



LUND UNIVERSITY

Macular appearance by means of OCT and electrophysiology in members of two families with different mutations in RDS (the peripherin/RDS gene).

Schatz, Patrik; Abrahamson, Magnus; Eksandh, Louise; Ponjavic, Vesna; Andréasson, Sten

Published in:
Acta Ophthalmologica Scandinavica

DOI:
[10.1034/j.1600-0420.2003.00134.x](https://doi.org/10.1034/j.1600-0420.2003.00134.x)

2003

[Link to publication](#)

Citation for published version (APA):
Schatz, P., Abrahamson, M., Eksandh, L., Ponjavic, V., & Andréasson, S. (2003). Macular appearance by means of OCT and electrophysiology in members of two families with different mutations in RDS (the peripherin/RDS gene). *Acta Ophthalmologica Scandinavica*, 81(5), 500-507. <https://doi.org/10.1034/j.1600-0420.2003.00134.x>

Total number of authors:
5

General rights

Unless other specific re-use rights are stated the following general rights apply:
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: <https://creativecommons.org/licenses/>

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

Macular appearance by means of OCT and electrophysiology in members of two families with different mutations in *RDS* (the peripherin/*RDS* gene)

Patrik Schatz,¹ Magnus Abrahamson,² Louise Eksandh,¹ Vesna Ponjavic¹ and Sten Andréasson¹

¹Department of Ophthalmology, University Hospital, Lund, Sweden

²Department of Clinical Chemistry, University Hospital, Lund, Sweden

ABSTRACT.

Purpose: To describe the phenotype using electroretinography and optical coherence tomography (OCT) in members of two families with different mutations in *RDS*.

Methods: DNA was extracted from blood samples and used for mutation screening by denaturing gradient gel electrophoresis (DGGE) and nucleotide sequencing of *RDS* exons. Patients were examined with clinical evaluation, full-field electroretinography (ERG), multifocal electroretinography (mfERG) and OCT.

Results: An Arg-46 → stop codon conversion and a Ser-125 → Leu substitution were found, respectively, in affected members of the two families. Phenotypes included retinitis pigmentosa, central areolar choroidal dystrophy, macular dystrophy and adult vitelliform maculopathy. The vitelliform lesion was clearly delineated on OCT, but mfERG showed preserved function. Optical coherence tomography showed attenuation of retinal reflectivity in two cases.

Conclusion: By combining traditional investigations with mfERG and OCT, we were able to obtain a more refined evaluation of contributing macular and generalized retinal dysfunction, respectively, in patients with hereditary retinal disease.

Key words: peripherin – retinitis pigmentosa – maculopathy – mfERG – OCT

Acta Ophthalmol. Scand. 2003; 81: 500–507
Copyright © Acta Ophthalmol Scand 2003. ISSN 1395-3907

Introduction

Peripherin is a photoreceptor specific glycoprotein located in the rod and cone outer segment membranes (Moloday et al. 1987; Travis et al. 1991; Arikawa et al. 1992) that appears to be important in the development and stability of discs in the photoreceptors

(Kedzierski et al. 1997), forming a heterodimer in rods with rod outer segment protein 1 (ROM-1) (Bascom et al. 1992; Goldberg et al. 1995; Kedzierski et al. 1996).

Different defects in the gene coding for peripherin, called *RDS*, have been described in association with different clinical manifestations of degenerative

retinal disease, aside from retinitis pigmentosa, including macular dystrophy (Wells et al. 1993; Nakazawa et al. 1995), central areolar choroidal dystrophy (Reig et al. 1995), and cone-rod dystrophy (Nakazawa et al. 1996). Specifically, mutations in this gene can give rise to degenerations with general retinal involvement, but also localized macular involvement.

We therefore decided to combine traditional investigative methods such as full-field electroretinography (ERG) and visual fields with newer methods such as optical coherence tomography (OCT) and multifocal electroretinography (mfERG), for further evaluation of macular structure and function, in members of two families which were found to harbour mutations in *RDS*.

Material and Methods

The members of two families were examined (Fig. 1, Table 1). Informed consent was obtained.

Blood samples from the subjects were collected in tubes containing EDTA as an anticoagulant and genomic DNA was isolated from the leucocyte fraction (Miller et al. 1988). Eight fragments covering the three exons constituting the coding region of *RDS* with

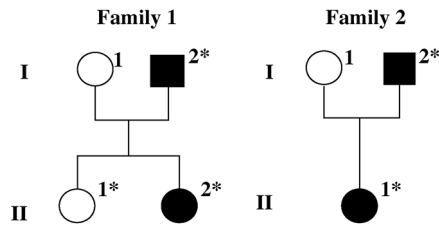


Fig. 1. Pedigrees of both families are shown. Examined individuals are marked with an asterisk.

flanking intron sequences were amplified by polymerase chain reaction (PCR) and screened for alterations using a denaturing gradient gel electrophoresis (DGGE) procedure described previously (Ekström et al. 1998). Similarly, PCR fragments covering the coding region of the ROM-1 gene were

analysed by DGGE to detect possible mutations (Jacobson et al. 1999). The DNA sequences of PCR products with possible alterations detected by DGGE were determined on both strands by dye dideoxy sequencing using reagents in the BigDye Terminator Cycle Sequencing kit, and an ABI 310 sequencer (PE

Applied Biosystems, Foster City, CA, USA). In the case of *RDS* exon 1 fragment 1A, oligonucleotides MS011 (5'-AGC TGT GCT GTG GGA AGC AA-3') and UE172 (Ekström et al. 1998) were used as sequencing primers for the upper and lower strands, respectively. For *RDS* exon 1 fragment 1C, oligonucleotides MS021 (5'-ACC CAG CCA AGT ATG CCA GA-3') and MS022 (5'-TGC AGC ATG TCG ATG GTC TT-3') were used to sequence the upper and lower strands, respectively. The sequences were evaluated using Sequencher (Gene Codes Corp., Ann Arbor, Michigan, USA).

Ophthalmological examination included assessment of best corrected visual acuity (VA), slit-lamp inspection,

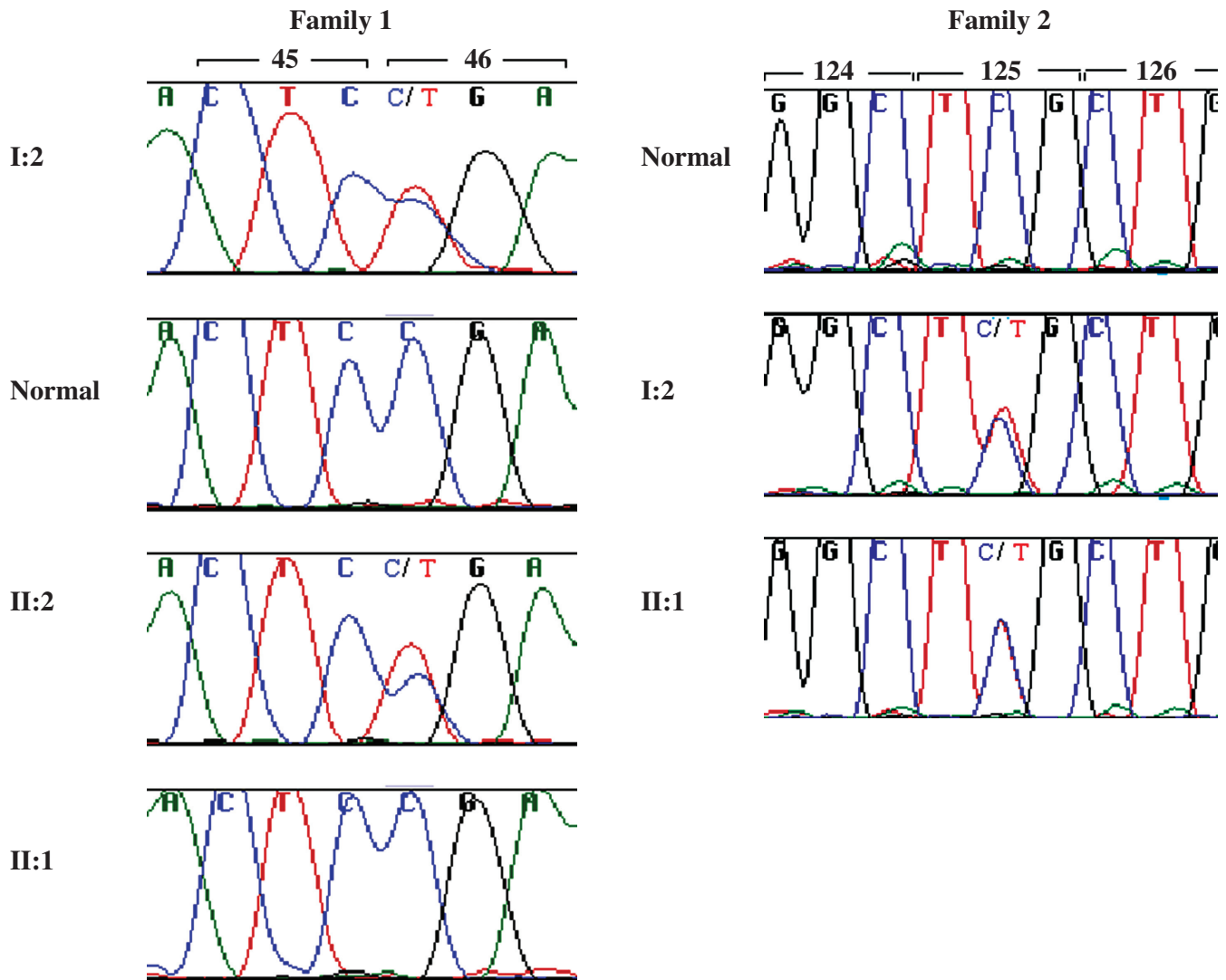


Fig. 2. *RDS* alterations in the families investigated. Mutation screening by DGGE indicated alterations in exon 1 in both families. The results from further analysis of exon 1 fragments by DNA sequencing are shown. In affected individuals of family 1, a C → T substitution in codon 46 is seen in one of the alleles of the gene, resulting in the heterozygous change Arg-46 → stop. In affected individuals of family 2, a C → T substitution in codon 125 is at hand in one of the alleles of the gene, resulting in the heterozygous change Ser-125 → Leu at the protein level. No other deviations from the published gene sequence of *RDS* were detected.

ophthalmoscopy and fundus photography. Visual fields were examined with kinetic perimetry with a Goldmann perimeter (V_{4c} and I_{4c}).

Full-field electroretinograms were recorded in a Nicolet analysis system (Nicolet Biomedical Instruments, Madison, Wisconsin, USA), after dark adaptation of subjects for 40 min, dilatation of the pupils with topical cyclopentolate 1% and metaoxedrine 10% and topical anaesthesia, with a Burian Allen bipolar contact lens and a ground electrode applied to the forehead. Responses were obtained with a wide band filter (-3 dB at 1 Hz and 500 Hz) stimulating with single full-field flash (30 μ s) with blue light (Wratten filter #47, 47A and 47B) and with white light (0.81 cd-s/m² and 3.93 cd-s/m²). Cone responses were obtained with 30 Hz flickering white light (0.81 cd-s/m²) averaged from 20 sweeps.

The procedure described above basically adheres to the standardized protocol for clinical electroretinography, International Society for Clinical Electrophysiology of Vision (ISCEV) (Marmor & Zrenner 1999), with a few slight

modifications: recordings of isolated cone responses were obtained without background illumination on the Ganzfield screen. Moreover, the ISCEV standard does not specify how to measure residual ERG responses. If responses measuring less than 10 μ V were recorded with single white flashes, recordings were also obtained with computer averaging (30 flashes), a bipolar artefact rejecter and a line frequency notch filter (50 Hz). To obtain small cone responses, stimulation also included 200 flashes of flickering white light (30 Hz) and an analogue narrow band pass filter (Narrow Band Tracking Filter, model 3800; Kron-Hite, Avon, Massachusetts, USA) added to the Nicolet machine. The narrow band filter was tuned at 30 Hz (-12 dB at 29 Hz and 31 Hz), to enable measurements of signals down to 0.1 μ V (Andréasson et al. 1988).

Multifocal electroretinograms were recorded using a visual evoked response imaging system (VERIS 4; EDI, San Mateo, California, USA). After dilation of the pupils and topical anaesthesia according to the above, a Gold bipolar ERG electrode was applied to the ocular surface and a

ground electrode to the forehead. For recording purposes, 103 stimulus hexagonal elements were used. The fixation was controlled using a fundus camera and illumination with infrared light from the recording electrode (Sutter & Tran 1992; Bearse & Sutter 1996). P1 amplitudes and latencies in ring areas 1–6 were calculated according to the guidelines for basic mfERG (Marmor et al. 2003). Responses from areas 1 and 2 were averaged together as '1 + 2'.

Electro-oculography (EOG) was performed using a Nicolet analysis system (Nicolet Biomedical Instruments, Madison, WI, USA). Skin electrodes were placed at the nasal and temporal canthi of both eyes and a ground electrode was placed on the forehead. The patients were pre-adapted to room light prior to the dark adaptation phase. The EOG was performed according to the ISCEV EOG Standard described previously (Marmor & Zrenner 1993).

Optical coherence tomography was performed with a OCT-2 scanner (Zeiss Humphrey Instruments, Dublin, CA, USA). Single line scans were obtained over the macula.

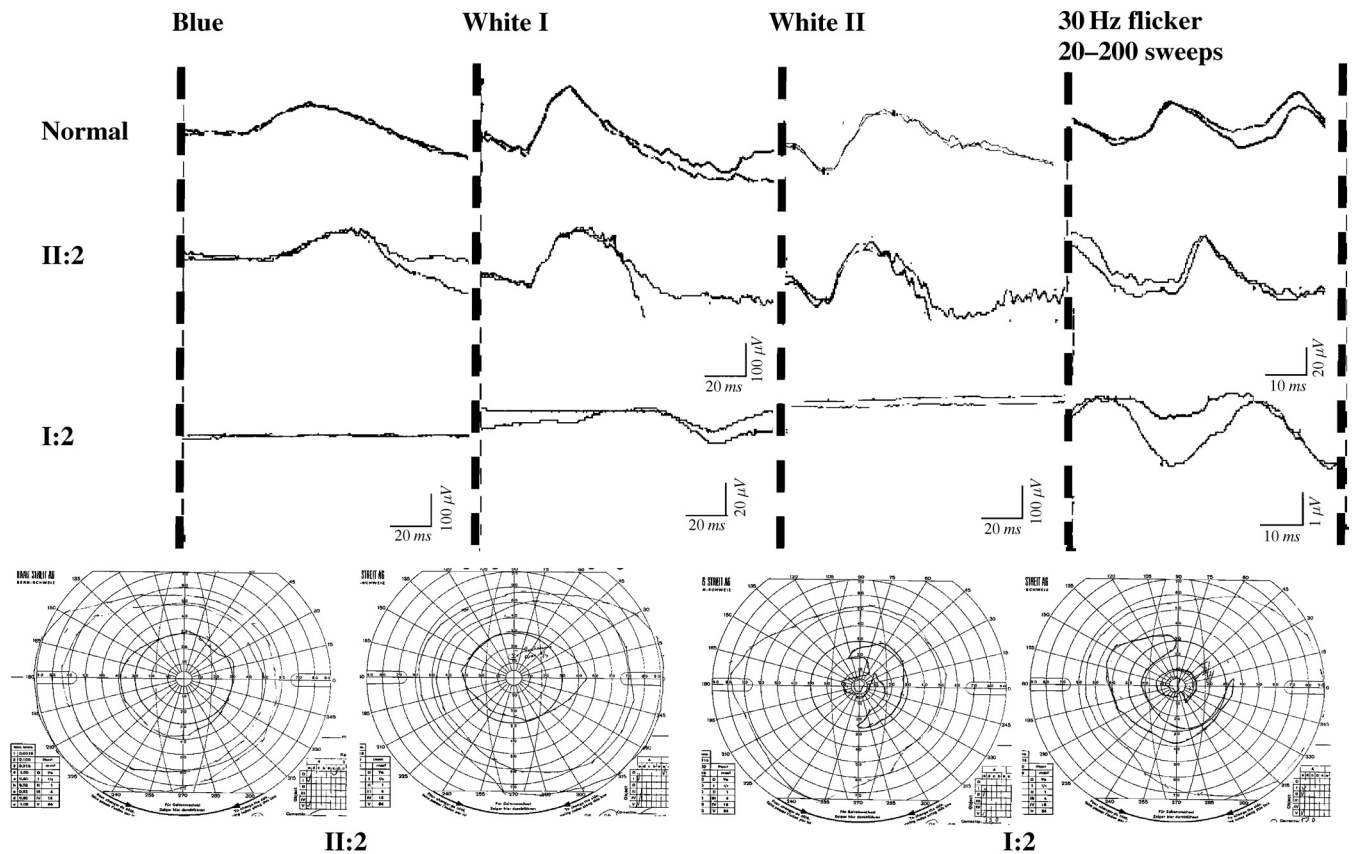


Fig. 3. Family 1. Full-field ERG and visual fields. Top and bottom left: the daughter shows somewhat reduced ERG responses but normal visual fields. The father's ERG readings are presented below and visual fields to the right, with severely reduced readings and narrowing of the visual fields.

Results

Molecular genetics

Subjects from families 1 and 2 had earlier been screened for mutations in the rhodopsin gene, with results showing that no alterations were at hand. On analysis of *RDS* of patient I:2 of family 1, DGGE revealed an aberrant band pattern for one of the PCR-amplified segments covering the 5' part of exon 1 (fragment 1A). DNA sequencing identified a mutation in codon 46, a C → T substitution resulting in the heterozygous change Arg-46 → stop at the protein level (Fig. 2). Analysis of the subject's daughters revealed that the mutation was also present in one allele of *RDS* from daughter II:2 but not in the gene from II:1 (Fig. 2). Further analysis of the entire coding sequence of the ROM-1 gene in all three individuals by DGGE screening did not demonstrate any aberrations in this gene. In family 2, DGGE analysis showed deviating patterns for *RDS* exon 1 fragment 1C. DNA sequencing identified a mutation in codon 125, a C → T substitution

resulting in the heterozygous change Ser-125 → Leu at the protein level (Fig. 2). No other deviations from the published gene sequence of *RDS* were detected.

Clinical examination

Family 1

The father had moderately reduced VA and the daughter had slightly reduced VA. Visual fields were markedly reduced in the father but the daughter presented normal visual fields. Examination of the father revealed slightly pale discs, narrowing of the vessels, central atrophic changes and central as well as mid-peripheral pigment mottling. The daughter presented degenerative changes mainly in the macular region (Figs 3 and 5).

Family 2

The father had a history of open-angle glaucoma in his right eye, which had been successfully operated on previously, with trabeculectomy, cataract surgery and YAG-laser capsulectomy. The peripheral retina was unremarkable.

He had a moderate cataract in his left eye. A yellowish atrophy at the macular area was documented in previous records. Now, he presented clinical signs characteristic of central areolar choroidal dystrophy (Ponjavic et al. 1994). His VA was accordingly affected. The visual fields were largely preserved in the periphery, but scotomas were present centrally. The daughter presented with slightly reduced VA and normal visual fields. Both fundi were affected with vitelliform deposits and pigmentary changes in the macular area (Figs 4 and 6).

Electrophysiological examination

Family 1

Full-field ERG demonstrated no rod response on stimulation with blue light in the father and reduced but still remaining rod response in the daughter. A markedly reduced cone response with a delayed implicit time was found in the recording from the father and a somewhat reduced cone response in the daughter.

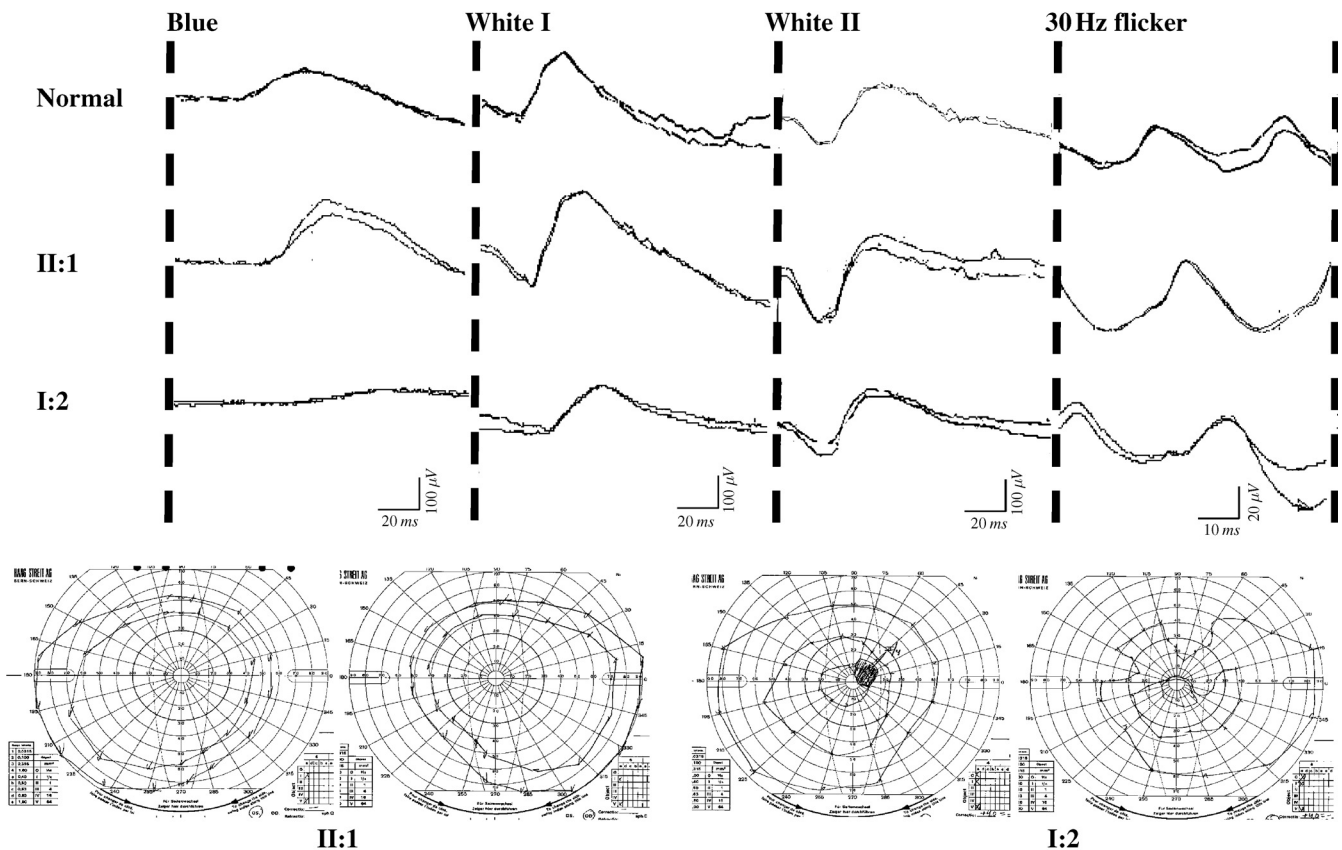


Fig. 4. Family 2. Full-field ERG and visual fields. Top and bottom left: the daughter shows normal findings. The father's ERG readings are presented below showing reduction of the rod response and prolonged increased 30 Hz flicker implicit time. His visual fields are displayed to the right, with central scotoma in the left visual field and narrowing of the right visual field.

Multifocal electroretinography, which reflects the central part of the retinal function, revealed severely reduced function in both father and daughter (Figs 3 and 5, Tables 1 and 2).

Family 2

The daughter presented with a normal full-field ERG. She was also examined with EOG to exclude Best's vitelliform maculopathy, demonstrating a normal result and Arden ratios of 1.9 and 2.0 in the right and left eyes, respectively. The macular function was relatively well preserved on mfERG, although some reduction of amplitude could be seen in the more severely affected eye. The father showed slightly reduced full-field ERG readings, including a reduction of the rod response to dim blue light and an increase in implicit time on stimulation with 30 Hz flicker, and severe depressions could be seen on mfERG (Figs 4 and 6, Tables 1 and 2). On EOG

the Arden ratio was slightly reduced in the left eye compared to the right (1.6 and 2.1, respectively).

OCT examination

Family 1

The father presented with slightly reduced retinal reflectivity but an otherwise unremarkable single line scan over the macular area. The posterior hyaloid face could also be seen, detached in the central area. The daughter presented with an unremarkable single line scan (Fig. 5).

Family 2

The father presented with an OCT that showed reduced retinal reflectivity in the macular areas. The vitelliform changes seen in the daughter's macular area were clearly delineated by the OCT as a thickened, highly reflective lesion (Fig. 6).

The daughter in family 1 who did not carry the mutation presented with normal findings in the investigations above.

Discussion

The clinical phenotype in families with mutations in *RDS* has been discussed in several papers over the years, as these families demonstrate an extensive variety of retinal disorders (Wells et al. 1993; Weleber et al. 1993; Nakazawa et al. 1995, 1996; Reig et al. 1995). It has been especially interesting to note that this gene defect is associated with phenotypes with mainly macular involvement, but also with widespread retinal degeneration as in retinitis pigmentosa (RP). Similar phenotypic diversity has been described in association to mutations in other genes such as *ABCR*, *RLBP1* and, recently, *RPGR*

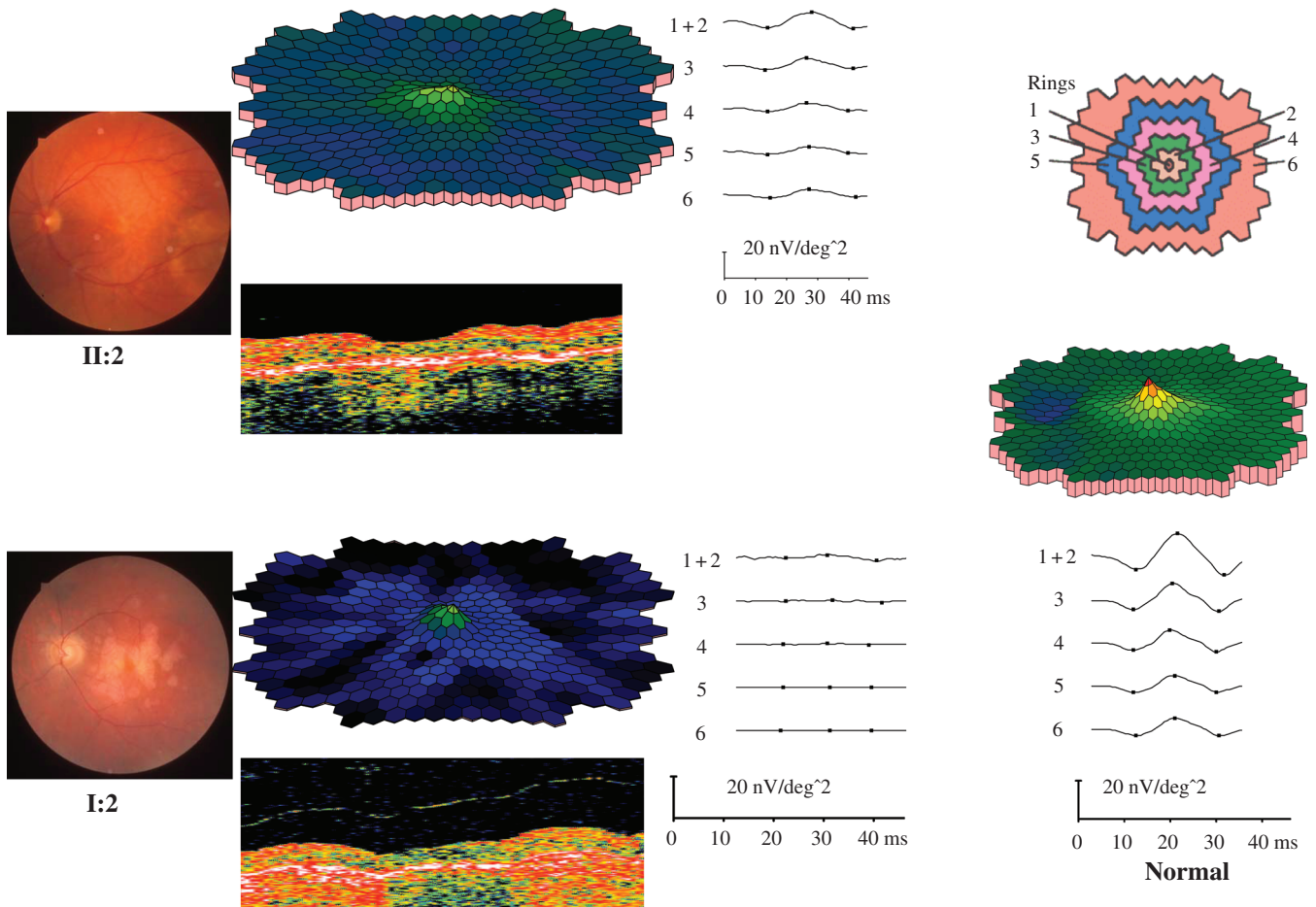


Fig. 5. Family 1. Top left: fundus picture of the daughter, with some degenerative changes centrally. Her OCT is unremarkable, but mfERG1 shows reduced amplitudes. Bottom left: the father's fundus is shown, with severe central and paracentral atrophy and vascular attenuation. His OCT shows reduced retinal reflectivity, parafoveal atrophy of the pigment epithelium and a detached posterior hyaloid face. MfERG shows severely reduced function. Top right: ring areas in which amplitudes and latencies were calculated; responses from areas 1 and 2 were averaged together as '1 + 2'. Bottom right: ring averages and plot, averaged from examinations of eight normal individuals.

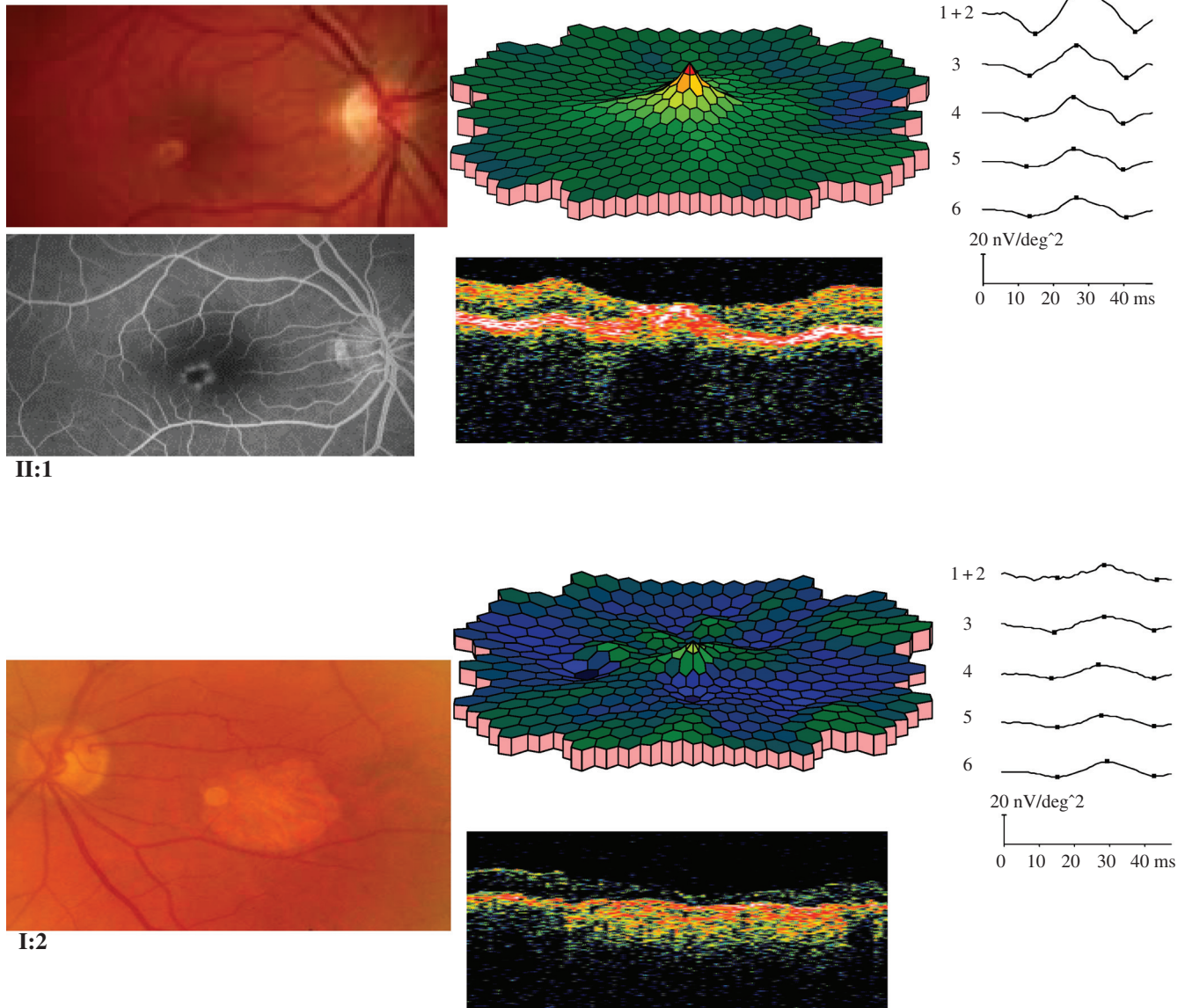


Fig. 6. Family 2. Top: fundus of the daughter, showing a vitelliform lesion in the fovea, and corresponding angiography, showing a ring of hyperfluorescence in the area, due to transmission defect in the RPE. Her OCT and mfERG are displayed to the right, showing a highly reflective thickened band in the fovea, but relatively well preserved amplitudes, respectively. Bottom: the father's fundus picture with central areolar choroidal dystrophy. OCT shows attenuation at the macula and mfERG reveals severely decreased amplitudes.

Table 1. Age, visual acuity, ERG amplitudes (microvolts) and 30 Hz flicker implicit time (milliseconds). Normal values for ERG responses developed by our clinic, based on examinations of 56 individuals (6–72 years old, mean age 31 years). White I: 0.81 cd-s/m², White II: 3.93 cd-s/m².

	Age (years)	Visual acuity OD	Visual acuity OS	Blue OD/OS	White I OD/OS	White II OD/OS	Implicit time 30 Hz flicker OD/OS
Family 1	I:2 74	20/50	20/50	0/0	0/0	0/0	36.3/39.1
	II:2 28	20/20	20/25	25/95	115/175	120/180	29.1/29.1
Family 2	I:2 81	20/200	counting fingers	95/25	195/145	230/175	32.3/37.5
	II:1 45	20/25	20/20	180/170	360/205	350/205	29.5/29.6
Normal controls (n = 56)							
Mean (2 SD)				167 (105)	308 (144)	304 (179)	29.2 (3.6)

(Ayyagari et al. 2002; Briggs et al. 2002; Eichers et al. 2002).
 The Arg-46 → stop codon mutation found in family 1 has previously been

described in association with autosomal dominant RP, and also in a clinical phenotype resembling fundus flavimaculatus (Stone et al. 1993; Apfelstedt-

Sylla et al. 1995). In this study, the two patients with Arg-46 → stop codon mutation presented with a quite diverse clinical phenotype, with the father showing what could be described as 'typical' RP, with severely affected full-field ERGs, whereas his daughter presented with a somewhat atypical phenotype. Although her VA and visual fields were only slightly affected and the OCT was unremarkable, the central and paracentral retinal function were severely depressed when measured with mfERG, showing that the mfERG is a sensitive method of discovering and characterizing the nature of central retinal affection.

Table 2. MfERG P1 amplitudes and latencies for patients, corresponding to Figs 5 and 6, and normal values corresponding to Fig. 5, bottom right, based on examinations of eight individuals.

Patients		Family 1		Family 2		Normal ± 2 SD
		I:2	II:2	I:2	II:1	
P1 amplitude (nV/deg ²)	ring 1 + 2	2.1	13	9.2	19.3	29.1 ± 9.1
	3	0.8	8.7	10.6	20.7	21.2 ± 9.7
	4	0.5	6.4	10.2	15.1	16.5 ± 7.3
	5	0	5.7	8.2	12.1	13.7 ± 6.9
	6	0.2	6.4	10.6	12.2	14.1 ± 6.4
Latency (ms)	ring 1 + 2	29.2	28.3	29.2	28.3	27.8 ± 3.2
	3	30.8	26.7	29.2	26.7	26.3 ± 2.8
	4	29.2	26.7	27.5	25.8	25.8 ± 1.7
	5	30	27.5	28.3	25.8	26.5 ± 2.7
	6	30	27.5	30	26.7	26.9 ± 2.5

The *RDS* mutation Ser-125 → Leu found in family 2 has to our knowledge not been described before. In this family, the father presented with central areolar choroidal dystrophy. His ERG readings showed a somewhat reduced rod response and an increase in 30 Hz flicker implicit time. These findings have been described earlier in patients with central areolar choroidal dystrophy (Ponjavic et al. 1994). His daughter presented with adult onset vitelliform maculopathy with only slightly affected visual function, in comparison, and her macular function on mfERG was only slightly affected. The vitelliform changes were clearly delineated by a thickened, highly reflective band extending from the retinal pigment epithelial layer as demonstrated with OCT. Recently, similar OCT findings were consistently reported in 43 patients with adult onset foveomacular dystrophy, whereas subretinal fluid was found in patients with Best's disease (Pierro et al. 2002).

Both father and daughter had normal Arden ratios on EOG, which is considered to represent pigment epithelial function, distinguishing this kind of maculopathy from Best's disease, in which Arden ratios are reduced (Blodi & Stone 1990; Ponjavic et al. 1999). Despite the similarity of the macular lesions in the two conditions, the latter is associated with mutations in the *VMD2* gene, and is a condition in which the pigment epithelium is considered to be primarily involved. Peripherin, on the other hand, is a photoreceptor specific protein and *RDS* mutations have been estimated to cause 20% of cases of adult vitelliform maculopathy (Felbor et al. 1997).

In both families, the fathers showed OCT scans with slightly reduced reflectivity in the fovea. This finding has been described previously in patients with RP, and can be caused by cystic macular oedema, a well recognized condition in these patients (Hamada et al. 2000). In our cases, however, the reduced reflectivity was probably due to atrophy, as thickness was not increased and no cystic spaces were visible on the scans.

RDS mutations cause dominant transmission of disease, with the exception of digenic RP, found in four cases with a simultaneous Leu-185 → Pro mutation in *RDS* and three different mutations in the *ROM-1* gene (Kajiwara et al. 1994; Dryja et al. 1997). Heterozygosity for these mutations in either gene does not lead to disease. As *RDS* and *ROM-1* reside on different chromosomes, an affected individual from unrelated and unaffected parents would have a 25% risk of transmitting disease to offspring. In our study, no mutations could be demonstrated in the *ROM-1* gene with a screening method previously utilized to identify novel *ROM-1* mutations (Jacobson et al. 1999), so at least in family 1 there is no evidence for a digenic disease which perhaps might explain the varying phenotype in the different family members. Subjects were heterozygous for the mutations in *RDS*, which would imply dominant disease transmission, meaning that the risk of offspring being affected would be 50%.

The mechanism by which peripherin acts remains unknown, but has been proposed to be as a photoreceptor specific membrane fusion protein, in processes such as disc morphogenesis and shedding (Boesze-Battaglia et al.

1992, 1997, 1998). In general, as with other fusion proteins, fusion competency requires the ability to assemble into oligomers (Pecheur et al. 1999). In the case of peripherin, this seems to be determined mainly by the second intradiscal loop of the molecule, which contains a cysteine residue at position 150 through which peripherin assembles into disulfide linked oligomers (Goldberg et al. 1998). These then assemble non-covalently with *ROM-1* to form heterotetramers (Goldberg et al. 1995). A fusion peptide domain from residues 311–325 in peripherin has been identified (Boesze-Battaglia et al. 2000), which would be located downstream from the residues involved in this study. Recently, however, it has been shown that mutations involving the highly conserved second intradiscal loop of peripherin, which would be the locus of the Ser-125 → Leu mutation, might interfere with the fusion competency of this protein, probably by interfering with its assembly into oligomers (Boesze-Battaglia & Stefano 2002). In the case of the Arg-46 → stop codon mutation, this mutation would be expected to lead to a non-functional severely truncated protein, possibly without any second intradiscal loop.

In conclusion, this study shows again the diversity of the phenotypes associated with mutations in *RDS*, one of which, to our knowledge, has not been described earlier. It also emphasizes newer diagnostic means including mfERG and OCT for improved functional and topographic evaluation of the disease manifestations.

Acknowledgements

This study was supported by grants of the Kronprinsessans Margaretas Arbetsnämnd Fond, Segerfalk Foundation, Swedish Medical Research Council (projects no. 73 × 12597-03 A, 14P-12964-01AK). An abstract on this material was presented at the Annual General Meeting of the Swedish Society of Medicine, November 27–29, 2002.

References

- Andréasson S, Sandberg M & Berson E (1988): Narrow-band filtering for monitoring low-amplitude cone electroretinograms in retinitis pigmentosa. *Am J Ophthalmol* **105**: 500–503.
- Apfelstedt-Sylla E, Theischen M, Ruther K, Wedemann H, Gal A & Zrenner E (1995): Extensive intrafamilial and interfamilial phenotypic variation among patients with

- autosomal dominant retinal dystrophy and mutations in the human RDS/peripherin gene. *Br J Ophthalmol* **79**: 28–34.
- Arikawa K, Molday L, Molday RS & Williams DS (1992): Localization of peripherin/RDS in the disc membranes of cone and rod photoreceptors: relationship to disc membrane morphogenesis and retinal degeneration. *J Cell Biol* **116**: 659–667.
- Ayyagari R, Demirci FY, Liu J et al. (2002): X-linked recessive atrophic macular degeneration from RPGR mutation. *Genomics* **80**: 166–171.
- Bascom RA, Manara S, Collins L, Molday RS, Kalnins VI & McInnes RR (1992): Cloning of the cDNA for a novel photoreceptor membrane protein (ROM-1) identifies a disc rim protein family implicated in human retinopathies. *Neuron* **8**: 1171–1184.
- Bearse MA & Sutter EE (1996): Imaging localized retinal dysfunction with the multifocal electroretinogram. *J Opt Am* **13**: 634–640.
- Blodi CF & Stone EM (1990): Best's vitelliform dystrophy. *Ophthalmic Paediatr Genet* **11**: 49–59.
- Boesze-Battaglia K, Albert AD & Yeagle PL (1992): Fusion between disc membranes and plasma membrane of bovine photoreceptor cells is calcium dependent. *Biochemistry* **31**: 3733.
- Boesze-Battaglia K, Kong F, Lamba OP, Stefano FP & Williams DS (1997): Purification and light dependent phosphorylation of a candidate fusion protein, photoreceptor peripherin/RDS. *Biochemistry* **36**: 6835–6846.
- Boesze-Battaglia K, Lamba OP, Napoli A, Sinha S & Guo Y (1998): Fusion between retinal rod outer segment membranes and model membranes: a role for photoreceptor peripherin/RDS. *Biochemistry* **37**: 9477–9487.
- Boesze-Battaglia K & Stefano FP (2002): Peripherin/RDS fusogenic function correlates with subunit assembly. *Exp Eye Res* **75**: 227–231.
- Boesze-Battaglia K, Stefano FP, Fenner M & Napoli A (2000): A peptide analogue to a fusion domain within photoreceptor peripherin/RDS promotes membrane adhesion and depolarization. *Biochim Biophys Acta* **1463**: 343–354.
- Briggs CE, Rucinski D, Rosenfeld PJ, Hirose T, Berson EL & Dryja TP (2002): Mutations in ABCR (ABCA4) in patients with Stargardt macular degeneration or cone-rod degeneration. *Am J Hum Genet* **70**: 955–964.
- Dryja TP, Hahn LB, Kajiwara K & Berson EL (1997): Dominant and digenic mutations in the peripherin/RDS and ROM-1 genes in retinitis pigmentosa. *Invest Ophthalmol Vis Sci* **38**: 1972–1982.
- Eichers ER, Green JS, Stockton DW et al. (2002): Newfoundland rod cone dystrophy, an early onset retinal dystrophy, is caused by splice junction mutation in RLBP1. *Am J Hum Genet* **70**: 955–964.
- Ekström U, Ponjavic V, Andréasson S, Ehinger B, Nilsson-Ehle P & Abrahamson M (1998): Detection of alterations in all three exons of the peripherin/RDS gene in Swedish patients with retinitis pigmentosa using an efficient DGGE system. *J Clin Pathol: Mol Pathol* **51**: 287–291.
- Felbor U, Schilling H & Weber BHF (1997): Adult vitelliform macular dystrophy is frequently associated with mutation in the peripherin/RDS gene. *Hum Mutat* **10**: 301–309.
- Goldberg AFX, Loewen CJ & Molday RS (1998): Cysteine residues of photoreceptor peripherin/RDS: role in subunit assembly and autosomal dominant retinitis pigmentosa. *Biochemistry* **37**: 680–685.
- Goldberg AFX, Moritz OL & Molday RS (1995): Heterologous expression of photoreceptor peripherin/RDS and ROM-1 in COS-1 cells: assembly, interactions and localization of multisubunit complexes. *Biochemistry* **34**: 14213–14219.
- Hamada S, Yoshida K & Chihara E (2000): Optical coherence tomography images of retinitis pigmentosa. *Ophthalmic Surg Lasers* **31**: 253–256.
- Jacobson SG, Cideciyan AV, Bascom RA et al. (1999): Digenic inheritance of a ROM-1 gene mutation with a peripherin/RDS or rhodopsin mutation in families with retinitis pigmentosa. *Dig J Ophthalmol* **5**: No. 1.
- Kajiwara K, Berson EL & Dryja TP (1994): Digenic retinitis pigmentosa due to mutations at the unlinked peripherin/RDS and ROM-1 loci. *Science* **264**: 1604–1607.
- Kedzierski W, Lloyd M, Birch DG, Bok D & Travis GH (1997): Generation and analysis of transgenic mice expressing P216L-substituted RDS/peripherin in rod photoreceptors. *Invest Ophthalmol Vis Sci* **38**: 498–509.
- Kedzierski W, Moghrabi WN, Allen AC, Jablonski-Stiemke M, Bok D & Travis GH (1996): Three homologues of RDS/peripherin in *Xenopus laevis* photoreceptors that exhibit covalent and non-covalent interactions. *J Cell Sci* **109**: 2551–2560.
- Marmor MF, Hood DC, Keating D, Kondo M, Seeliger MW & Miyake Y (2003): Guidelines for basic multifocal electroretinography (mfERG). *Doc Ophthalmol* **106**: 105–115.
- Marmor MF & Zrenner E (1993): Standard for clinical electro-oculography. *Arch Ophthalmol* **111**: 601–604.
- Marmor MF & Zrenner E (1999): Standard for clinical electroretinography. *Doc Ophthalmol* **97**: 143–156.
- Miller SA, Dykes DD & Polesky HF (1988): A simple salting out procedure for extracting DNA from human nucleated cells. *Nucl Acid Res* **16**: 1215.
- Molday RS, Hicks D & Molday L (1987): Peripherin: a rim-specific membrane protein of rod outer segment discs. *Invest Ophthalmol Vis Sci* **28**: 50–61.
- Nakazawa M, Kikawa E, Chida Y, Wada Y, Shiono T & Tamai M (1996): Autosomal dominant cone-rod dystrophy associated with mutations in codon 244 (Asn244His) and codon 184 (Tyr184Ser) of the peripherin/RDS gene. *Arch Ophthalmol* **114**: 72–78.
- Nakazawa M, Wada Y & Tamai M (1995): Macular dystrophy associated with monogenic Arg172Trp mutation of the peripherin/RDS gene in a Japanese family. *Retina* **15**: 518–523.
- Pecheur E, Sainte-Marie J, Bienvenue A & Hoekstra D (1999): Peptides and membrane fusion: towards an understanding of the molecular mechanism of protein-induced fusion. *J Membr Biol* **167**: 1–17.
- Pierro L, Tremolada G, Introini U, Calori G & Brancato R (2002): Optical coherence tomography findings in adult onset foveomacular vitelliform dystrophy. *Am J Ophthalmol* **134**: 675–680.
- Ponjavic V, Andréasson S & Ehinger B (1994): Full-field electroretinograms in patients with central areolar choroidal dystrophy. *Acta Ophthalmol Scand* **72**: 537–544.
- Ponjavic V, Eksandh L, Andréasson S, Sjöström K, Bakall B, Ingvast S, Wadelius C & Ehinger B (1999): Clinical expression of Best's vitelliform macular dystrophy in Swedish families with mutations in the bestrophin gene. *Ophthalmic Genet* **20**: 251–257.
- Reig C, Serra A, Gean E, Vidal M, Arumi J, De la Calzada M, Antich J & Carballo M (1995): A point mutation in the RDS-peripherin gene in a Spanish family with central areolar choroidal dystrophy. *Ophthalmic Genet* **16**: 39–44.
- Stone EM, Vandelburgh SK, Kimura AE et al. (1993): Novel mutations in the peripherin (RDS) and rhodopsin genes associated with autosomal dominant retinitis pigmentosa (ADRP). *Invest Ophthalmol Vis Sci* **34**: 1149.
- Sutter EE & Tran D (1992): The field topography of ERG components in man. I. The photopic luminance response. *Vision Res* **32**: 433–446.
- Travis GH, Sutcliffe JG & Bok D (1991): The retinal degeneration slow (RDS) gene product is a photoreceptor disc membrane-associated glycoprotein. *Neuron* **6**: 61–70.
- Weleber RG, Carr RE, Murphey WH, Sheffield VC & Stone EM (1993): 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* **111**: 1531–1542.
- Wells J, Wroblewski J, Keen J et al. (1993): Mutations in the human retinal degeneration slow (RDS) gene can cause either retinitis pigmentosa or macular dystrophy. *Nature Genet* **3**: 213–218.

Received on February 6th, 2003. Accepted on June 5th, 2003.

Correspondence:
Patrik Schatz MD
Department of Ophthalmology
Lund University Hospital
221 85 Lund
Sweden
Tel: +46 46 17 14 17
Fax: +46 46 211 50 74
Email: patrik.schatz@telia.com