SCIENTIFIC REPORT

Intrafamilial phenotypic variability in families with *RDS* mutations: exclusion of *ROM1* as a genetic modifier for those with retinitis pigmentosa

B P Leroy, A Kailasanathan, J-J De Laey, G C M Black, F D C Manson

Br J Ophthalmol 2007;91:89–93. doi: 10.1136/bjo.2006.101915

Objectives: To identify suspected *RDS* mutations in families in which different people have been identified with either generalised retinal dystrophy or macular dystrophy.

Methods: Two families with a retinal dystrophy were extensively phenotyped and blood was taken for mutation analysis of the *RDS* (all) and *ROM1* (retinitis pigmentosa patients only) genes.

Results: A novel p.Trp94X mutation in *RDS* was found in all three affected members of a two-generation family that was associated with retinitis pigmentosa in the son, pattern dystrophy in the daughter and fundus flavimaculatus in the mother. In the second family, the proband with retinitis pigmentosa carried a p.Arg220Trp mutation. The mother, who was unavailable for mutation screening, had adult vitelliform macular dystrophy. No *ROM1* mutations were found in those with retinitis pigmentosa in either family.

Conclusion: Mutations in *RDS* can be associated with an intrafamilial variation in retinal disease. The phenotypes range from Stargardt-like macular dystrophy to classic retinitis pigmentosa.

Clinical relevance: Intrafamilial phenotypic variation may be due to the presence of environmental or genetic modifying factors. The presence of a modifying-sequence change in the coding region of *ROM1* for two people with retinitis pigmentosa from two families with intrafamilial variation in *RDS* mutation phenotype has been excluded in this study.

The stability of the rod outer segment disc is critical for normal photoreceptor function. All membrane-bound phototransduction proteins, such as the photopigment rhodopsin, are targeted to the rod outer segment, where they are embedded in the lipid bilayer of the rod outer segment discs. Disc morphology is provided by structural proteins including *RDS*, a transmembrane structural glycoprotein that belongs to the tetraspanin family of proteins.¹ This is found exclusively in the membrane of photoreceptor disc rims where it forms heterotetramers with a second transmembrane protein *ROM1*.²

Mutations in *RDS* can cause a variety of retinal degenerations, including autosomal dominant retinitis pigmentosa,³ fundus flavimaculatus,^{4–6} retinitis punctata albescens,⁷ central areolar choroidal atrophy,^{8–11} diffuse choriocapillaris atrophy,¹² cone-rod dystrophy,¹³ age-related macular degeneration-like maculopathy,^{14–15} choroidal neovascularisation¹⁶ pattern dystrophy,^{17–18} butterfly-shaped pigment dystrophy^{19–21} and adult-onset foveomacular dystrophy.²² Additionally, numerous mutations that are associated with different levels of penetrance, expression and severity have been reported.^{9–23–31}

To date, most mutations are believed to act in a dominant manner, although the only known digenic form of retinitis

pigmentosa is caused by a protein-truncating or null-sequence change in *ROM1* in conjunction with a single mis-sense mutation (p.Leu185Pro) in *RDS*.^{32–33}

RDS mutations that are associated with intrafamilial phenotypic variation have been reported previously, including those at codons 172 and 210.^{4–5–25–26–29–34–35} Such variable expressivity can be attributed to the influence of modifier genes or environmental factors.

We describe different *RDS* mutations in two families in which different people have been identified with either a generalised retinal dystrophy or a macular dystrophy, in whom we exclude a *ROM1* mutation as a contributing genetic factor in people with retinitis pigmentosa.

PARTICIPANTS AND METHODS

Informed consent was obtained from all participants before conducting investigations. Ethical approval was obtained from ethics committees at the participating centres.

All four members of family A and the two affected members of family B were included in the study (fig 1).

Clinical examination of all members of the two affected families was performed and included best-corrected Snellen visual acuity testing, slit-lamp biomicroscopy, funduscopy, International Society for Clinical Electrophysiology of Vision-standard full-field,³⁶ pattern electroretinography³⁷ and electro-oculography,³⁸ autofluorescence imaging and fluorescein angiography. Colour vision testing was performed with the Ishihara pseudo-isochromatic plates, Farnsworth Panel D-15, tritan plate and the American Optical Hardy-Rand-Rittler test. The Goldmann perimeter and Humphrey automatic perimeter (10-2) protocol were used for testing the visual field.

With the exception of a clinically affected member of family B (I₂), blood was taken from all family members by phlebotomy and genomic DNA extracted.

Mutational screening by direct sequencing was performed on by polymerase chain reaction amplified DNA fragments corresponding to all three exons of *RDS* and *ROM1*. Primers were designed against sequences taken from the National Centre for Biotechnology Information (www.ncbi.nlm.nih.gov/entrez/; *RDS* accession number NM_000322, *ROM1* accession number NM_000327).

Primer sequences were as follows:

RDS: exon 1, forward 5'-TTT GGG GTG GGA GCT GTG CTG-3', reverse 5'-GTG TCC CCA ATA TAT TCA TAG CTC-3'; exon 2, forward 5'-CTG TTG AGA AGC CCG GGA AGC-3', reverse 5'-CGG AGG CTC TCC TTA CCC TC-3'; exon 3, forward 5'-CCC AGC GAT TCT CCC AGA TTG-3', reverse 5'-TTG GAG TGC ACT ATT TCT CAG TG-3'.

Abbreviations: BCVA, best-corrected visual acuity; ERG, electroretinography; PERG, pattern electroretinopathy

Figure 1 Top: Pedigrees of family A (left) and family B (right). Bottom: Sequence electropherograms. Heterozygotic substitution at nucleotide 281 (c.281G→A) in exon 1 of RDS in an affected member of family A; the residue is highlighted (left). A heterozygotic substitution at nucleotide 658 (c.658C→T) in exon 2 of RDS in the proband (II₂) of family B; the residue is highlighted (right).

ROM1: exon 1, forward 5'-TTC CAT CCC TGA CAC CTC TGC-3', reverse 5'-GGA GGG AGC CTG TCC AG-3'; exon 2, forward 5'-AGG CCT CTA TCT CCA GAC ATC-3', reverse 5'-GAG GAG GTG TCA GAT GCT TTG-3', exon 3, forward 5'-CCG CTG ACT CTC CCT GAC TC-3', reverse 5'-GTT GTG AGG TTT TCA GAC TTG TC-3'.

RESULTS

We examined two families in which one or more members have an isolated macular dystrophy, while another member has a generalised retinal dystrophy.

Phenotypes

In family A, there are three affected members in two generations (fig 1A).

Patient I₂ was asymptomatic. Fundus examination showed perifoveal pigment epithelial abnormalities, with widespread intraretinal or subretinal white flecks extending to just beyond the vascular temporal arcades and nasal to the optic disc. These flecks were indistinguishable from those seen in a classic flavimaculatus phenotype (fig 2A). These were hyperfluorescent on autofluorescence imaging (fig 2B). Fluorescein angiography showed some perifoveolar window defects, with staining of some, but not all, of the flecks in the late stages.

Full-field flash electroretinography (ERG) and electro-oculography were normal. Pattern electroretinography (PERG) was within the lower limits of normal. Goldmann visual fields and colour vision tests were normal. Macular dystrophy of the fundus flavimaculatus type was diagnosed. Little change was noted during a 5-year follow-up.

The proband, patient II₁, noted visual symptoms from the age of 29 years, when she had best-corrected visual acuities (BCVAs) of 6/9 in both eyes. Vitelliform-like pigment epithelial abnormalities were seen on funduscopy at both foveas and were associated with a limited number of small, intraretinal or subretinal white flecks in the perimacular region (fig 2D). We found no abnormalities in the peripheral retina. Autofluorescence imaging better visualised the flavimaculatus-type lesions (fig 2E). Fluorescein angiography showed foveal window defects, with limited staining of some of the white fundus flecks in both eyes and a dark choroid (fig 2C). Visual fields and colour vision were normal. Full-field flash ERG showed reduction of rod-specific amplitudes to 55%, and of cone-specific amplitudes to 70% of normal. Hence, a rod-cone dystrophy seemed to accompany the macular pattern dystrophy in this patient. The electro-oculography light_{peak}:dark_{trough} ratio was reduced to 154% in the right eye and to 147% in the left eye, in keeping with the

Table 1 Clinical characteristics of patients					
Patients	Age (years)	Clinical phenotype	Flash ERG	Pattern ERG	EOG
Family A					
Mother (I ₂)	59	Stargardt-like macular dystrophy	Normal	Normal	Normal
Daughter (II ₁)	34	Pattern dystrophy	Cone-rod dystrophy	Normal	Mild attenuation
Son (II ₂)	30	RP	Absent	Attenuated	Flat
Family B					
Mother (I ₂)	53	Adult vitelliform macular dystrophy	Normal	nd	Normal
Son (II ₂)	29	RP	Absent	nd	nd

EOG, electro-oculography; ERG, electroretinography; nd, not determined; RP, retinitis pigmentosa.

Figure 2 Fundus features of all patients from families A and B. (A,B) Fundus picture and composite of the autofluorescence (AF) image of the left eye of patient II₂ of family A; note flavimaculatus lesions. (C–E) Fluorescein angiography, fundus picture and AF image of right eye of patient II₁ (proband) of family A; note dark choroid, adult vitelliform lesion with limited white flecks better seen on AF. (F,G) Fundus picture and AF image of the right eye of patient II₂ of family A; note outer retinal atrophy and spicular intraretinal pigmentation in periphery, with a rather small hyperautofluorescent ring surrounding a better area of the central macula. (H) Redfree fundus image of the right eye of patient II₂ of family B; note adult vitelliform lesion in fovea. (I) Fundus picture of right eye of patient II₂ of family B; note outer retinal atrophy and limited spicular intraretinal pigmentation in mid-periphery, with relative preservation of macula albeit with premacular gliosis.

rather mild generalised retinal dystrophy. Goldmann visual fields and PERG were normal (fig 3A). PERG indicates that the overall function of the central 12° of the macula is normal. Again, little evolution was noted over 5 years of follow-up.

Patient II₂, aged 30 years, had had night blindness since the age of 17 years. His BCVAs were 6/9 in the right eye and 6/6 in the left eye. Funduscopy showed a normal central macula, but outer retinal atrophy with spicular intraretinal pigment migration in the mid-periphery, vessel attenuation and disc pallor (fig 2F). Goldmann perimetry showed typical mid-peripheral scotomata with preservation of central sensitivity. Colour vision was normal. His scotopic rod-specific ERG was extinguished with only minimal residual cone activity. PERG showed amplitudes of 33% of normal, with preservation of the P₅₀:N₉₅

ratio in both eyes (fig 3B), in keeping with the relatively small hyperfluorescent macular ring seen on autofluorescence imaging (fig 2G). Rod–cone dystrophy of the retinitis pigmentosa type was diagnosed.

In family B there are two affected members. The proband's mother, I₂, was diagnosed with macular dystrophy at the age of 49 years after reduced central vision. Her BCVAs were 6/12 in the right eye and 6/24 in the left eye. Funduscopy showed bilateral pale and slightly raised foveal lesions consistent with a diagnosis of adult vitelliform dystrophy (fig 2H). Full-field flash ERG was entirely normal.

The proband (II₂) in family B presented at 24 years of age with restricted visual fields. BCVAs were 6/6 in the right eye and 6/9 in the left eye. Fundus examination showed marked bilateral mid-peripheral outer retinal atrophy with intraretinal

Figure 3 Pattern electroretinography (PERG) of the left eye (two takes). (A) Patient II₁ of family A: note the normal amplitudes of P₅₀ and N₉₅. (B) Patient II₂ of family A: note the proportionally reduced amplitudes of P₅₀ and N₉₅. (C) Normal age-matched control for purposes of comparison.

pigmentation, vessel attenuation and premacular gliosis, consistent with a generalised rod–cone dystrophy (retinitis pigmentosa; fig 2I). Rod-specific and cone-specific ERG responses were absent.

Table 1 summarises the clinical details of all patients.

Genotypes

Sequencing of all exons of the *RDS* gene showed a heterozygotic c.281G→A change (p.Trp94X) in all affected members of family A (fig 1). This change was absent in the unaffected member (I₁). A c.658C→T (p.Arg220Trp) sequence change was found in the proband (II₂) of family B (fig 1).

In view of the descriptions of digenic retinitis pigmentosa caused by simultaneous mutations in both *RDS* and *ROM1*,^{32,33} we sequenced the *ROM1* coding sequence from the patients with retinitis pigmentosa in each family (AII₂ and BII₂). No sequence changes potentially associated with disease were identified.

COMMENT

We describe two mutations in the *RDS* gene that are associated with marked intrafamilial phenotypic variability. The phenotypes include Stargardt-like macular dystrophy, pattern dystrophies resembling adult vitelliform macular dystrophy, and generalised rod–cone dystrophy (retinitis pigmentosa) in separate people.

In family A there is a novel p.Trp94X mutation, which affects the small cytoplasmic loop between amino acids 80 and 101. A three-amino acid deletion in this region, between residues 87 and 89, has been associated with pattern dystrophy.³⁹ A premature stop codon in exon 1 of a three-exon gene is likely to result in the mRNA undergoing nonsense-mediated decay, and the resulting haploinsufficiency is therefore the probable cause of disease in this family.

The p.Arg220Trp missense mutation in family B has previously been reported to cause pattern dystrophy,³⁹ and so has a p.Arg220Gln missense change.^{12,39,40} Neither mutation has previously been associated with retinitis pigmentosa or intrafamilial phenotypic variation. The mechanism of disease is most likely a dominant negative effect. The region around, and including, this residue is well conserved in vertebrates including *Xenopus* and zebrafish, indicating that it is functionally important.

The intrafamilial variation in phenotype observed in both families is probably due to the action of environmental or genetic modifiers, although this is difficult to prove. Prematurely truncated proteins have been described in the literature to be associated with different phenotypes. An p.Arg46X mutation in *RDS* has been reported in four families^{4,6,41,42} and has been reported in other single pedigrees.^{7,12} In all these families, rod–cone dystrophy (when present) was seen in male members, whereas female members had a macular disease, and this was also observed in both families described here. This raises the possibility of an X-linked modifier gene. Mutational analysis was not performed on the proband's mother (who has adult vitelliform macular degeneration) in family B as DNA was unavailable. In this case, the intrafamilial variable phenotype is assumed but not proved.

As *RDS*-associated mutations are associated with a variable retinal phenotype and because mutations in *ROM1*, the only known genetic modifier of *RDS*, causes retinitis pigmentosa, we screened the patients with retinitis pigmentosa from two *RDS*-variable families for *ROM1* mutations. None were detected, suggesting the presence of a different modifier.

Intrafamilial phenotypic variation of the type described here is now recognised for both nonsense and missense mutations in *RDS*. Among the mutations previously described are a three-base pair deletion of codons 153 or 154⁵ and the missense change p.Arg172Trp.³⁴ In general, the risk of developing retinitis pigmentosa for those with *RDS*-related macular dystrophy is low. Interestingly, in the case of the family described by Michaelides *et al*,³⁴ the members with retinitis pigmentosa lay in one branch of the pedigree, consistent with the presence of a

genetic modifier. In such families, the risk of children developing retinitis pigmentosa (rather than macular dystrophy) may be considerably higher for those individuals with RDS-related retinitis pigmentosa, compared with those with macular dystrophy.

Authors' affiliations

B P Leroy*, **J-J De Laey**, Department of Ophthalmology, Ghent University Hospital, Ghent, Belgium

A Kailasanathan*, **G C M Black**, **F D C Manson**, Academic Unit of Ophthalmology, The University of Manchester, Manchester, UK

*These authors have contributed equally to this work.

Competing interests: None declared.

GCMB is a Wellcome Trust Senior Clinical Research Fellow.

Correspondence to: Dr F D C Manson, Centre for Molecular Medicine, The University of Manchester, Stopford Building, Oxford Road, Manchester M13 9PT, UK; forbes.manson@manchester.ac.uk

Accepted 13 August 2006

Published Online First 17 August 2006

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