SCIENTIFIC REPORT

Clinical characterisation of a family with retinitis pigmentosa caused by mutation in the *Mertk* gene

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Background/aim: MERTK, a tyrosine kinase receptor protein expressed by the retinal pigment epithelium (RPE), is mutated in both rodent models and humans affected by retinal disease. This study reports a survey of families for *Mertk* mutations and describes the phenotype exhibited by one family.

Methods: 96 probands with retinal dystrophy, consistent with autosomal recessive segregation, were screened by direct sequencing. A family homozygous for a likely null allele was investigated clinically.

Results: A novel frame shifting deletion was identified in one of 96 probands. Other polymorphisms were detected. The deletion allele occurred on both chromosomes of four affected family members. Electrophysiology demonstrated early loss of scotopic and macular function with later loss of photopic function. Visual acuities and visual fields were preserved into the second decade. Perception of light vision was present in a patient in the fourth decade. A ''bull's eye'' appearance and a hyperautofluorescent lesion at the central macula were consistent clinical findings.

Conclusions: Mutations in *Mertk* are a rare cause of ARRP in humans. The study extends the phenotypic characteristics of this retinal dystrophy and shows distinctive clinical signs that may improve its clinical identification. The moderate severity and presence of autofluorescence implies that outer segment phagocytosis is not entirely absent.

Retinitis pigmentosa (RP) is a a group of disorders affecting the retina in which there is progressive loss of rod then cone photoreceptor cells, with consequent loss of scotopic then photopic visual function. It affects approximately one in 3500 people. Currently there are no proved preventative or curative measures. It is highly heterogeneous genetically, with over 35 genes causing non-syndromic disease (http://www.retnet.org). This degree of heterogeneity hinders efforts to obtain a molecular diagnosis. Thus, we have adopted a strategy in which probands are screened initially for mutations in genes that may in the future be addressed with a specific therapeutic intervention.

In 2000, D'Cruz and colleagues identified *Mertk* as the gene mutated in the Royal College of Surgeons (RCS) rat, a well studied animal model of retinal degeneration.[1] This model develops a spontaneous retinal degeneration characterised by the accumulation of debris between the retinal pigment epithelium (RPE) and neurosensory retina with subsequent death of the outer retina. The MERTK protein is a member of the Axl/Mer/Tyro3 receptor tyrosine kinase family, is expressed in RPE cells, and is required for phagocytosis, but not binding of photoreceptor outer segments by the RPE.[2] Importantly, the RCS rat has been widely used as a model for the investigation of treatment strategies, including subretinal transplantation of RPE cells and other cell lines,[3 4] treatment with growth factors such as bFGF,[3] and gene replacement therapies using viral vectors.[5–7]

Mutations in the human *Mertk* gene were first identified as a cause of retinal disease by Gal and colleagues.[8] They identified three likely disease causing variants on five alleles of three patients with recessive retinal dystrophy. A fourth patient was later described in detail by McHenry and colleagues.[9] Here we describe four affected members of one family who are homozygous for a single base deletion in the *Mertk* gene. Mutation in *Mertk* causes a retinopathy with some distinctive features. The milder phenotype shown by this family compared to previous reports suggests the existence of modifier influences and might allow a window of opportunity for possible therapeutic intervention.

PATIENTS AND METHODS

A panel of 96 patients with simplex and autosomal recessive retinal dystrophy were ascertained from the medical retinal clinic at Moorfields Eye Hospital. There was no significant bias between males or females in the panel, and the likelihood of X linked disease in males was minimised by examination of female relatives where possible. All patients had a history and examination compatible with a retinal dystrophy and abnormalities of both rod and cone full field electroretinograms (ERGs). The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by Moorfields Hospital ethics committee.

PCR and sequencing

Blood samples were collected in EDTA tubes and the DNA was extracted using a Nucleon Genomic DNA Extraction Kit (BACC2, Tepnel Life Sciences plc) following the manufacturer's instructions.

Primers were designed corresponding to intronic sequences for PCR amplification of all 19 exons of *Mertk* (table 1). All polymerase chain reactions (PCR) were performed in a total volume of 50 µl using 200 µM dNTPs (Promega UK), 0.5 µM of each primer, 2 µM DNA, magnesium containing Optimase reaction buffer (Transgenomic UK), and 2.5 U Optimase polymerase (Transgenomic UK). Reactions were cycled using a Techne Touchgene Thermal Cycler. Optimal annealing temperatures were calculated using the program PrimerSelect (DNAStar inc). Cycle conditions were 95℃ for 5 minutes, 30 cycles of 60 seconds/95℃, 15 seconds/annealing temperature, 15 seconds/72℃, and a final 10 minutes at 72℃.

Abbreviations: ARRP, autosomal recessive retinitis pigmentosa; ERGs, electroretinograms; FFA, fluorescein angiography; HRR plates, Hardy-Rand-Rittler plates; OCT, optical coherence tomography; PCR, polymerase chain reaction; PERG, pattern ERGs; RCS, Royal College of Surgeons; RP, retinitis pigmentosa; RPE, retinal pigment epithelium

Table 1 Sequences and annealing temperature of primers

Mertk	Forward primer 5′-3′	Reverse primer 5′-3′	Ta (℃)
Exon 1	gacaggttcgggagggtccatctg	ccctgtggacgcgctccctccccag	60
Exon 2	ggacaccccagtgctctctcttc	gtccaactgtgtgtttgaaggcaag	60
Exon 3	cacagcatatgacaaagaagttg	cagagttataaaataggcaggc	59
Exon 4	ctttgggctctgtctctgtttt	ttgatcctgtccgctattagaga	52
Exon 5	tgtttctctgctgctggtctc	cctcaccagctcccagaac	65
Exon 6	gtagctgtagcctgtcatctataa	cccacagagagcaccaa	50
Exon 7	tgcctgacattcccaccac	tgggaagggttgttgaatca	65
Exon 8	atgagaatacatctgtgtgtgcttt	agttgaaaggagatgactaatcg	50
Exon 9	ctgcagtttgcccagacctc	gaccatcacatcctatcagccc	50
Exon 10	tgactatttgttcttccctgttac	taacaaccttgtcaataccagtg	50
Exon 11	agtagccctgtttttatagtgaag	gtctattgatccttcttttgttctc	48
Exon 12	caagtgaaagaaaacacgctg	aaactgctaccttcttatcccac	52
Exon 13	tggtcagggaagagtttgc	gcacccaatactgaagcaac	52
Exon 14	cccacccactcccctt	cacagagcagatcagcagag	60
Exon 15	tggtcacagtaacaaggactc	tcacataagccctgagaagt	42
Exon 16	cccccggcagaaact	tgcaaagaccaaacacca	58
Exon 17	gtgttttcacctgtgtctga	tatgccctcctctttgtg	48
Exon 18	gctttgtggaaaggcttg	tgtgtttccgagggtcagtg	50
Exon 19	ggcatggattgcacaaagagatgggtg	catcaggtacaattggattctc	60

Primers were designed to cover the entire coding region and splice sites of the human *Mertk* gene using the program PrimerSelect.

Amplified DNA fragments were purified by ExoSAP-IT (Usb Corporation) treatment in a total volume of 18 µl using approximately 10 ng of DNA and 0.5 µl ExoSAP-IT enzyme with sterile dH_2O. The purification mix was incubated for 15 minutes at 37℃ and then the enzyme was inactivated for 15 minutes at 80℃. Samples were sequenced using a BigDye Terminator v1.1 Cycle Sequencing Kit (Applied Biosystems). A volume of 1 µl Big Dye v1.1 and either 0.8 µM forward or 0.8 µM reverse primer were added to each ExoSAP IT treated sample.

Cycling conditions were 30 seconds at 95℃, 30 seconds at 50℃, and 4 minutes at 60℃ for 30 cycles. Samples were purified using a Millipore Montage Cleanup Kit (Millipore Corporation) following the manufacturer's instructions. Samples were run overnight on an ABI Applied Biosystems 373A DNA Sequencer. Sequences were analysed using the DNASTAR software package (DNASTAR Inc) and compared to the normal human *Mertk* sequence (NT 022135).

Cryosections

Eyes from dystrophic RCS rats were prepared for cryosectioning. Sections 12 µm thick were mounted on to APES coated slides, counterstained with propidium iodide, and analysed using a Leitz Diaplan microscope fitted with appropriate filters and a Leica DC 500 digital camera.

Clinical assessment

Individuals in which a pathogenic change was identified then underwent more detailed clinical evaluation including slit lamp examination, assessment of visual acuity, colour vision assessment, and Goldmann field testing. Retinal imaging included fundus autofluorescence imaging with a confocal scanning laser ophthalmoscope (c-SLO-AF, HRA-2, Heidelberg engineering, Heidelberg Germany), standard clinical electroretinography (ERG), fluorescein angiography (FFA) (proband only), and optical coherence tomography (OCT).

Colour vision was evaluated using the Hardy-Rand-Rittler (HRR) plates (American Optical Company, NY, USA). Goldmann kinetic visual fields were determined using the V4e and II4e targets on a standard background. ERG assessment included full field pattern ERGs (PERG), performed to incorporate the protocols recommended by the International Society for Clinical Electrophysiology of Vision Standard (http://iscev.org/standards/index.html). Corneal gold foil recording electrodes were used for both full field and pattern ERGs.

RESULTS

Molecular analysis

Of 96 samples screened for mutations in the coding and splice site sequences of the *Mertk* gene, 11 variants from the Genbank sequence (accession number NT022135 build 35

Table 2 *Mertk* sequence variants

Mutation/ polymorphism	Exon	Change	Remark
Deletion	17	2214delT, C738W	Frameshift, premature termination before codon 770. Reported in this family
Missense	1	R20T	Only found in 1 ARRP patient
Intronic	IVS 1+19	*g→a*	Equally prevalent in patients and controls
Missense*	2	N118S	Equally prevalent in patients and controls
Intronic	IVS 3+13	*t→c*	Common polymorphism
Missense*	9	R466K	Equally prevalent in patients and controls
Synonymous	9	Q451Q	Not found in controls
Missense*	10	N498S	Equally prevalent in patients and controls
Missense*	10	I518V	Equally prevalent in patients and controls
Intronic	IVS 15+11	*t→c*	Common polymorphism
Missense*	19	V870I	Equally prevalent in patients and controls

Sequence variants in *Mertk* were identified by sequencing DNA from individuals affected by RP. The table summarises all changes found in the present study. *Also reported by Gal *et al*[9] (adapted from Retina International's Scientific Newsletter).

version 1) were detected (table 2). Of these, four variants would not be expected to change the sequence of the encoded protein, being intronic or synonymous in nature. None of these, however, has been reported previously. Six base changes causing missense substitutions were found. Of these, five had been reported previously and their prevalence in 192 control chromosomes from people of white race not significantly different from that of the 96 samples. The remaining missense change, R20T, was detected on both alleles of a 54 year old patient with severe autosomal recessive retinitis pigmentosa. Sequence alignments showed that this arginine is a fully conserved residue in all members of the human axl protein subfamily but is not conserved between different species. Furthermore, R20S is a known polymorphism in the human *Mertk* gene.[8] The substitution was not found in 96 samples from white patients or in 41 samples from Pakistani patients.

Finally, we identified a novel frameshifting single base deletion (2214delT) within exon 17 of the *Mertk* gene in both alleles of a patient with RP. This sequence change would cause a premature stop codon (TGA) 31 codons downstream of the mutation and 41 base pairs upstream of the penultimate splice site which may render the RNA a target for nonsense mediated decay.[10 11] If translated, the resulting protein would contain 31 foreign amino acids and would lack 262 amino acids from the carboxyl end of the 999 amino acid long protein. Sequence alignment of Mertk proteins show that the mutation is located in a region that is fully conserved between the human, chimpanzee, mouse, rat, and chicken proteins (fig 1) and also highly conserved between other members of the human axl subfamily of tyrosine receptor kinases—namely, Axl and Tyro3.

All three affected siblings and one affected cousin were homozygous for the deletion. The unaffected mother and father were both heterozygotes. Figure 2 shows electropherograms from a control sample, the probands' mother and the proband. The pedigree structure is shown in figure 3.

A

Mertk sequence of different species

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Chicken   MTVCVADFGLSKKIYSGDYYRQGRIAKMPVKWIAIESLADR
Rat       MTVCVADFGLSKKIYSGDYYRQGRIAKMPVKWIAIESLADR
Mouse     MTVCVADFGLSKKIYSGDYYRQGRIAKMPVKWIAIESLADR
Human     MTVCVADFGLSKKIYSGDYYRQGRIAKMPVKWIAIESLADR
Mutation  MTVWLRTSASLRRFTVAIITAKAALLRCLLNGSPStop
          C738W
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B

Members of the human axl family

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Mertk     MTVCVADFGLSKKIYSGDYYRQGRIAKMPVKWIAIESLADR
Axl       MSVCVADFGLSKKIYNGDYYRQGRIAKMPVKWIAIESLADR
Tyro3     MTVCVADFGLSRKIYSGDYYRQGCASKLPVKWLALESLADN
          *:*********:***.*******  :*:****:*:*****.
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Figure 1 Amino acid sequences (aa735–aa775). Sequences were aligned using SDSC Biology WorkBench. (A) Amino acid alignments of different species show that the mutation occurred in a highly conserved domain of MERTK. The predicted sequence caused by a single base pair deletion of the affected probands is shown in the lowest line. The mutation leads to a frameshift and a premature translation termination signal within the tyrosine kinase domain of the protein. (B) Amino acid sequence comparison of different members of the human axl tyrosine kinase receptor family shows that the region in which the mutation occurred is highly conserved between all members. This suggests that this domain is important for proper function. *Single, fully conserved residue; : , conservation of strong groups; . , conservation of weak groups

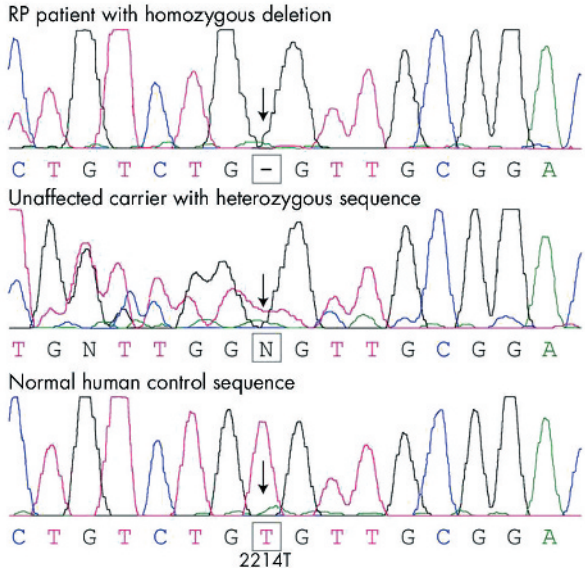

Figure 2 DNA sequence chromatograms (bp2207–bp2222). A novel mutation was identified in a patient with RP. The deletion (2214delT) was found in affected individuals (top). The sequence of the unaffected mother (middle) and control are shown (bottom).

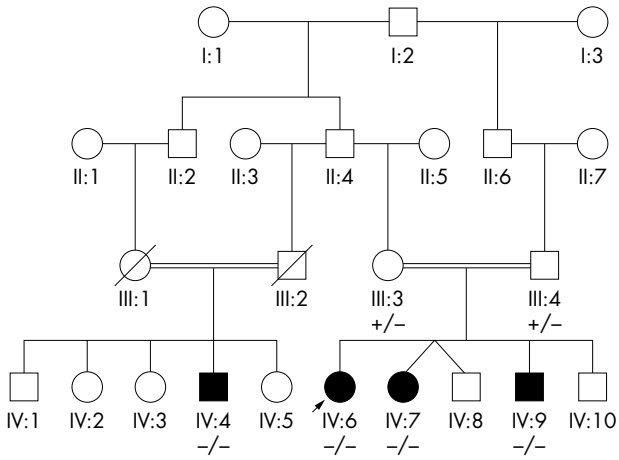

Figure 3 Abridged pedigree structure. Circles represent females and squares represent males: open symbols, unaffected, solid symbols, affected. Double lines indicate inter-related marriages.

Clinical examinaton

The proband (IV:6, figure 3), a 19 year old girl of Middle Eastern origin, was diagnosed with RP at the age of 12 years. She had no significant history of systemic disease or of medication. She noticed nyctalopia since she was 12 years old, did not experience problems with navigation but found reading fine detail difficult. At the age of 16 years, her best corrected visual acuities were 20/30 right eye and 20/40 left eye. Three years later (at age 19 years) her visual acuity had not changed. There was no nystagmus and the anterior segments were normal. Fundus examination showed attenuated vessels, a pale reflex form the RPE, and a bull's eye lesion at the maculas (fig 4) There was no intraretinal pigmentation (bone spicules), or macular oedema evident on biomicroscopy.

Monocular perimetry (Goldmann, V4e, and II4e) showed well preserved visual fields (fig 5). Colour vision assessment with HRR plates showed both red-green and blue-yellow

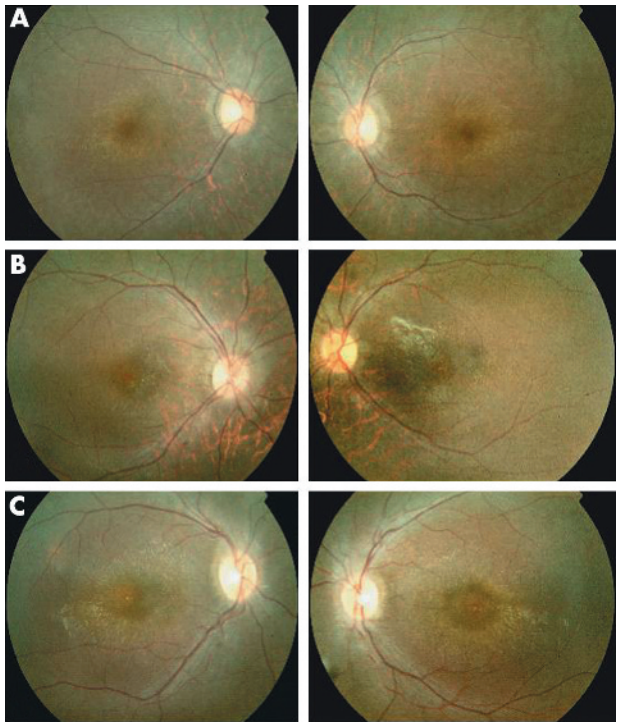

Figure 4 Fundus photographs from the three affected siblings. (A) Fundus photograph of patient IV:6 showing attenuated vessels, a pale reflex form the retinal pigment epithelium (RPE), and a bull's eye lesion at the macular. (B) Fundus photograph of patient IV:7 showing fine crystals present at the central macula. (C) Fundus photograph of patient IV:9.

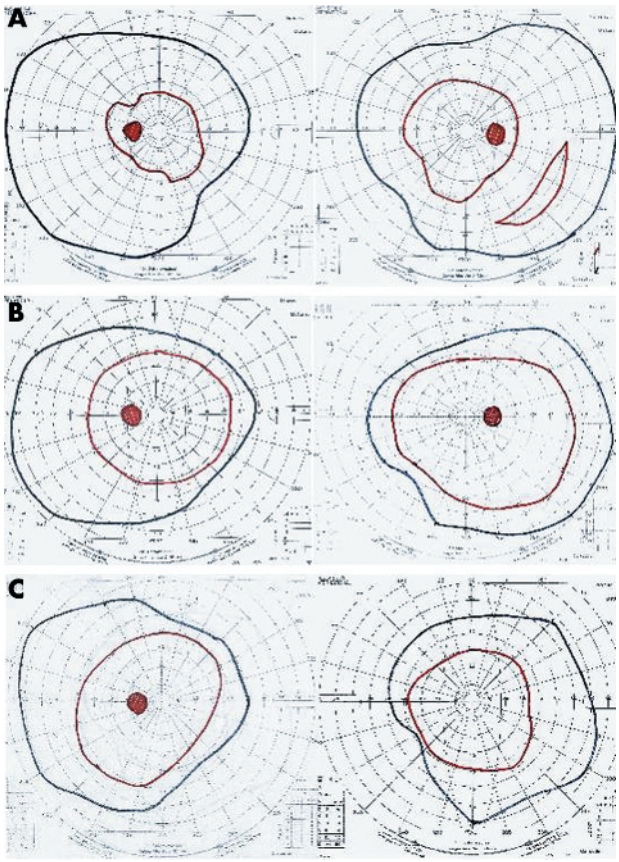

Figure 5 Goldmann visual fields. Monocular perimetry (Goldmann, V4e and II4e) showing well preserved visual fields from patients IV:6 (A), IV:7 (B), IV:9 (C).

defects. Autofluorescent imaging of the RPE layer showed a relatively homogeneous signal from the posterior pole but was unusual in that it demonstrated a central area of hyper-autofluorescence of approximately 500 μm in diameter at the central macula (fig 6) encircled by an area of relative decreased autofluorescence. Fluorescein angiography (at 16 years) showed a region of hypofluorescence at the central macula throughout the transit (fig 6). There was no retinal oedema. OCT was unremarkable and the retinal thickness normal (data not shown). Electrophysiology (at 16 years) showed a significant abnormality of both scotopic and photopic ERGs. The attenuated 30 Hz flicker showed significant delay. The pattern ERG was undetectable in keeping with severe macular involvment (fig 7).

The proband's affected younger sister (IV:7) was diagnosed with RP at the age of 10 years. By age 14, she experienced difficulty navigating and discerning colours in the dark, but did not have problems reading. Her acuities were 20/30 in both eyes best corrected (−2D spheres both eyes). Fundus examination was similar to her sister, although she had fine intraretinal crystals present at the central macula. Goldmann perimetry, colour vision, OCT imaging, and autofluorsecent imaging were

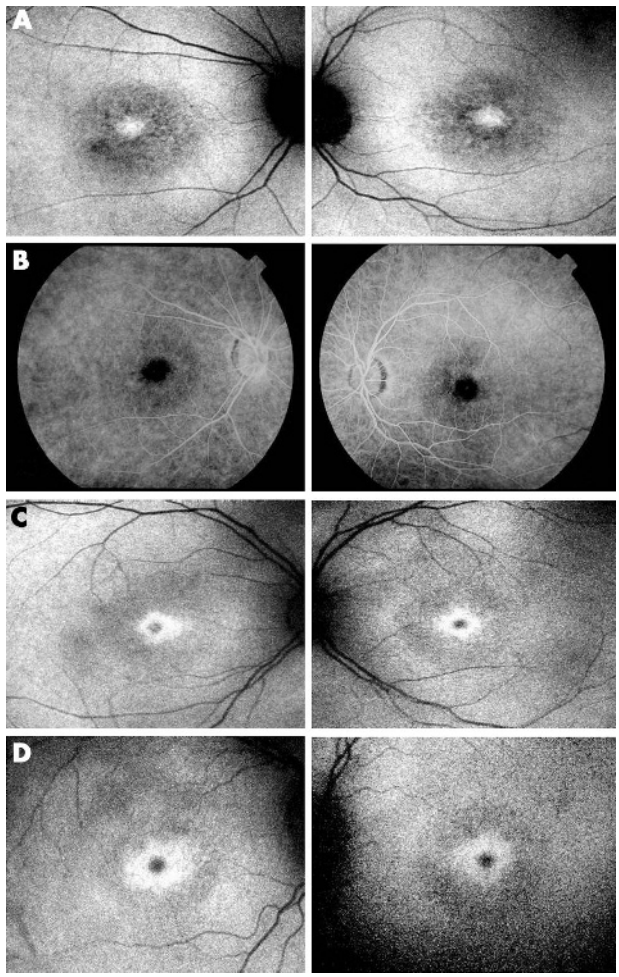

Figure 6 Fundus autofluorescence and fundus fluorescein angiography (FFA). (A) Fundus autofluorescence of patient IV:6 showing a bilateral area of increased autofluorescence encircled by an area of relative decreased signal. (B) FFA from patient IV:6 performed at the age of 16 years showing a region of hypofluorescence throughout the transit at the central macula. (C) Fundus autofluorescence of patient IV:7. (D) Fundus autofluorescence of patient IV:9 each shows a bilateral area of increased autofluorescence encircled by an area of relative decreased signal.

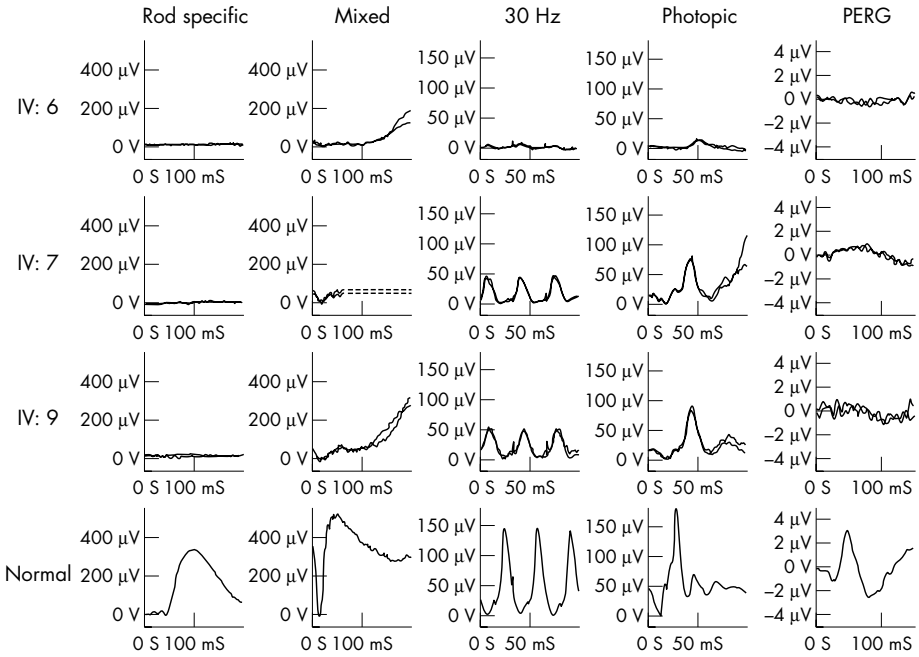

Figure 7 Representative electrophysiological traces. ERGs from three patients showing a rod-cone pattern of abnormality. Patient IV:6 shows no detectable rod specific ERG, a severely reduced bright flash ''mixed'' ERG, profoundly reduced and delayed 30 Hz and single flash cone ERGs, and an undetectable pattern ERG (PERG). Overall, the findings are those of a severe rod-cone dystrophy with severe macular involvement. Patients IV:7 and IV:9 also show severe rod system dysfunction. There is better preservation of generalised cone function than in patient IV:6, but still with marked delay and amplitude reduction. There is some preservation of macular function shown by the very low amplitude but detectable PERGs

also similar. ERG testing performed at the age of 10 years showed attenuation of rod and cone responses, delay of the cone implicit times, and barely detectable pattern ERGs.

The youngest affected sibling (IV:9) had noticed nyctalopia by the age of 10 years but otherwise was asymptomatic. At this age, his acuities were 20/20 in both eyes unaided. Fundus examination revealed some pallor of the RPE in the peripheral retina and some fine crystalline deposits near the fovea. Goldmann perimetry, colour vision, OCT imaging, and autofluorescent imaging were similar to his sisters although the area of macular hyperautofluorescence was larger. Electrophysiology showed an absent scoptic response, a severely attenuated maximal response, and delayed and attenuated reponses to photopic stimuli. The pattern ERG P50 was just recordable.

An older affected maternal half cousin of the proband (IV:4) was unavailable for examination but gave a detailed history at the age of 46 years. He started experiencing problems seeing in the dark at the age of 9 years. Then, his corrected visual acuities were normal. He was examined extensively in his early teens but was not diagnosed with RP until the age of 15 years. He learnt to drive, although he was advised to stop at the age of 18 years. For the next few years he managed well, attending university without assistance, but by the age of 24 he benefited from the use of a closed circuit TV monitor. At the age of 34 years, he required a permanent guide for navigation. By the age of 38, he no longer found use for his monitor owing to further deterioration of vision and, currently, at the age of 46 years only has perception of light vision. There was no history of significant systemic illness in any of the four affected individuals.

Retinal examinations of one other unaffected twin male sibling (IV:8) and the mother (III:3) were both normal.

DISCUSSION

This study presents the first detailed clinical and molecular report of multiple family members affected by RP caused by mutation in the *Mertk* gene and describes a novel mutation. Common to other reported surveys, the disorder is likely to be a rare cause of autosomal recessive RP (ARRP). Only one family was identified in a screen of 96 probands suggesting that mutations in *Mertk* count for approximately 1% of all ARRP. The possibility of heterozygous deletions or duplications that affect primer binding sites cannot be excluded. One previously unreported missense change, R20T, was detected in this study on both alleles in one person of Pakistani origin with ARRP. The fact that this residue is polymorphic in the human population (R20S) and that it is not conserved in other species suggests that it is likely to be a non-disease causing variant although a rare one.

A hyperfluorescent area, situated at the central macula, of up to half a disc area in size, was seen in the three affected siblings. It was smaller in older individuals and showed hypofluorescence on fluorescein angiography. This clinical sign may represent debris from non-phagocytosed photoreceptor discs lying between the RPE and neurosensory retina with inherent autofluorescence but which masks choroidal fluorescence during angiography. In support, the debris characteristic of the degeneration in the RCS rat retina is

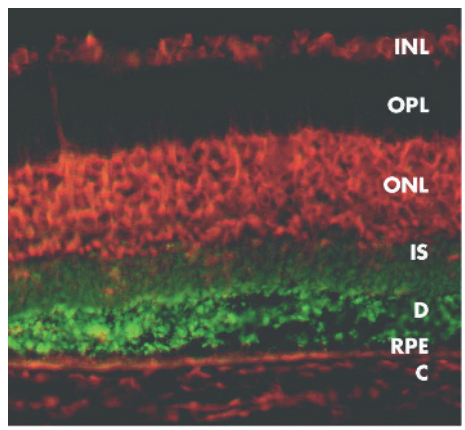

Figure 8 Fluorescence micrograph. The picture was taken of a 5 week old dystrophic RCS rat. Owing to the phagocytotic defect of the RPE cells, a debris layer consisting of broken off outer segment and membranous waste material has accumulated. Photoreceptor outer segments and RPE cells show strong autofluorescence, a characteristic feature of the degenerating retina. INL, inner nuclear layer, OPL, outer plexiform layer, ONL, outer nuclear layer, IS, inner segments, D, debris layer, RPE, retinal pigment epithelium, C, choroid.

also autofluorescent to light of a comparable wavelength (fig 8). However, no such debris layer could be detected on OCT examination. This sign may be useful in the clinical identification of Mertk deficient disease when examining families with RP. It should be emphasised that the appearance of this ring is much smaller than that reported by Robson *et al* and others which can occur in some patients with RP.[12] The homogeneous autofluorescence elsewhere implies that phagocytosis of outer segments is not completely deficient and in this regard would be different from the RCS rat.

The disease observed in the three affected members reported here, appears milder than those previously described for a patient of comparable age with a different *Mertk* genotype (R722X/R844C) who had vision reduced to 20/200 at 13 years and restricted visual fields.[9] In contrast, the oldest member of the present sibship maintained acuites of 20/20 at the age of 18 years with more extensive visual fields. Interestingly, a common feature is the appearance of a ring of RPE depigmentation in a ''bull's eye'' pattern on funduscopy in all four photographed patients which in our family corresponded to the area of hyper-autofluorescence. This difference in severity may be the result of the influence of genetic factors or environmental modifiers on the expression of the Mertk deficiency, and these influences may vary due to differences of ethnicity between reported families. Alternatively, if RNAs expressed from the 2214delT allele were to escape nonsense mediated decay, then part of the tyrosine-kinase domain would remain intact and might result in a partially functioning protein.[13] Partial function is less likely to follow expression of the R722X allele which is significantly shorter, and so this might explain the relative preservation of function of the family presented here compared to that of the case reported by McHenry *et al*.[9]

The decline of retinal function, as measured by electrophysiology, appears at an early stage in this family with loss of both macular and scotopic function at the age of 5 years (IV:9) accompanied by delay in the cone flicker ERG. By the age of 16 years all responses were severely attenuated and delayed. This early dysfunction, in which the rod system is more affected than the cone system, is similar to that seen in the rat and mouse models. The disorder can still progress significantly as the older relative had perception of light in his fourth decade. The preserved visual acuity and field into the second decade suggests that the visual system develops normally, an important consideration given the prospect of therapeutic intervention. The detailed description of the phenotype exhibited by the human *Mertk* mutation described here might assist the identification of eligible patients and families from among the many molecular types of RP.

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