*RDS* gene mutation might be rare in Japanese patients. **Jpn J Ophthalmol 1998;42:186–192.** © 1998 Japanese Ophthalmological Society

Key Words: DNA polymorphism, macular dystrophy, peripherin/RDS, retinal dystrophy, retinitis pigmentosa.

Introduction

The peripherin/*RDS* (retinal degeneration slow) gene located on the short arm of chromosome 6 consists of 3 exons and 346 amino acid residues. It codes for the photoreceptor-specific glycoprotein expressed in the disc membranes of photoreceptor outer segments of both rods and cones. The glycoprotein is considered to be important to the structural stability of the rim of outer segments.[1–3] Several mutations of one or a few base pairs resulting in deletion, insertion, or a missense mutation in the peripherin/*RDS* gene have been identified. These mutations give striking variations of retinal dystrophies such as autosomal dominant retinitis pigmentosa (ADRP), butterfly-shaped pigment dystrophy of the fovea, autosomal dominant retinitis punctata albescens, macular dystrophy, cone-rod dystrophy, and fundus flavimaculatus.[4–18] In addition, digenic retinitis pigmentosa because of mutations of the unlinked peripherin/*RDS* and *ROM1* genes has been found,[19] in which only double heterozygotes develop retinitis pigmentosa.

The purpose of the present study is to identify peripherin/*RDS* gene defects in Japanese patients with ADRP and other retinal dystrophies.

Materials and Methods

We analyzed 133 unrelated Japanese patients with retinal dystrophies, including 52 with ADRP, 36 with autosomal recessive retinitis pigmentosa (ARRP), 3 with simplex retinitis pigmentosa (RP), 12 with cone-rod dystrophy, 5 with rod-cone dystrophy, 3

Received October 31, 1997

Address correspondence and reprint requests to: Keiko FUJIKI, PhD, Department of Ophthalmology, Juntendo University School of Medicine, 2-1-1, Hongo, Bunkyo-ku, Tokyo 113-8421, Japan

Jpn J Ophthalmol 42, 186–192 (1998)

Published by Elsevier Science Inc.

0021-5155/98/$19.00
PII S0021-5155(97)00133-0

Table 1. Primer Sequences and Polymerase Chain Reaction Conditions

Aimed Locus	Primer Sequence	Anealing Temperature (°C)	Length of Fragment (bp)
Exon 1–1	Sense: 5′-GGGAAGCAACCCGGACTACA-3′ Antisense: 5′-CAGAATTATTCATCACATCG-3′	50	197
Exon 1–2	Sense: 5′-TTCCTGAAGATTGAACTCCG-3′ Antisense: 5′-TAGCCAGGTACGGCTTCAGC-3′	52	182
Exon 1–3	Sense: 5′-TATGCCAGATGGAAGCCCTG-3′ Antisense: 5′-TCTTCATGAAACACCTGCCA-3′	52	190
Exon 1–4	Sense: 5′-AGTACTACCGGGACACAGAC-3′ Antisense: 5′-TCTGACCCCAGGACTGGAG-3′	52	194
Exon 2–1	Sense: 5′-AAGCCCATCTCCAGCTGTCT-3′ Antisense: 5′-TCGTAACTGTAGTGTGCTGA-3′	52	162
Exon 2–2	Sense: 5′-CCCTGCATCCAGTATCAGAT-3′ Antisense: 5′-TTACCCTCTACCCCCAGCTG-3′	50	200
Exon 3–1	Sense: 5′-TAAATCTCCTCTCCCACCAC-3′ Antisense: 5′-CGGCACGCTCTTCTCCAGCA-3′	50	182
Exon 3–2	Sense: 5′-AGAGCGAGAGCGAGGGCTGG-3′ Antisense: 5′-GCCCTTGCCCAGCTTCTTCA-3′	52	182
Exon 3–3	Sense: 5′-TGCCGGAGACCTGGAAGGCC-3′ Antisense: 5′-TGGGGCCTGGCCTGCGCCTG-3′	62	203
Exon 3–4	Sense: 5′-CCAGGTGGAAGCCGAGGGCG-3′ Antisense: 5′-GGAGATTCAGACTTTCGGAG-3′	62	203

with vitelliform macular dystrophy (Best's disease), 4 with macular dystrophy, 2 with cone dystrophy, 2 with fundus flavimaculatus, 2 with fundus albipunctatus, and 12 with RP with macular degeneration, as well as 40 unrelated normal persons.

Sample Preparations

Genomic DNAs were extracted from leukocytes of peripheral blood. Exons 1 and 3 of the peripherin/*RDS* gene were cut into four fragments, and exon 2 was cut into two fragments. These were amplified by PCR (polymerase chain reaction) with a pair of primers at each condition of amplification (Table 1).[5]

Analyses by Single Strand Conformation Polymorphism

The DNA fragments were screened using two kinds of single strand conformation polymorphism (PCR-SSCP).[20] For non-radioisotopic (RI)-SSCP, aliquots of PCR products (3–5 μL) were mixed with 2 vol. of formamide sample buffer (95% formamide, 20 mM ethylenediaminetetraacetic acid (EDTA), 0.05% bromophenol blue, 0.05% xylene cyanol, 10 mM NaOH), heated at 94°C for 15–20 minutes, and applied on a nondenaturing 8% acrylamide gel containing 10% glycerol (gel size: 10 × 10 × 0.1 cm, 10 lanes). Electrophoresis was done at 300 V, 45 mA, for 3 hours using 1 × Tris-borate/EDTA electrophoresis buffer (TBE) under running water in the cold room (4°C). The gel was stained by silver stain (PlusOne™, Pharmacia Bioteck, A.B., Uppsala, Sweden). For RI-SSCP, the primers labeled with [γ-^{32}P] adenosin 5′-triphosphate (ATP) were used for PCR. The 2 μL of PCR products were mixed with 2 μL of formamide sample buffer (95% formamide, 20 mM EDTA, 0.05% bromophenol blue, 0.05% xylene cyanol, and 10 mM NaOH), heated at 94°C for 3 minutes, and applied on a nondenaturing 6% acrylamide gel containing 10% glycerol (gel size: 33 × 30 × 0.04 cm, 48 lanes). Electrophoresis was done at 1300–1500 V, 50–64 mA for 2–3 hours using 1 × TBE with an aluminum plate attached to one side of the glass plates. The gel was dried on filter paper and then exposed to x-ray film at −80°C for 1–12 hours with an intensifying screen.

Table 2. Mutations Identified in the Present Study

Exon	Codon	Nucleotide Wild→Mut	Amino acid Wild→Mut
1	98	CTG→TTG	Leu→Leu
	106	GTC→GTT	Val→Val
	189	TCC→TCT	Ser→Ser
	266	GGT→GGA	Gly→Gly
3	303	AGC→AGT	Ser→Ser
	304	GAG→CAG	Glu→Gln
	338	GGC→GAC	Gly→Asp
3′ noncoding region	1294[a]	C→T	

[a]Nucleotide position. Leu: leucine, Val: vallin; Ser: serine; Gly: glycine; Glu: glutamic acid; Gln: glutamine; Asp: aspartic acid.

Jpn J Ophthalmol
Vol 42: 186–192, 1998

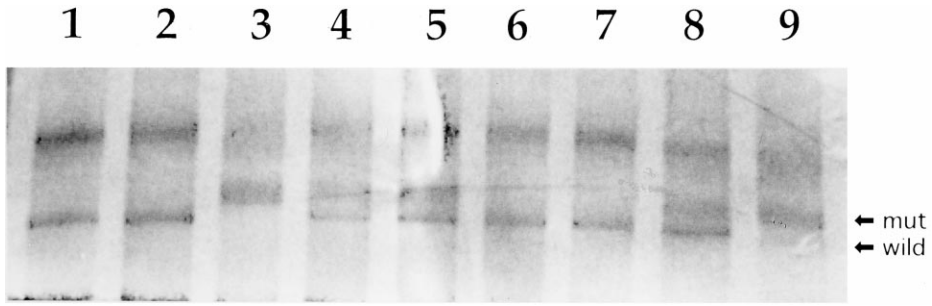

Figure 1. The 8% acrylamide gel electrophoretic pattern of the fragments of exon 1–3 of peripherin/*RDS* by non-RI-single strand conformation polymorphism. The upper band coincides with transition from C to T in the third nucleotide position of codon 106. No substitution of amino acid takes place. The lower band is the wild type. Lanes 1, 2, 6, and 7 are homozygous of wild type; 3 and 9 are homozygous of mutant alleles; and 4, 5, and 8 are heterozygotes.

DNA Sequencing

The DNA fragments suspected of any mutations by PCR-SSCP were directly sequenced by Taq Dye Deoxy Terminator using Gene Scanner, Fluorescent Fragment Analyzer (Applied Biosystems, Foster City, CA, USA).

Analyses by Restriction Enzyme

To calculate the frequencies of codon 304 and 338 mutations among the patients and normal controls, DNA fragments containing these codons were digested by restriction enzyme, where codon 304 mutation (GAG→CAG) is a recognition site of *Mva* I and codon 338 mutation (GGC→GAC) is the site of *Hga* I.

Statistical treatments[21]

The proportion, p, of substitution of the nucleotide and standard deviation (SD) were calculated by the following formulas:

$$p = (W/M + 2 \times M/M)/N$$

and

$$\mathrm{SD} = \sqrt{p(1-p)/2N},$$

where W refers to wild and M to mutant allele at the codon. W/M is the number of heterozygotes of mutant and wild allele. M/M is the number of homozygotes of the mutant allele. N is the total number of individuals investigated. Significance between patients and normal controls for substitution of nucleotide was analyzed by a test of proportions.

Results

Eight kinds of mutations were detected (Table 2) by sequencing of the fragments. However, they were not cosegregated with the disease, although amino acids were substituted.

Figure 1 shows the electorphoretic pattern of the 190 base-pair fragments of exon 1–3 of the peripherin/*RDS* gene by non-RI-SSCP. The mutant band coincided with a transition from C to T at codon 106 (GTC→GTT, Val106Val).

Figure 2 shows electrophoretic fragment patterns of exons 3–1 as analyzed by RI-SSCP, where mutant bands were detected. The mutant bands were coin-

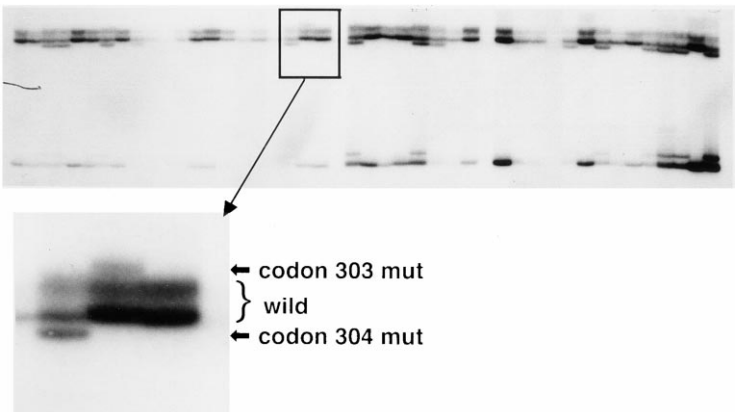

Figure 2. The 6% acrylamide gel electrophoretic pattern of the fragments of exon 3–1 by RI-single strand conformation polymorphism, where all lanes are patients except the four rightmost lanes. Codon 303 and 304 mutations were identified by direct sequencing of the patient's exons. The upper band coincides with the mutant codon 303, and the lower band is codon 304. The lower band was observed in many patients.

cided with the transition from C to T of codon 303 (AG<u>C</u>→AG<u>T</u>, Ser303Ser) and transversion from G to C of codon 304 (<u>G</u>AG→<u>C</u>AG, Glu304Gln). Transition from G to A of codon 338 (G<u>G</u>C→G<u>A</u>C, Gly338Asp) was also detected.

Figure 3 shows the sequencing around codons 304 and 338 and the agarose gel pattern of DNA fragments digested by restriction enzyme—*Mva* I for codon 304 and *Hga* I for codon 338. These two mutations were also found in the normal controls in spite of the substitution of amino acid.

Table 3 shows the frequencies of the transversion from G to C at codon 304 and transition from G to A at codon 338 among the patients and normal controls. There were no significant differences in the proportion of the substitution of nucleotide between patients and normal controls in both codons.

The conservation of the amino acid of codons 304 and 338 among human,[3] bovine,[22] mouse,[23] rat,[24] and feline species (cat)[25] was compared (Figure 4). Although the amino acid of codon 304 was well conserved, codon 338 in humans was different from other mammals and interestingly showed a high frequency of the mutation to the amino acid, Asp.(D), of other mammals.

Discussion

Several mutations in the peripherin/*RDS* gene cause retinal dystrophies. Various phenotypes are manifested by these mutations from macular dystrophies to RP. Now more than 25 distinct mutations in the peripherin/*RDS* gene have been found in patients with ADRP and other retinal dystrophies all over the world.[4–18] Most cases are diagnosed as ADRP, but some mutations are found in patients with macular dystrophy, vitelliform macular dystrophy, fundus flavimaculatus, and so on. In the USA, approximately 5-6% of patients with nonrhodopsin ADRP have a defect in the peripherin/*RDS* gene.[26] In Japan, five point mutations in five families have been reported: Cys214Ser mutation in ADRP,[14] Asn244Lys mutation in ADRP with bull's eye,[15] Asn244His mutation in cone-rod dystrophy,[16] Arg172Trp mutation in macular dystrophy,[17] and Tyr184Ser mutation in cone-rod dystrophy.[18]

We have tried to check for other mutations in the

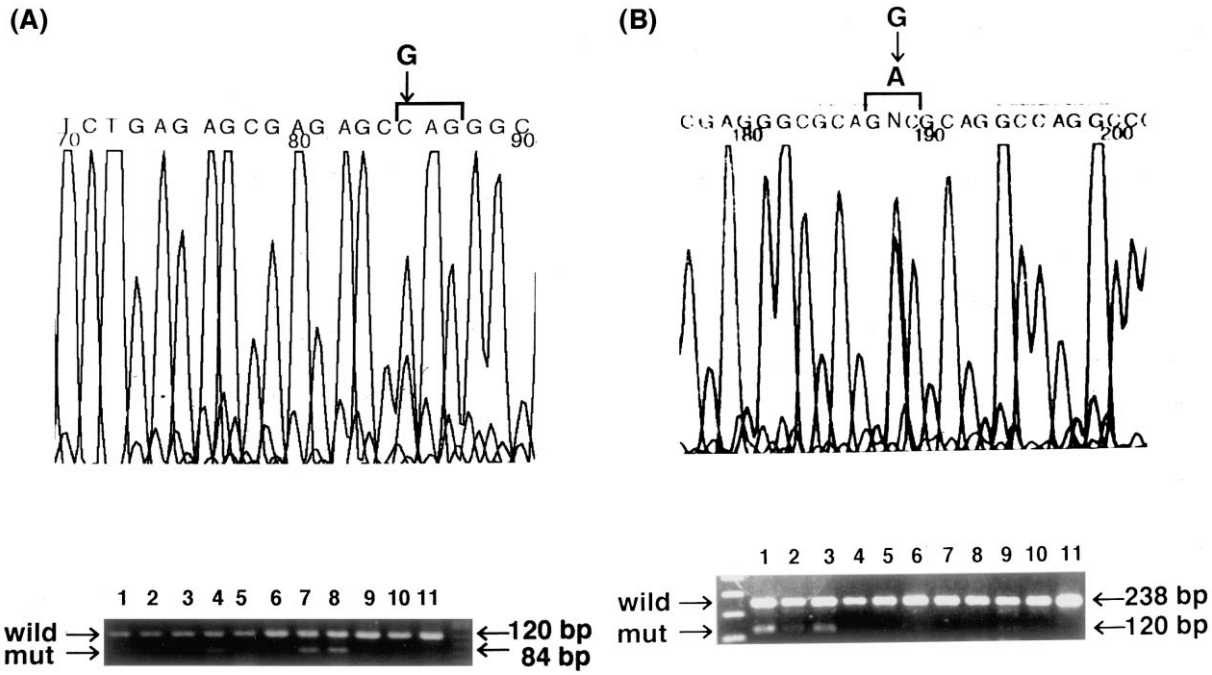

Figure 3. Nucleotide sequences and detection by restriction enzyme. (**A**) Glu304Gln(<u>G</u>AG→<u>C</u>AG). The upper side shows the heterozygous transversion from G to C by direct sequencing. The lower side shows a 2% agarose gel electrophoretic pattern after *Mva* I digestion. All lanes are patients. Lanes 4, 7, and 8 are heterozygotes for the mutant allele of codon 304. (**B**) Gly338Asp(G<u>G</u>C→G<u>A</u>C). The upper side shows the heterozygous transition from G to A. The lower side shows 2% agarose gel electrophoretic pattern of fragments cut by *Hga* I digestion. Lanes 1, 2, and 3 are heterozygotes, and the others are homozygotes of wild type on codon 338.

Table 3. Frequency of Glu304Gln and Gly338Asp Mutation in the Patients and Normal Controls

Codon	Genotype	Number (%) of Patients	Number (%) of Controls	Total Number (%)
304				
	G/G	50 (62.5)	25 (64.1)	75 (63.0)
	G/C	29 (36.3)	13 (33.3)	42 (35.3)
	C/C	1 (1.3)	1 (2.6)	2 (1.7)
	Total	80[a](100)	39 (100)	119 (100)
	Proportion of transversion[b] from G to C	31/160 0.194 ± 0.031	15/78 0.192 ± 0.045	46/238 0.193 ± 0.026
338				
	G/G	30 (63.8)	17 (65.4)	47 (64.4)
	G/A	17 (36.2)	9 (34.6)	26 (35.6)
	A/A	—	—	—
	Total	47[c] (100)	26 (100)	73 (100)
	Proportion of transition[b] from G to A	17/94 0.181 ± 0.040	9/52 0.173 ± 0.053	26/146 0.178 ± 0.032

ADRP: autosomal dominant retinitis pigmentosa; ARRP: autosomal recessive retinitis pigmentosa.
[a]ADRP 38, ARRP 23, retinal dystrophies 19.
[b]There is no significant difference in the proportion between patients and normal controls.
[c]ADRP 18, ARRP 10, retinal dystrophies 19.

peripherin/*RDS* gene causing various retinal dystrophies. Our results were inconclusively lower. Although transitions have been detected for codon 338 and transversions for codon 304, none of these cosegregated with the disease. There was the same frequency of mutation in the patients and controls, suggesting spontaneity of instability of these codons. These codons also appear not to be vital for the proper function of the gene.

Other candidate genes may also be implicated for these retinal dystrophies. These candidate genes include the rhodopsin gene, of which the mutations were associated with the disease in four families[27–30] in Japanese ADRP patients in the past, and genes at chromosomes 7q31–q35,[31,32] 7p15.1–p13,[33] 8p11–q21,[34] 17p13,[35] and 19q13.4[36] in ADRP; 1q31–q32.1,[37] β-cGMP-PDE (phosphodiesterase) gene (4p16.3),[38] α-cGMP-PDE (5q31.2–q34),[39] and α-cGMP-gated channel[40] in ARRP; and at chromosome 11q13 in Best's disease.[41] For these patients, therefore, another candidate gene must be analyzed to determine if mutations are responsible for these heterogeneous retinal dystrophies. In the present study, although we attached much importance to clinical diagnosis for patients with retinal dystrophies except ADRP and ARRP, the patients with affected relatives in three or more

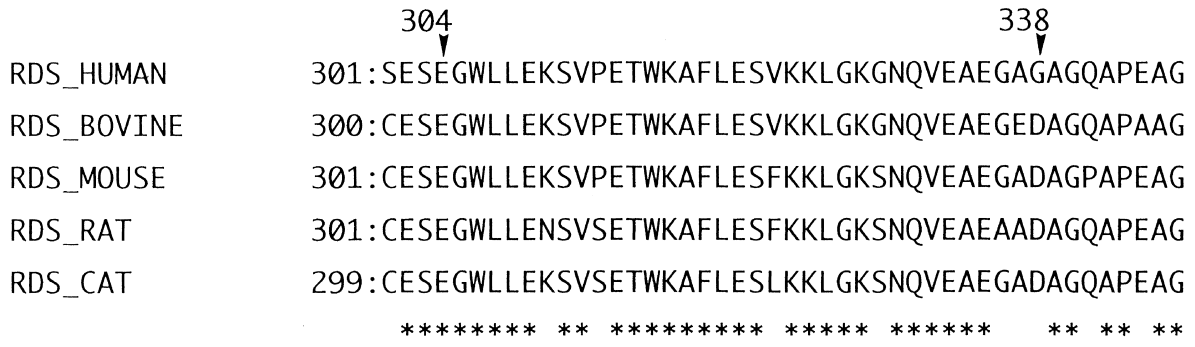

Figure 4. Conservation of amino acid of codons 304 and 338 of the peripherin/*RDS* gene in human, bovine, mouse, rat, and feline species. Although the amino acid of codon 304 was well conserved, codon 338 in humans was different from other mammals. Interestingly, Gly338Asp (G338D) mutation in humans showed the same amino acid as other mammals. Asterisks show homologous amino acid in the species compared.

consecutive generations, which show strongly autosomal dominant inheritance, might have been selected and analyzed separately.

On the DNA polymorphism in the peripherin/*RDS* gene, three sequence alterations giving rise to amino acid substitutions at codons 304, 310, and 338 have also been reported,[42] where the proportion of the transversion from G to C at codon 304 was 0.51 in normal controls and 0.58 in ADRP patients. The transition from A to G at codon 310 was 0.53 in normal controls and 0.45 in ADRP patients, and transition from G to A at codon 338 was 0.59 in the normals and 0.70 in ADRP patients. These values were higher than that of the present study. We did not find the mutation at codon 310 in the 30 patients randomly selected, although the substitutions at codons 304 and 338 were found in relatively high frequencies. Because three mutations are for both normal and affected ADRP patients, it appears that substitution in these codons could not be used to determine predisposition to retinal dystrophy. However, it might be useful in studying racial differences. For example, frequency of polymorphism in the rhodopsin gene varies for Japanese and Americans. The transition from A to G at nucleotide (nt) position 269 in the 5′ noncoding region, the transition from G to A at nt position 5145 in the 4th intron, and transversion from C to A at nt position 5321 in the 3′ noncoding region were 0.57, 0.36, and 0.05, respectively, in Japanese.[43] In the Americans[44] these values were 0.14, a few, and 0.13, respectively. These facts may therefore be useful for studying Japanese anthropological origin.

The authors are grateful to Dr Kazuto Kajiwara for his kind suggestions and informations on primer sequencing and PCR conditions. This work was supported by a grant from retinochoroidal atrophy research from the Ministry of Health and Welfare of Japan and a Grant-in-Aid for Scientific Research (B)(2) 08457468 by the Ministry of Education, Science and Culture of the Japanese Government.

References

1. Arikawa K, Molday LL, Molday RS, Williams DS. Localization of peripherin/*rds* in the disk membranes of cone and rod photoreceptors: Relationship to disc membrane morphogenesis and retinal degeneration. J Cell Biol 1992;116:659–67.
2. Travis GH, Sutcliffe JG, Bok D. The retinal degeneration slow(*rds*) gene product is a photoreceptor disc membrane-associated glycoprotein. Neuron 1991;6:61–70.
3. Travis GH, Christerson L, Danielson PE, et al. The human retinal degeneration slow (*RDS*) gene: Chromosome assignment and structure of the mRNA. Genomics 1991;10:733–9.
4. Farrar GJ, Kenna P, Jordan SA, et al. A three-base-pair deletion in the peripherin-*RDS* gene in one form of retinitis pigmentosa. Nature 1991;354:478–80.
5. Kajiwara K, Hahn LB, Mukai S, Travis GH, Berson EL, Dryja TP. Mutations in the human retinal degeneration slow gene in autosomal dominant retinitis pigmentosa. Nature 1991;354:480–3.
6. Nichols BE, Sheffield VC, Vandenburgh K, Drack AV, Kimura AE, Stone EM. Butterfly-shaped pigment dystrophy of the fovea caused by a point mutation in codon 167 of the RDS gene. Nat Genet 1993;3:202–7.
7. Kajiwara K, Sandberg MA, Berson EL, Dryja TP. A null mutation in the human peripherin/RDS gene in a family with autosomal dominant retinitis punctata albescens. Nat Genet 1993;3:208–12.
8. Nichols BE, Drack AV, Vandenburgh K, Kimura AE, Sheffield VC, Stone EM. A 2 base pair deletion in the RDS gene associated with butterfly-shaped pigment dystrophy of the fovea. Hum Mol Genet 1993;2:601–3.
9. Wells J, Wroblewski J, Keen J, et al. Mutations in the human retinal degeneration slow (*RDS*) gene can cause either retinitis pigmentosa or macular dystrophy. Nat Genet 1993;3:213–8.
10. Weleber RG, Carr RE, Murphey WH, Sheffield VC, Stone EM. Phenotypic variation including retinitis pigmentosa, pattern dystrophy, and fundus flavimaculatus in a single family with a deletion of codon 153 or 154 of the peripherin/*RDS* gene. Arch Ophthalmol 1993;111:1531–42.
11. Wroblewski JJ, Wells JA III, Eckstein A, et al. Macular dystrophy associated with mutations at codon 172 in the human retinal degeneration slow gene. Ophthalmology 1994;101:12–22.
12. Kemp CM, Jacobson SG, Cideciyan AV, Kimura AE, Sheffield VC, Stone EM. RDS gene mutations causing retinitis pigmentosa or macular degeneration lead to the same abnormality in photoreceptor function. Invest Ophthalmol Vis Sci 1994;35:3154–62.
13. Kim RY, Dollfus H, Keen TJ, et al. Autosomal dominant pattern dystrophy of the retina associated with a 4-base pair insertion at codon 140 in the peripherin/*RDS* gene. Arch Ophthalmol 1995;113:451–5.
14. Saga M, Mashima Y, Akeo K, Oguchi Y, Kudoh J, Shimizu N. A novel Cys-214-Ser mutation in the peripherin/RDS gene in a Japanese family with autosomal dominant retinitis pigmentosa. Hum Genet 1993;92:519–21.
15. Kikawa E, Nakazawa M, Chida Y, Shiono T, Tamai M. A novel mutation (Asn244Lys) in the peripherin/RDS gene causing autosomal dominant retinitis pigmentosa associated with bull's-eye maculopathy detected by nonradioisotopic SSCP. Genomics 1994;20:137–9.
16. Nakazawa M, Kikawa E, Chida Y, Tamai M. Asn244His mutation of the peripherin/RDS gene causing autosomal dominant cone-rod degeneration. Hum Mol Genet 1994;3:1195–6.
17. Nakazawa M, Wada Y, Tamai M. Macular dystrophy associated with monogenic Arg172Trp mutation of the peripherin/RDS gene in a Japanese family. Retina 1995;15:518–23.
18. Nakazawa M, Kikawa E, Chida Y, Wada Y, Shiono T, Tamai M. Autosomal dominant cone-rod dystrophy associated with mutations in codon 244 (Asn244His) and codon 184 (Tyr184Ser) of the peripherin/*RDS* gene. Arch Ophthalmol 1996;114:72–8.
19. Kajiwara K, Berson EL, Dryja TP. Digenic retinitis pigmentosa due to mutations at the unlinked peripherin/*RDS* and *ROM1* loci. Science 1994;264:1604–8.
20. Orita M, Suzuki Y, Sekiya T, Hayashi K. Rapid and sensitive detection of point mutations and DNA polymorphism using the polymerase chain reaction. Genomics 1989;5:874–9.
21. Emery AEH. Methodology in medical genetics: An introduction to statistical methods. London: Churchill Livingstone, 1976.

22. Connell GJ, Molday RS. Molecular cloning, primary structure, and orientation of the vertebrate photoreceptor cell protein peripherin in the rod outer segment disk membrane. Biochemistry 1990;29:4691–8.
23. Travis GH, Brennan MB, Danielson PE, Kozak CA, Sutcliffe JG. Identification of a photoreceptor-specific mRNA encoded by the gene responsible for retinal degeneration slow (*rds*). Nature 1989;338:70–3.
24. Begy C, Bridges CD. Nucleotide and predicted protein sequence of rat retinal degeneration slow (rds). Nucleic Acids Res 1990;18:3058.
25. Gorin MB, Snyder S, To A, Narfstrom K, Curtis R. The cat RDS transcript: Candidate gene analysis and phylogenetic sequence analysis. Mamm Genome 1993;4:544–8.
26. Kajiwara K, Berson EL, Dryja TP. Screen for mutations in the entire coding sequence of the human *RDS*/peripherin gene in patients with hereditary retinal degenerations. Invest Ophthalmol Vis Sci 1993;34:1149.
27. Fujiki K, Hotta Y, Hayakawa M, et al. Point mutations of rhodopsin gene found in Japanese families with autosomal dominant retinitis pigmentosa (ADRP). Jpn J Hum Genet 1992;37:125–32.
28. Fujiki K, Hotta Y, Murakami A, et al. Missense mutation of rhodopsin gene codon 15 found in Japanese autosomal dominant retinitis pigmentosa. Jpn J Hum Genet 1995;40:271–7.
29. Hayakawa M, Hotta Y, Imai Y, et al. Clinical features of autosomal dominant retinitis pigmentosa with rhodopsin gene codon 17 mutation and retinal neovascularization in a Japanese patient. Am J Ophthalmol 1993;115:168–73.
30. Saga M, Mashima Y, Akeo K, Oguchi Y, Kudoh J, Shimizu N. Autosomal dominant retinitis pigmentosa: A mutation in codon 181 (Glu→Lys) of the rhodopsin gene in a Japanese family. Ophthalmic Genet 1994;15:61–7.
31. Jordan SA, Farrar GJ, Kenna P, et al. Localization of an autosomal dominant retinitis pigmentosa gene to chromosome 7q. Nat Genet 1993;4:54–8.
32. McGuire RE, Gannon AM, Sullivan LS, Rodriguez JA, Daiger SP. Evidence for a major gene (RP10) for autosomal dominant retinitis pigmentosa on chromosome 7q: Linkage mapping in a second, unrelated family. Hum Genet 1995;95:71–4.
33. Inglehearn CF, Carter SA, Keen TJ, et al. A new locus for autosomal dominant retinitis pigmentosa on chromosome 7p. Nat Genet 1993;4:51–3.
34. Blanton SH, Heckenlively JR, Cottingham AW, et al. Linkage mapping of autosomal dominant retinitis pigmentosa (RP1) to the pericentric region of human chromosome 8. Genomics 1991;11:857–69.
35. Greenberg J, Goliath R, Beighton P, Ramesar R. A new locus for autosomal dominant retinitis pigmentosa on the short arm of chromosome 17. Hum Mol Genet 1994;3:915–8.
36. Al-Maghtheh M, Inglehearn CF, Keen TJ, et al. Identification of a sixth locus for autosomal dominant retinitis pigmentosa on chromosome 19. Hum Mol Genet 1994;3:351–4.
37. van Soest S, van den Born LI, Gal A, et al. Assignment of a gene for autosomal recessive retinitis pigmentosa (RP12) to chromosome 1q31-q32.1 in an inbred and genetically heterogeneous disease population. Genomics 1994;22:499–504.
38. McLaughlin ME, Sandberg MA, Berson EL, Dryja TP. Recessive mutations in the gene encoding the β-subunit of phosphodiesterase in patients with retinitis pigmentosa. Nat Genet 1993;4:130–4.
39. Huang SH, Pittler S, Huang X, Oliveira L, Berson EL, Dryja TP. Autosomal recessive retinitis pigmentosa caused by mutations in the α subunit of rod cGMP phosphodiesterase. Nat Genet 1995;11:468–71.
40. Dryja TP, Finn JT, Peng Y-W, McGee TL, Berson EL, Yau K-W. Mutations in the gene encoding the α subunit of the rod cGMP-gated channel in autosomal recessive retinitis pigmentosa. Proc Natl Acad Sci USA 1995;92:10177–81.
41. Stone EM, Nichols BE, Streb LM, Kimura AE, Sheffield VC. Genetic linkage of vitelliform macular degeneration (Best's disease) to chromosome 11q13. Nat Genet 1992;1:246–50.
42. Jordan SA, Farrar GJ, Kenna P, Humphries P. Polymorphic variation within "Conserved" sequences at the 3′ end of the human RDS gene which results in amino acid substitutions. Hum Mutat 1992;1:240–7.
43. Fujiki K, Kawano H, Hotta Y, et al. Frequencies of polymorphisms in the rhodopsin gene of Japanese retinitis pigmentosa and normal individuals. Jpn J Hum Genet 1995;40:203–6.
44. Sung CH, Davenport CM, Hennessey JC, et al. Rhodopsin mutations in autosomal dominant retinitis pigmentosa. Proc Natl Acad Sci USA 1991;88:6481–5.