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

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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

Introduction

Peripherin is a photoreceptor specific glycoprotein located in the rod and cone outer segment membranes (Mollay 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
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. 1. Pedigrees of both families are shown. Examined individuals are marked with an asterisk.

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 (V4e and I4e).

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 metaxdoline 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 μs) 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 Ganzfeld screen. Moreover, the ISCEV standard does not specify how to measure residual ERG responses. If responses measuring less than 10 μV 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 μV (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 mERG (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 \textit{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$\rightarrow$T substitution resulting in the heterozygous change Arg-46$\rightarrow$stop at the protein level (Fig. 2). No other deviations from the published gene sequence of \textit{RDS} were detected.

Clinical examination

\textit{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).

\textit{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. 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 fundus were affected with vitelliform deposits and pigmentary changes in the macular area (Figs 4 and 6).

Electrophysiological examination

\textit{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.

\textbf{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.](image-url)
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 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.

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

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.
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 mERG 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 mERG and OCT for improved functional and topographic evaluation of the disease manifestations.

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