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**Characterization of Severe Rod-Cone Dystrophy in a Consanguineous Family
with a Splice Site Mutation in the *MERTK* Gene**

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25 Key words: *MERTK*, rod-cone dystrophy, retinitis pigmentosa, RCS rat,
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40 **Purpose:** To characterize the ocular phenotype of a family segregating the splice site mutation c.2189+1G>T in the tyrosine kinase receptor gene *MERTK*.

Methods: Five affected children of a consanguineous Moroccan family were investigated by ophthalmic examinations, including fundus photography, autofluorescence (FAF) imaging, optical coherence tomography (OCT),
45 psychophysical and electrophysiological methods.

Results: Affected children were between five and 19 years of age, allowing an estimation of disease progression. Electroretinography demonstrated loss of scotopic and photopic function in the first decade of life. Younger siblings showed drusen-like deposits with focal relatively increased FAF in the macular area. With increasing age,
50 a yellowish lesion with relatively increased FAF and subsequent macular atrophy developed. Visual acuity deteriorated with age and ranged between 20/50 in the best eye of the youngest affected and 20/400 in the worst eye of the oldest affected sibling. Spectral-domain OCT revealed debris-like material in the sub-neurosensory space.

55 **Conclusion:** The splice site mutation c.2189+1G>T in *MERTK* causes rod-cone dystrophy with a distinct macular phenotype. The debris in the sub-neurosensory space resembles that in the Royal College of Surgeons (RCS) rat being the *merlk* animal model. Patients might therefore benefit from advances in gene therapy that were previously achieved in the RCS rat.

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Mutations in the *MERTK* gene cause retinal dystrophies in humans as well as in animal models.¹⁻⁷ The gene product, a tyrosine kinase receptor, consists of an intracellular kinase domain, a transmembrane region, and an extracellular domain.^{8;9} During the physiological renewal of photoreceptor outer segments, membrane discs
70 are shed and phagocytised by the retinal pigment epithelium (RPE) cells. *MERTK* plays a key role in this process by triggering photoreceptor outer segment ingestion.¹⁰

Mutation in *merlk* causes spontaneous retinal degeneration due to impaired phagocytic activity of RPE cells in the Royal College of Surgeons (RCS) rat.¹ In this
75 widely used animal model, shed membranes from photoreceptor outer segments accumulate in the sub-neurosensory space,¹¹ and photoreceptor cells subsequently undergo apoptosis.¹² The retinal pathology of the RCS rat has been studied extensively,^{11;13;14} and treatment strategies for retinal degenerations, including gene therapy, have been investigated.¹⁵⁻¹⁷ Specifically, viral-mediated gene therapy as a
80 treatment of patients with retinal dystrophy due to mutations in *MERTK* appears to be feasible, since the introduction of the gene into the eyes of juvenile rats, which already display significant pathology, resulted in areas of near normal-appearing retina.¹⁵

In 2000, Gal and co-workers identified human mutations in the *MERTK* gene
85 in patients with recessively inherited panretinal dystrophy.² This was the first conclusive evidence implicating RPE-mediated outer segment phagocytosis pathway in human retinal disease. Subsequently, other groups have also reported *MERTK* mutations in patients with panretinal dystrophies.^{3;4;6;7} In order to select patients who might benefit from future gene-specific therapies, accurate phenotyping appears
90 crucial.

Here, we present detailed characteristics of the ocular phenotype in eight members of a consanguineous Moroccan family previously described by our group segregating a splice site mutation in *MERTK*.¹⁸ The mutation, c.2189+1G>T, results in skipping of exon 16 with a subsequent frameshift and predicted shortening of the protein to 696 residues (wildtype: 999 residues). Five out of six children carry the mutation in homozygous state and developed cone rod dystrophy. The age of the patients ranged from five to 19 years, allowing an estimation of disease progression which is further substantiated by longitudinal data in a subset of affected siblings.

Methods

All family members underwent detailed clinical investigation including best-corrected visual acuity (VA), slit lamp examination, and stereoscopic funduscopy. Goldmann kinetic fields were obtained with the targets III4e, I4e, and I2e on a standard background with the exception of patients II:1 and II:2.

Electroretinography (ERG) was carried out in accordance with the International Society for Clinical Electrophysiology of Vision (ISCEV) standard,¹⁹ beginning after 30 minutes of dark adaptation using 10 msec xenon flashes in a Ganzfeld bowl. Pupils were fully dilated using phenylephrine (10%) and tropicamide (1%), and Burian-Allan bipolar corneal electrodes were applied after topical anesthesia with propacaine (0.5%). Retinal imaging included digital fundus photography (Zeiss FF450; Zeiss, Oberkochen, Germany), fundus autofluorescence imaging (FAF) by means of confocal scanning laser ophthalmoscopy (cSLO, HRA2 or Spectralis HRA-OCT, Heidelberg Engineering, Heidelberg, Germany) and time domain optical coherence tomography (OCT; Stratus OCT; Zeiss, Oberkochen, Germany). During acquisition of FAF images, the software allows to digitally enhance

image contrast by assigning 255 gray values even if the difference between the lowest and the highest gray value is very low ("image normalization"). Absolute FAF intensity can not be analyzed quantitatively from images recorded with the cSLO.²⁰ However, the required setting of the signal detector allows a rough estimation of the FAF intensity, and when image normalization is deactivated, relative intensity within a region of interest of a given image can be evaluated. All FAF images are composed of multiple averaged images resulting in an increased signal to noise ratio. Additional high resolution spectral domain OCT imaging (Spectralis HRA-OCT, Heidelberg Engineering, Heidelberg, Germany) was performed in family members II:4 and II:5 who were available for a follow up examination two years later. The study was conducted in adherence to the tenets of the Declaration of Helsinki and was approved by the Ethics Committee, University of Bonn.

Results

None of the family members had a significant history of systemic diseases or of medication. Only the parents (being heterozygous) and the second youngest sibling (carrying the wild type allele homozygously) were unaffected (the pedigree is shown in supplementary Fig. 1). The epidemiological data are summarized in Table 1.

The parents (I:1 and I:2) as well as one son (II:2) did not complain about visual symptoms. Visual acuity was 20/20 bilaterally in both parents and 20/25 bilaterally in the healthy son. Kinetic perimetry as well as colour vision were normal in these three family members who had no visual complaints. In all three, ophthalmoscopy, OCT and FAF imaging showed normal findings.

Pedigree no.	Age	Sex	VA	Refraction spheric / cylindric		Colour vision Ishihara test plates
				right eye	left eye	
I-1	46	M	20/20 20/20	+0.5 / -0.5	+0.5 / -1.0	1
I-2	37	F	20/20 20/20	-1.25 / -0.25	-1.25 / -0.5	1
II-1	5	M	20/50 20/63	not performed (np)		np
II-2	6	M	20/25 20/25	np		np
II-3	9	M	20/50 20/63	-2.5 / -1,25	-1.5 / -1,0	2
II-4	16	M	20/200 20/50	0 / -1.0	0 / -0.75	2
II-5	18	M	20/50 20/50	-2.0 / -2.0	-1.5 / -2.5	2
II-6	19	F	20/100 20/400	0 / -2.5	0	2

Table 1: Descriptive data of the consanguineous family with severe rod-cone dystrophy with a splice site mutation in the *MERTK* Gene. Bold pedigree number (according to supplementary Fig. 1): affected family member. VA: visual acuity.

145 Coding of colour vision: 1 = no significant errors. 2 = no number recognized.

Visual symptoms in family members with visual impairment were first noted in the first or early second decade of life. The 16 years old son (II:4) reported a decrease in visual acuity for the last 3 years. Reading was still possible. The oldest sibling (II:6) reported deteriorating visual acuity over the last years as well as poor orientation in the dark.

The findings of the individual examinations in family members with retinal disease were as follows:

- **Visual acuity** (Table 1) in the better eye was reduced to 20/50 in the two youngest siblings and to 20/100 in the oldest sister. In the fellow eye, VA was

20/63 in the youngest to 20/400 in the oldest siblings. Two brothers were available for a follow up examination two years later. In II:4, visual acuity had deteriorated to 20/400 in the right eye and to 20/63 in the left eye. In II:5, it had decreased to 20/400 in the right eye and remained 20/50 in the left eye.

- 160 • **Nystagmus** was not observed in any of the affected family members.
- **Goldmann kinetic perimetry** (Fig. 1) was relatively well preserved for Goldmann III4e, but showed variable concentric constriction for the test stimulus I4e. Due to insufficient cooperation, perimetric examination was not possible in the two youngest brothers.
- 165 • **Biomicroscopy:** In all affected siblings, a posterior subcapsular cataract, vitreous destructions and vitreous cells were present to different degrees. The retinal vessels were only mildly attenuated, and there was no significant optic disc pallor. Ophthalmoscopy revealed increased reflectivity with a wrinkled appearance of the inner retina which was accentuated at the posterior pole (Fig. 2A-D). In the
170 youngest patient (II:1), the macula showed white-yellowish small subretinal deposits (Fig. 2A) that showed increased FAF (see below). In the older siblings, a yellowish macular atrophy had developed that was most severe in the oldest affected patient (II:6) who, in addition, showed crystalline retinal deposits. There was apparent salt-like pigment mottling at the midperiphery in the three oldest
175 siblings (Fig. 2E-G). Only in patient II:6, there was focal intraretinal bone spicule-like pigment clumping in the outer periphery of the left eye (Fig 2G).

At the follow up examination of II:4 and II:5 two years later, both showed progression of the retinal findings. In II:4, the atrophy had enlarged and a multitude of superficial retinal crystalline deposits were visible at the posterior
180 pole, now resembling the findings in the eldest sibling (II:6) two years earlier.

There was now also few intraretinal pigment clumping surrounding peripheral retinal vessels. In II:5, small atrophic patches of the central retina had developed that were similar to the findings in II:4 in the baseline assessment.

- **FAF-imaging** (Fig. 3) revealed spotted increased FAF at the posterior pole (relative to the adjacent areas) in II:1 and, to a lesser degree, in II:3. In these two individuals, there was a small central spot of decreased FAF surrounded by an increased FAF. The older siblings showed patches of decreased FAF corresponding to the funduscopically visible atrophic areas. These patches were surrounded by focally (relatively) increased FAF. Around this area, there was a ring of decreased FAF. The FAF signal was generally low compared to a normal control (Fig. 3I,J).
- **OCT-imaging** revealed thinning of the neurosensory retina that was mainly confined to the outer retina with a thinned outer nuclear layer and major alterations external to the external limiting membrane. Spectral domain OCT images were available from subjects II:4 and II:5 and revealed debris-like material in the sub-neurosensory space. (Fig. 4). The hyper-reflective border between inner and outer photoreceptor segments that usually is visible on spectral domain OCT-scans was absent. Underneath the preserved external limiting membrane there was debris-like material in the sub-neurosensory space. Moreover, a peculiar wavelike appearance of the innermost neurosensory retina was present correlating to the wrinkled appearance of the inner retina on funduscopy.
- **ERG** (Fig. 5) showed a marked reduction of the cone specific b-wave amplitudes and absence of the rod specific b-wave in the youngest sibling (Patient II-1). In all other affected siblings, scotopic and photopic ERG responses were

undistinguishable from noise. Recordings of unaffected family members were in agreement with normative data. ERG responses were consistently reproducible.

Discussion

This study describes the specific phenotype of a rod-cone dystrophy with macular atrophy due to a recessive splice site mutation in *MERTK*. Five affected siblings at ages between five and 19 years were examined. Thus, the family provided a model to obtain quasi-longitudinal data of disease progression due to the c.2189+1G>T mutation in *MERTK*. The phenotype was indeed least severe in the youngest and most advanced in the oldest affected sibling, indicating progression of the disease during the natural history. This was further substantiated by longitudinal data in II:4 and II:5 exhibiting definite disease progression.

Gal and co-workers screened *MERTK* in 328 DNA samples from patients with various retinal dystrophies and found three mutations in three individuals with autosomal recessive retinitis pigmentosa.² In these patients, poor vision and night blindness were already present in childhood; however, the retinal phenotypes were not presented in detail. Two recent reports found further disease-associated *MERTK* mutations and characterized the retinal dystrophies of the respective patients: McHenry et al. described a female patient with severe early-onset rod-cone dystrophy and nystagmus.⁴ Her fundus showed disc pallor, vessel narrowing, bull's-eye macular atrophy, bone spicule pigment in all quadrants, dense parafoveal pigmentation, and heavy RPE granularity throughout the fundus. The visual field was constricted concentrically and the ERG showed a complete loss of responses to all rod and cone stimuli. Tschernutter and co-workers screened 96 patients with retinal dystrophy and identified one novel frame-shifting deletion in *MERTK* causing retinitis

pigmentosa.³ The researchers presented the first detailed clinical characterization of the retinal dystrophy associated with *MERTK* mutation in four affected members of a Middle Eastern family. As in the family presented herein, the patients reported first symptoms around the age of 10 years, and there was disease progression over time.³ In a 46 year old family member, visual function was reduced to perception of light. The phenotype of the family including FAF was very similar to our cases. Interestingly, their patients also had relatively preserved peripheral visual fields and a relatively increased FAF signal in the central macula. These findings, together with the generally reduced FAF signal, might be characteristic for retinal dystrophies associated with *MERTK* mutations and could be useful to distinguish these patients from other diseases such as RP or cone dystrophies due to other causative gene mutations. It appears that in *MERTK*-unrelated retinal dystrophies, FAF may show a well-defined ring of increased FAF that has no obvious correlate on fundus biomicroscopy.²¹ Furthermore, the perimetric hallmark of RP are concentrically constricted visual fields.

However, the expressivity of the retinal dystrophy due to mutations in the *MERTK* gene appears to be variable. Initial reports on human *MERTK* mutations^{2;4} described a more severe phenotype compared to the patients presented in our report and by Tschernutter and co-workers. Therefore, different *MERTK* mutations may be associated with different disease severity. However, as all mutations including the one described herein are truncating, there is no obvious genotype-phenotype correlation with respect to the mutation type.

Royal college of surgeon rats show debris in the subretinal space, most likely due to the inability of the pigment epithelium to clear shed photoreceptor outer segments.^{11;13} In two affected patients, spectral domain technology was used to

obtain cross sectional high-resolution images of the retina. The decrease in retinal thickness, mainly due to atrophy in the outer retinal layers is in accordance with histological findings in RCS rats. Moreover, there appeared to be subneurosensory debris which most likely is analogous to the debris found in RCS rats.^{11;13} This finding strongly supports the similar pathophysiology and biological consequence of the panretinal dystrophy due to a *MERTK* mutation in the RCS rat and humans. It furthermore makes viral-mediated gene therapy a therapeutic option for affected patients, since gene therapy experiments yielded very successful results in the RCS rat.¹⁵⁻¹⁷ Very recently, Bainbridge and co-workers reported promising results treating human panretinal dystrophies due to mutations in the *RPE65* gene by subretinal administration of recombinant adeno-associated virus vector.²² Their findings certainly support the research efforts to establish gene therapy for retinal dystrophies due to loss-of-function mutations in retinal disease genes. Identifying patients for such therapeutic intervention may turn out to be challenging and specific phenotypes may be crucially important. Our study provides evidence suggesting that such specific phenotypes can be identified especially by using multimodal retinal imaging techniques.

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Competing interest:

None of the authors has a conflict-of-interest or a financial conflict to disclose.

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Figure Legends

Figure 1

Goldmann Kinetic perimetry of the 16 years old patient II:5. The outer boarder for the testing stimulus III/4 shows a marginal concentric constriction. However, isopters for the stimulus I/4 and I/2 are markedly altered, showing a pronounced concentric constriction. The hatched field (stimulus III/4) marks the increased blind spot.

Figure 2

A-D: Central fundus photography of four of the five siblings with rod-cone dystrophy with macular atrophy due to a mutation in the *MERTK* gene. In the youngest brother (A, 9 years old), there are subretinal white-yellowish deposits. With increasing age, a yellowish macular atrophy becomes evident. The retinal surface shows an increased reflectivity with a wrinkled appearance at the posterior pole. Sibling II/4 has a slightly tilted disc which simulates temporal paleness. E-G: Peripheral fundus photography in two older siblings. A salt-like pigment mottling of the midperiphery is evident. Intraretinal pigment clumping was present only in the oldest sibling II:6 at one location (G).

Figure 3

Normalized fundus autofluorescence (FAF) images of the unaffected father (A) and all five affected siblings at first presentation (B-F). In the youngest, spotted increased FAF signal at the posterior pole was most apparent. Such focally increased FAF signal was not detected in the oldest siblings, in which central chorioretinal atrophy was present. Such atrophic areas may show adjacent patches of increased FAF.

At a follow up examination of II:4 and II:5 two years after baseline presentation, both showed progression of the atrophic macular alterations now resembling the findings in more affected siblings two years earlier (G,H). Asterisk (H): congenital hyperplasia of the retinal pigment epithelium (CHRPE) as a finding unrelated to the retinal dystrophy.

In affected family members, disregarding the relatively increased FAF signals, the overall FAF intensity was poor, and the acquisition settings had to be near the maximum sensitivity of the system. This is shown by recordings without image normalization of the left eyes of II:5 (additional four months after the recordings shown in (H)) and a male control subject of the same age, both having clear optical media (I,J). The laser power (excitation light) was constant, and images were acquired in succession without changing the settings of the detector sensitivity. If the latter resulted in a desirable signal in the control subject, the signal in the patient with the *MERTK* mutation was very low (I). A detector sensitivity set to its maximum resulted in an apparently close to normal overall signal strength, however, the same setting showed strong overexposure in the normal control subject (J). This implies that even such focal areas exhibiting a relative increase in FAF may indeed have a (sub-) normal FAF signal compared to normal.

Figure 4

Spectral domain optical coherence tomography in the two affected siblings II:4 (A) and II:5 (B). The black lines superimposed on the confocal infrared reflectance image show the location of the respective OCT scans. The black cut outs in A3 and B1 mark the area that is enlarged to point out retinal alterations in detail. There is wrinkling of the inner neurosensory surface and thinning of the outer retinal layers.

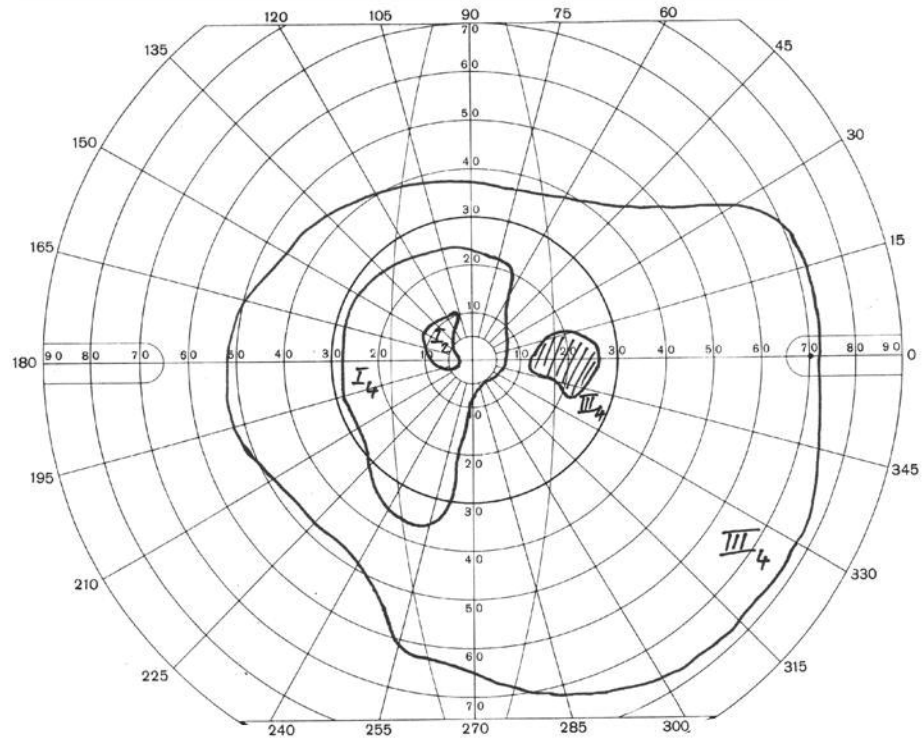
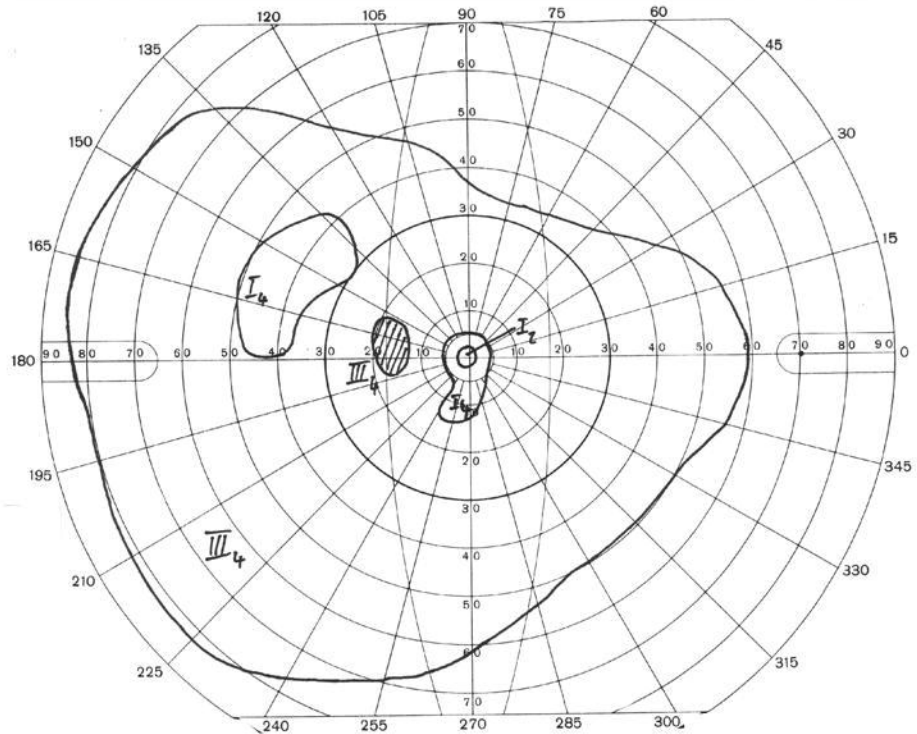
The external limiting membrane is continuously defined (arrow), but the hyperreflective line that usually marks the border between inner and outer photoreceptor segments is absent. Most notably, there is debris-like material in the sub-neurosensory space.

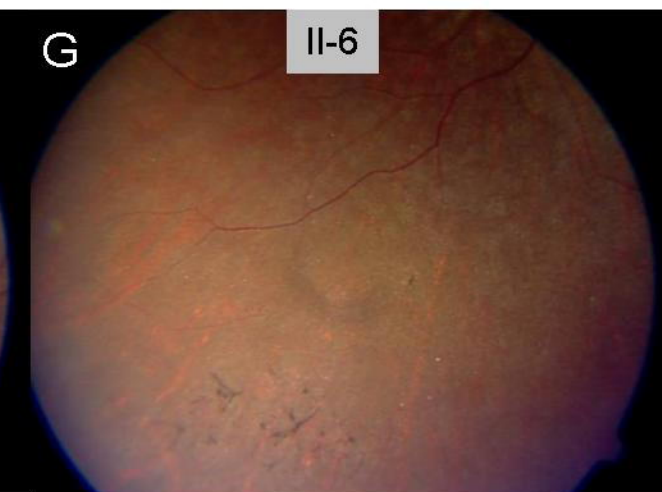
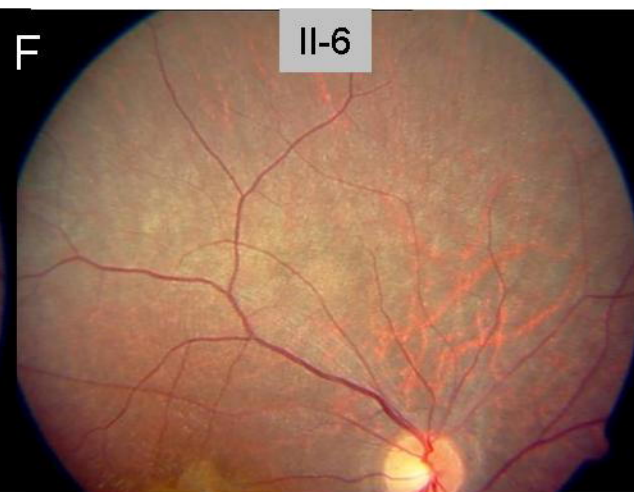
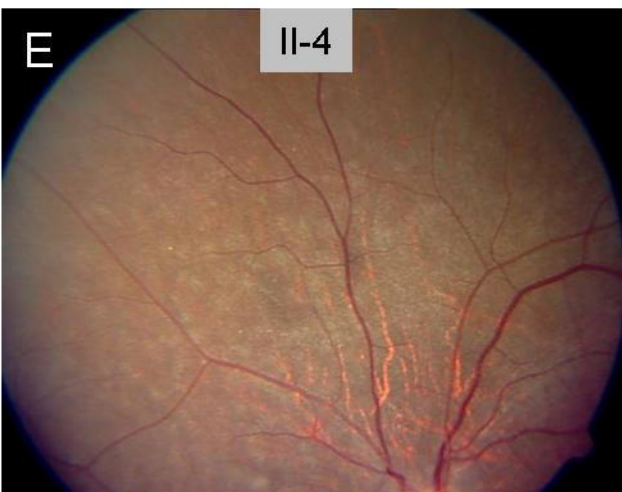
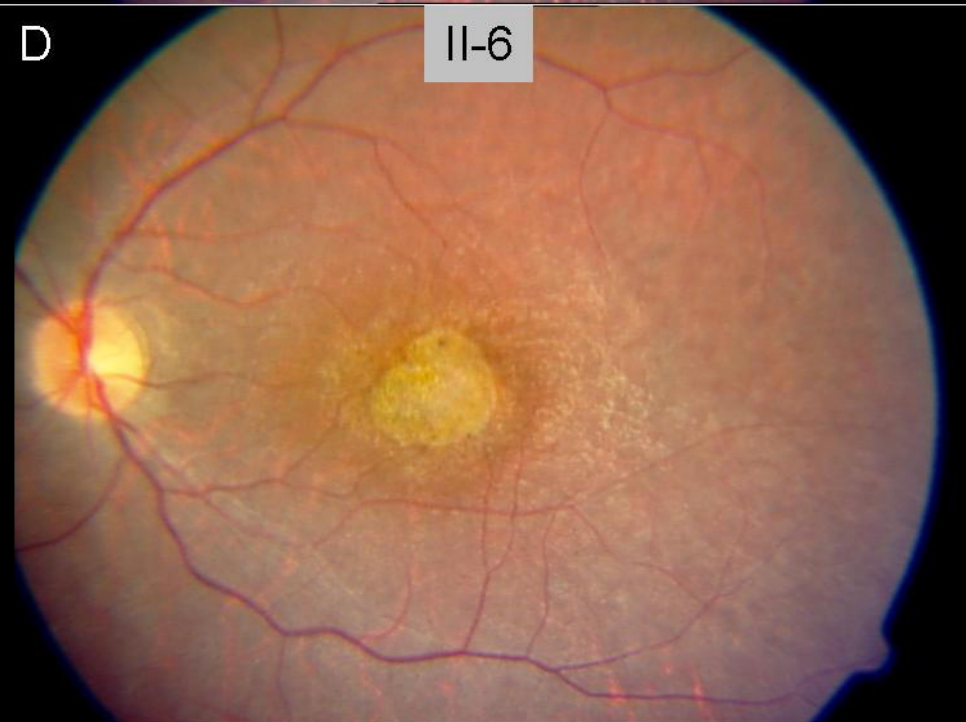
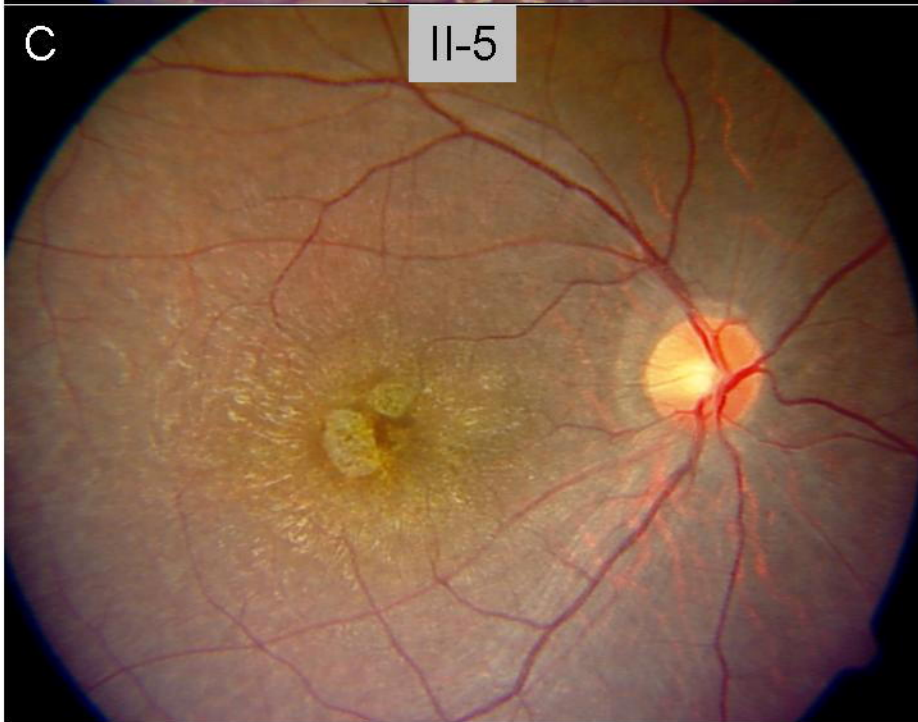
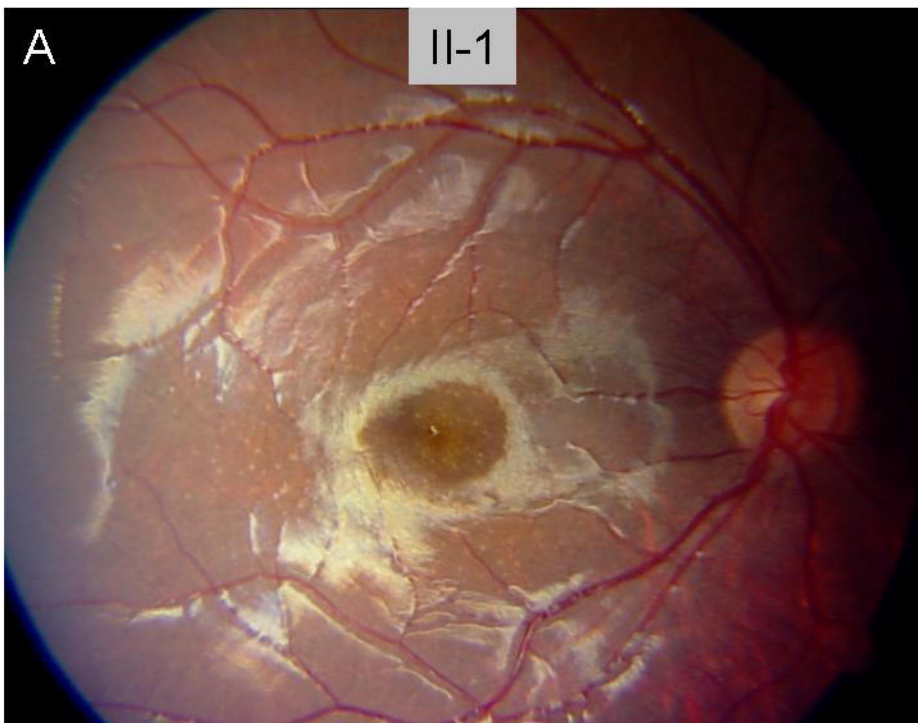
Figure 5

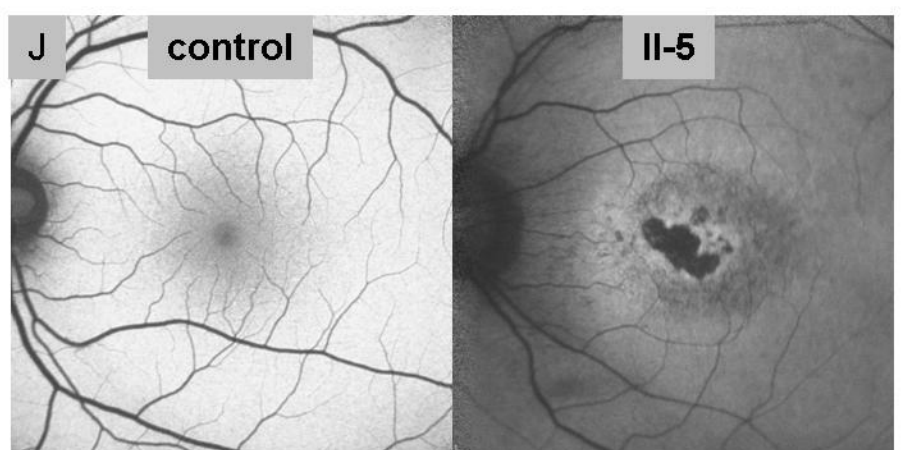
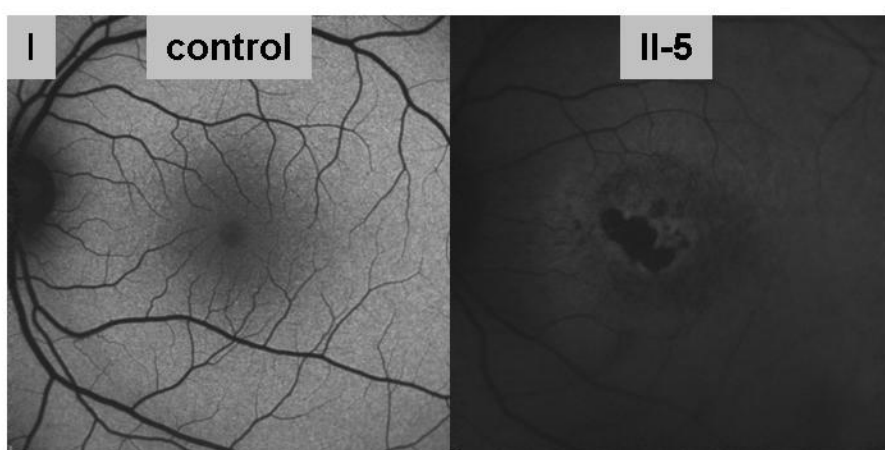
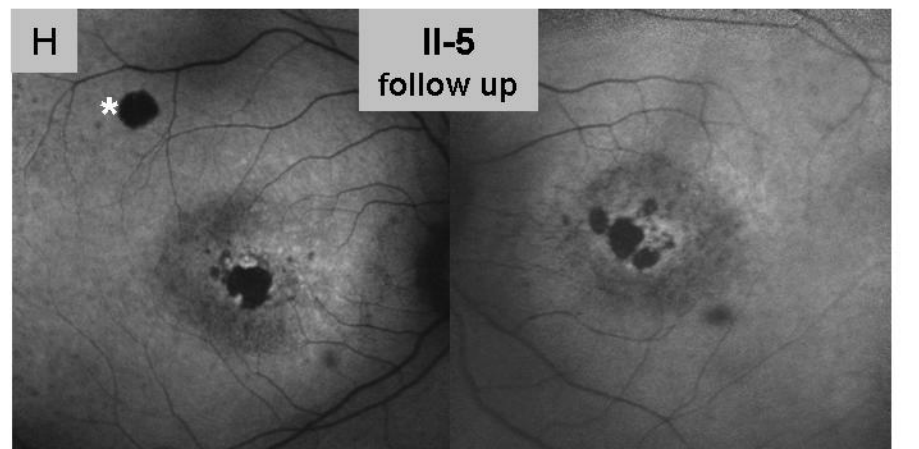
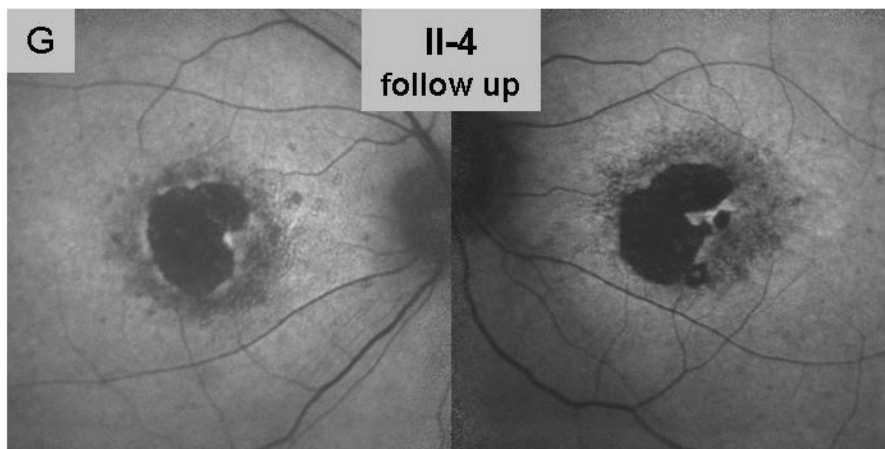
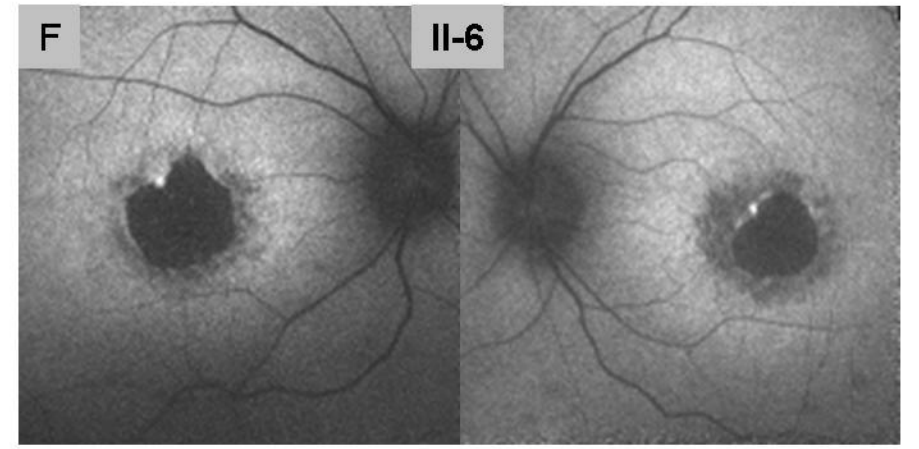
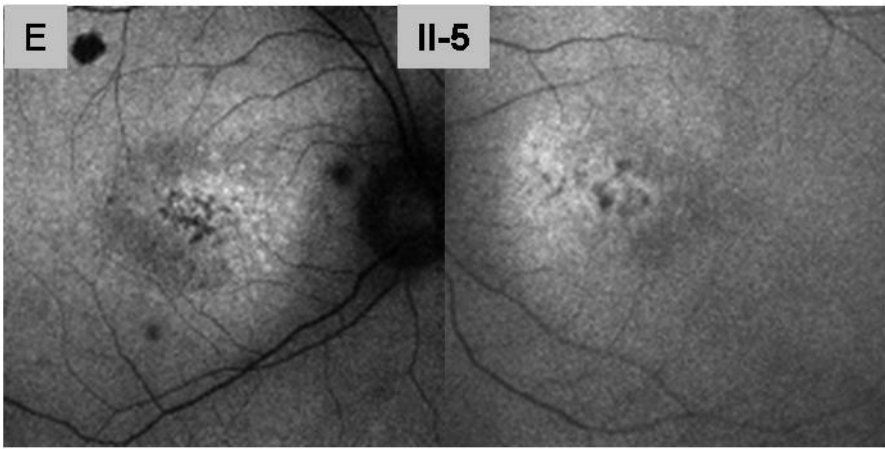
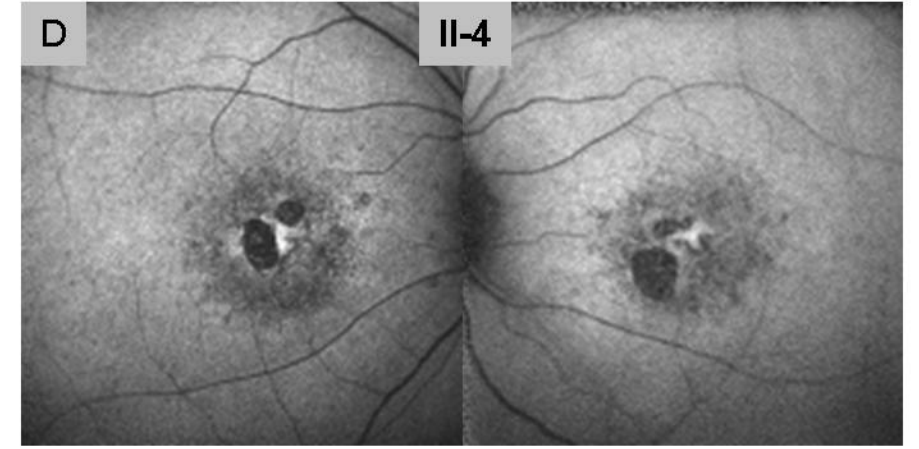
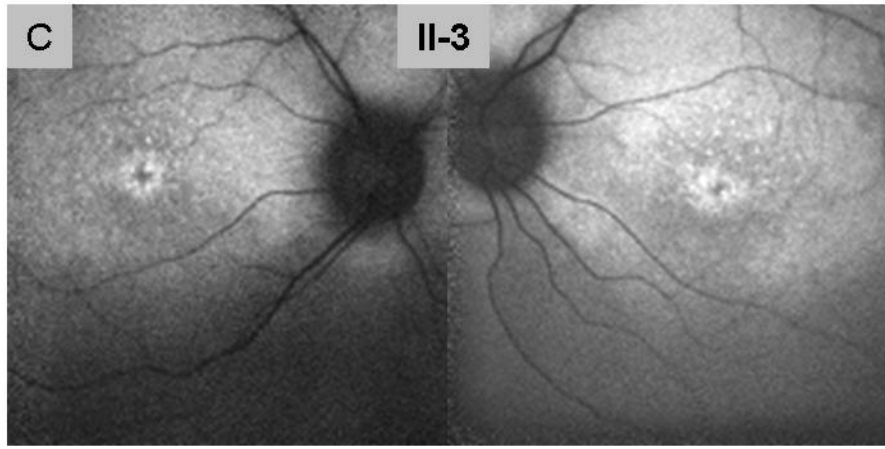
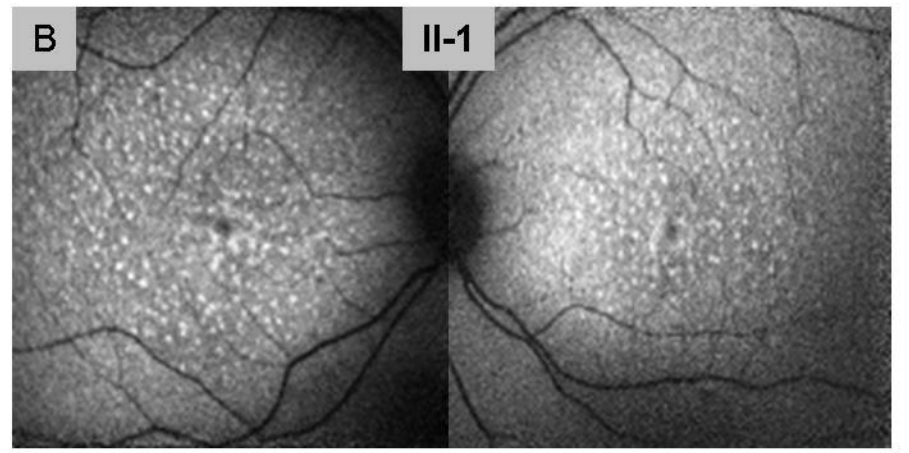
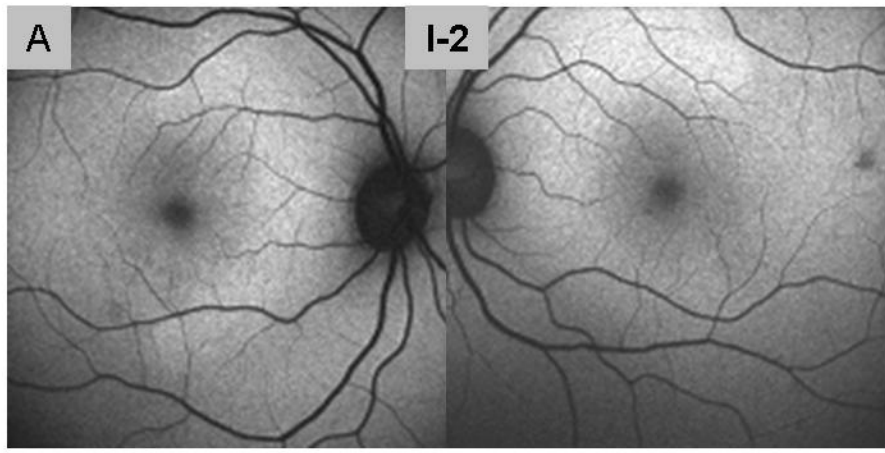
Electroretinography of the unaffected as well as of the youngest and oldest affected siblings with rod-cone dystrophy due to a mutation in the *MERTK* gene. There is a marked reduction of the cone specific b-wave amplitudes and an absent rod specific b-wave in the youngest sibling (II-1). In II:6, all ERG responses were undistinguishable from noise. All unaffected family members revealed ERG recordings in agreement with normative data

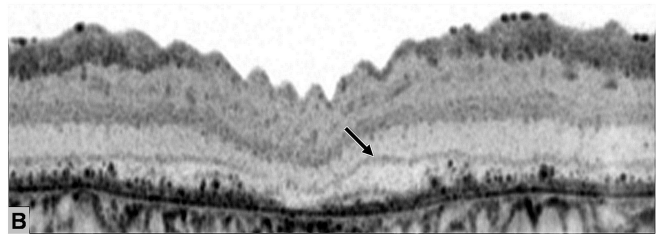
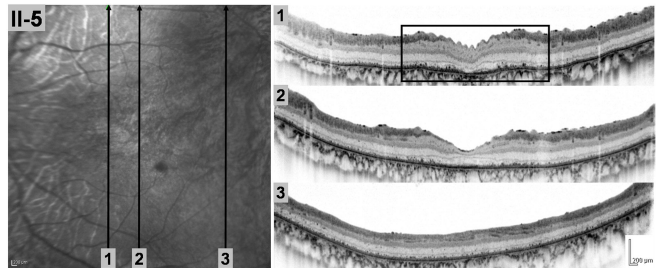
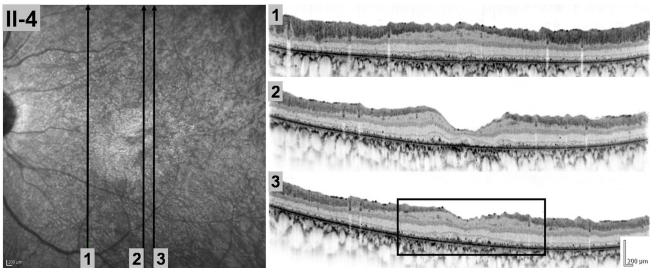
Supplementary Figure 1

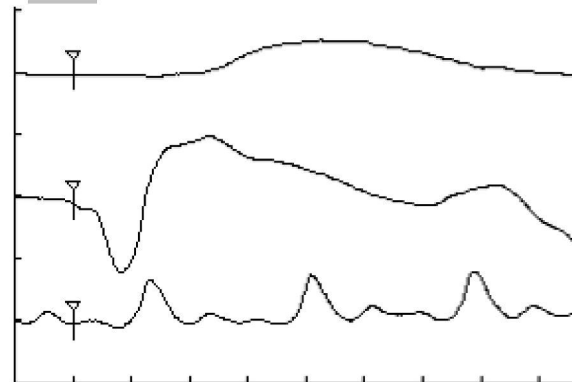
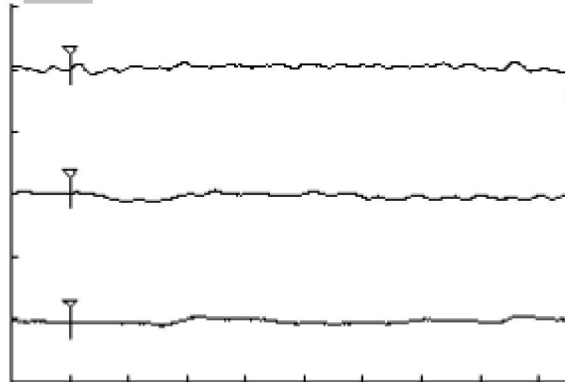
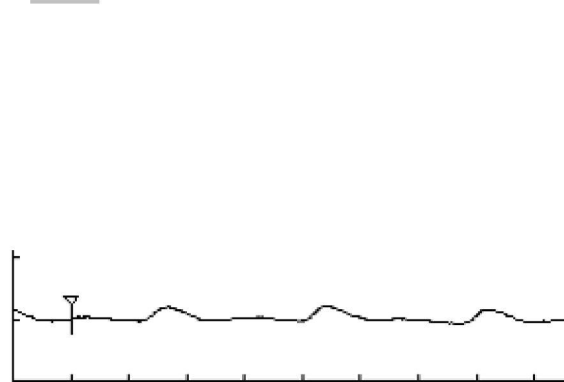
Four generation pedigree of a Moroccan family with autosomal recessive rod-cone dystrophy due to a mutation in the *MERTK* gene.









II:2**II:6****II:1**
**normative
values**
I:1**I:2****II:3-6****II:2****II:1**scotopic b-wave amplitude [μ V]

202 - 380

218 / 367

351 / 425

not detectable

245 / 236

not detectable

mixed response b-wave amplitude [μ V]

368 - 585

342 / 365

523 / 602

not detectable

543 / 436

71 / 117

photopic b-wave amplitude [μ V]

42 - 112

57 / 72

87 / 97

89 / 77

10 / 22

increased implicit
time