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Thr4Lys rhodopsin mutation is associated with autosomal dominant retinitis pigmentosa of the cone-rod type in a small Dutch family

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Abstract A mother and daughter with autosomal dominant retinitis pigmentosa (adRP) were found to carry a cytosine-to-adenine transversion mutation at codon 4 of the rhodopsin gene. This mutation predicts a substitution of lysine for threonine at one of the glycosylation sites in the rhodopsin molecule (Thr4Lys). Both patients presented with a similar phenotype including a tigroid pattern of the posterior pole and a regional predilection for degenerative pigmentary changes in the inferior retina with corresponding visual field defects. The electroretinographic pattern was suggestive of RP of the cone-rod type. This report documents the clinical findings associated with this defined mutation of the rhodopsin gene.

Key words Retinitis pigmentosa; autosomal dominant inheritance; rhodopsin mutation; cone-rod type

Introduction Retinitis pigmentosa (RP) is a clinically and genetically heterogeneous group of retinal degenerations.¹ Affected individuals typically report night blindness followed by visual field loss in adolescence. The mode of inheritance is either X-linked, autosomal recessive or autosomal dominant.

The autosomal dominant (ad) form accounts for about 25% of all RP cases.² Approximately 30% of the adRP families have mutations in the rhodopsin gene on chromosome 3q encoding the rod photoreceptor specific pro-

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tein rhodopsin. Rhodopsin is a transmembrane protein which, when photo-excited, initiates the visual transduction cascade. So far, more than 40 different mutations have been identified throughout the coding region of the rhodopsin gene.² For many of these mutations the ocular features have been described in detail.³⁻¹⁶ Some of the mutations cause a diffuse type of RP (type 1), while others lead to a regional (type 2) or sectoral form. Type 1 is characterized by childhood onset of night blindness and early and diffuse loss of rod sensitivity with a loss of cone sensitivity later.¹⁷ Type 2 adRP is characterized by onset of night blindness in adulthood with a more regionalized and simultaneous loss of rod and cone sensitivity.¹⁷ In sectoral RP the retinal degeneration is usually limited to the inferonasal quadrants with subnormal electro-retinographic responses.¹⁸ Not all rhodopsin mutations, however, manifest an RP phenotype; two missense mutations have been reported recently in cases with the clinical characteristics of congenital stationary night blindness.^{19,20}

Here, we report the ocular features associated with a transition of cytosine-to-adenine in codon 4 of the rhodopsin gene, resulting in a threonine-to-lysine (Thr4Lys) substitution at one of the glycosylation sites of the rhodopsin molecule.²¹ Patients with the Thr4Lys mutation appear to have RP with regional predilection for degenerative pigmentary changes and a cone-rod pattern in the ERG.

Material and methods

FAMILY AND DNA STUDIES Blood samples were collected from 22 different families with adRP registered at the Department of Ophthalmogenetics of The Netherlands Ophthalmic Research Institute. All individuals involved gave informed consent for DNA and clinical studies. Bunge *et al.*²² screened DNA of one affected individual from each family for mutation in the rhodopsin gene by heteroduplex and single-strand conformation polymorphism analyses. DNA samples showing an altered pattern in either of these tests were directly sequenced after PCR amplification of the corresponding rhodopsin exon (for molecular genetic methods see ref. 22).

OPHTHALMOLOGICAL STUDIES All members of the family described were questioned about complaints of poor night vision and visual field loss, and the age of onset of these. Best corrected visual acuities were obtained with ETDRS Light House Charts. Color vision was tested with the Ishihara Test for Colour Blindness and Lanthony's Desaturated 15 Hue Test according to Farnsworth-Munsell. Slitlamp examination of the anterior segment, lens, and vitreous body was performed. Applanation tonometry was used to record the intraocular pressure. A dilated fundus examination with direct and indirect ophthalmoscopy was used to detect any retinal abnormalities, which were subsequently documented by color fundus photography.

Ganzfeld electroretinograms (ERG) were obtained in all persons with Dawson Trick Litzkow electrodes according to the ISCEV protocol.²³ Stimulus duration was less than 80 ms with 2-s intervals. The ERG recording included an isolated cone response with the use of a 30 cd.m⁻² background illumination and a white flash of 1.9 cd.m⁻².s. Cone responses were also evaluated with a 30 Hz flicker of the same intensity. After 30 minutes of dark adaptation, isolated rod responses were measured using a 0.002 cd.m⁻².s (−3

log units) and a $0.02 \text{ cd.m}^{-2}.\text{s}$ (-2 log units) flash. Mixed cone and rod responses were obtained with flashes of $0.2 \text{ cd.m}^{-2}.\text{s}$ (-1 log units) and the $1.9 \text{ cd.m}^{-2}.\text{s}$ flash. ERG responses were amplified (5,000 times), digitized and averaged ($N > 10$) for display and storage. Normal values were obtained from 20 control subjects aged between 18 and 61 years.

Goldmann perimetry was performed using V-4-e, III-4-e and I-4-e targets. Both affected persons underwent photopic (stimulus size III) and scotopic (30 minutes dark adaptation) static perimetry with a Humphrey field analyzer (30-2 Program). Scotopic perimetry was conducted on a modified Humphrey field analyzer. A 3.6 log unit ND filter was placed into the projection arm filter holder. The stimulus bulb operated at 3.5 Volts. A custom ROM chip set was provided by Allergan Humphrey to avoid the calibration procedure for the background illumination. Background lights were switched off and it was made sure that no light from the perimeter itself could interfere with scotopic conditions. The stimulus consisted of white light (effective wave length 520 nm), the size was V and stimulus duration was 200 ms. The average sensitivity in 20 normal subjects varied from 36.1 to 41.3 dB. Standard deviations varied from 3.4 dB in the central localizations to 6.0 dB in the peripheral ones. The defects in the two RP patients were expressed in deviation (in dB) from the average sensitivity in normals. A Goldmann Weekers' dark adaptation curve was obtained in one affected person using an 11 degrees target 15 degrees below fixation point. Before dark adaptation the affected person was light adapted for 10 minutes with 3,000 lux. Dark adaptation curves of 21 normal subjects and the affected person were evaluated by curve fitting two independent exponential decay functions to both branches of the curve. This way a characteristic time constant (τ) and a final threshold (Th) for both cones and rods can be estimated.²⁴ For the cones this yielded for $\tau_{\text{cones}} = 0.51 \pm 0.15$ minutes and $\text{Th}_{\text{cones}} = 4.5 \pm 0.21 \text{ Log(I)}$. For the rods these figures were $\tau_{\text{rods}} = 8.3 \pm 2.5$ minutes and $\text{Th}_{\text{rods}} = 1.5 \pm 0.4 \text{ Log(I)}$.

Results

FAMILY AND DNA FINDINGS The index case (II-4) (Fig. 1) was found to carry a point mutation (C to A) at codon four in the first exon of the rhodopsin gene predicting the amino acid substitution Thr4Lys. To study segregation of the mutation with the disease phenotype, DNA samples of other family members were analyzed. The same mutation was identified in the clinically affected daughter, case III-1, while it was absent in cases II-2, II-3, and III-2 (Fig. 1) (for details on the molecular analysis see ref. 22). Although RP cases have been detected only in two subsequent generations, the nature of the mutation suggests an adRP.

OPHTHALMOLOGICAL FINDINGS Case II-4 was a healthy 58-year-old female, who was diagnosed as having RP at 41 years of age. In retrospect she remembered having dark adaptation problems from her 30th year onwards. Visual field impairment had been noticed a few years later. After a blunt injury of the right eye, she developed a cataract for which an extracapsular cataract extraction with posterior chamber implant took place at the age of 51 years. Her most recent recorded visual acuity was 20/50 in the right and 20/32 in the left eye. She missed all plates of the Ishihara color vision test,

Fig. 1. Pedigree of the family with Thr4Lys rhodopsin mutation.

Fig. 2. Fundus photograph of the right eye of case II-4, 58 years of age, with Thr4Lys rhodopsin mutation. Note the round areas of retinal pigment epithelium and choroidal atrophy with bone-corporuscle pigmentations.

while the desaturated D-15 panel showed some aspecific mistakes in the right and a tritanomalous defect in the left eye. Biomicroscopy revealed an intraocular posterior chamber lens in the right eye and a small central subcapsular cataract in the left eye. Intraocular pressures were normal. The vitreous body of both eyes contained sporadic cells. On fundoscopy the optic discs were of normal color. The arterioles appeared attenuated. Foveal hypopigmentation was present in both maculae together with preretinal fibrosis and surface wrinkling of the right macula. Paramacularly there was a tigroid pattern of the retinal pigment epithelium (RPE), which extended just beyond the vascular arcade of both eyes. Drusen-like deposits were visible at the border between hypopigmented and normal looking RPE in the superior retina. Bone-corporuscle pigmentations were located inferiorly with cobblestone-like degenerations (Fig. 2). On ERG, the a-b wave amplitude of the cone response was more reduced than the onset-b wave amplitude of the rod ERG (85% and 75% reduction from average, respectively) (Table 1, Fig. 3b). Cone-implicit times were prolonged, while rod implicit times were within normal range. Goldmann perimetry showed arcuate loss of the visual field in the superior hemisphere (Fig. 4) and central sensitivity loss of 15 dB, which was confirmed by static threshold perimetry. The latter might explain why this case (II-4) missed all plates of the Ishihara color vision test, since for this test more central visual field is necessary than for the Desaturated 15 Hue Test according to Farnsworth-Munsell. Dark adapted threshold perimetry, recorded with the Humphrey field analyzer, showed no measurable rod function in the superior hemisphere and an average threshold elevation of 15 dB in the inferior hemisphere.

In case III-1, 27 years of age, the diagnosis of RP was established due to complaints of decreased visual acuity when she was 19 years of age. She had never noticed any night blindness nor visual field loss. Visual acuity was 20/16 in the right and 20/20 in the left eye. Color vision was normal. Slit-lamp examination and intraocular pressures were normal. On ophthalmoscopy both

case no	age years	eye	scotopic											
			photopic cone-mediated ¹						rod-mediated ²					
			a-wave amp uV	a-wave imp ms	b-wave amp uV	b-wave imp ms	30Hz amp uV	30Hz imp ms	b-wave amp uV	b-wave imp ms	b-wave amp uV	b-wave imp ms	a-wave amp uV	a-wave imp ms
I1-4	58	R	5	21	21	37	17	38	20	99	63	104	7	32
		L	6	21	17	37	14	36	20	99	63	104	13	26
I11-1	27	R	18	20	26	34	22	30	45	115	102	74	36	27
		L	10	15	31	33	20	31	44	106	91	71	29	27
normals mean			30	16	123	31	67	29	85	115	230	83	48	29
mean±2SD			14	18	47	33	25	31	21	133	83	97	0	33
											b-wave amp uV	b-wave imp ms	a-wave amp uV	a-wave imp ms
											62	63	14	25
											88	66	31	25
											139	53	82	23
											130	53	74	23
													b-wave amp uV	b-wave imp ms
													84	53
													88	54
													170	56
													141	47
													390	47
													233	55

¹Standard flash intensity of 1.9 cd.m².s²Flash intensity of 0.002 cd.m².s³Flash intensity of 0.02 cd.m².s⁴Flash intensity of 0.2 cd.m².s⁵Amplitude⁶Implicit time

TABLE 1. Electroretinographic data on two cases with Thr4Lys rhodopsin mutation.

Fig. 3. Electrophoretograms measured under photopic and scotopic conditions. (a) In normal subject, 27 years of age. (b) In case II-4, 58 years of age, with Thr4Lys rhodopsin mutation. Note the reduced cone and rod amplitudes. (c) In case III-1, 27 years of age, with Thr4Lys rhodopsin mutation. Note the more reduced cone amplitudes than rod amplitudes.

the optic discs and maculae had a normal aspect. The inferior vessels were attenuated, whereas the superior ones appeared normal. The posterior poles revealed the same tigroid pattern as in her mother (Fig. 5). Bone-spicule pigmentary clumping with round hypopigmented spots occurred in the inferior retina. The superior retina appeared normal. In the ERG, cone amplitudes were reduced almost 80% of the average with borderline implicit times (Table 1, Fig. 3c). Rod amplitudes were reduced by about 50%, with normal implicit times. Kinetic visual fields showed small absolute scotomas and relative loss in the superior hemisphere (Fig. 6). On photopic threshold perimetry the parafoveal region showed a sensitivity loss of 10 dB (Fig. 7a). On scotopic perimetry there was no measurable rod function except for a small inferior region (Fig. 7b). The dark adaptation curve of this case virtually showed a cone branch only. The curve fitting procedure yielded the values $\tau_{\text{cones}} = 0.98$ minutes and $\text{Th}_{\text{cones}} = 4.74 \text{ Log}(I)$. Thus the cone adaptation showed a prolonged time course. The five age-matched subjects in our normal population all showed shorter than average characteristic cone adaptation time. So the value of case III-1 being outside a 3-standard deviation range of the normal population was considered a highly significant pathological finding. The final threshold reached after about three minutes was within normal limits.

Cases II-2, 61 years of age, II-3, 59 years of age, and III-2, 19 years of age, had normal color vision and no abnormalities on ophthalmological examination. ERG responses and visual fields were unremarkable. Cases I-1 and II-1 died, respectively, at 72 and 62 years of age without ever having any visual problems. Case I-2 had regular ophthalmological check-ups because

Fig. 4. Goldmann perimetry of the left eye of case II-4, 58 years of age, with Thr4Lys rhodopsin mutation. Note the arcuate loss of visual field in the superior hemisphere and the relative central loss.

Fig. 5. Fundus photograph of the right eye of case III-1, 27 years of age, with Thr4Lys rhodopsin mutation. Note the tigroid pattern in the posterior pole, the attenuation of the inferior vessels, and the bone-spicule pigmentations in the inferior part of the retina.

Fig. 6. Goldmann perimetry of the left eye of case III-1, 27 years of age, with Thr4Lys rhodopsin mutation. Note the two absolute scotomas and the relative loss in the superior hemisphere.

of diabetes mellitus type II, and was not affected by RP according to the files. She died at 80 years of age.

Discussion To our knowledge this is the first description of the clinical picture associated with a mutation involving codon 4 of the rhodopsin gene (Thr4Lys). In the small family described, the mutation co-segregated with the disease phenotype. Since neither medical records nor DNA samples of the parents of the index case were available, it remains unclear whether or not the mutation occurred *de novo*.

The Thr4Lys mutation is of special interest since it affects one of the two glycosylation sites of the rhodopsin molecule. Normally, glycosylation of

Fig. 7. Static threshold perimetry with Humphrey field analyzer (30-2 Program) of the left eye of case III-1, 27 years of age, with Thr4Lys rhodopsin mutation. Defects are expressed as loss of sensitivity (in dB) from average sensitivity of the normal population. (a) Photopic perimetry. Note the superior and parafoveal sensitivity loss. (b) Scotopic perimetry. Note the absence of measurable rod function, except for a small inferior region.

rhodopsin occurs on Asparagine (Asn) residues 2 and 15 at the NH₂-terminus of the polypeptide.²¹ Glycosylation of rhodopsin at Asn2 requires the amino acid sequence Asn-Xaa-Thr/Ser. Therefore, replacement of Thr4 would prevent glycosylation normally occurring at this position. Previous studies have shown that unglycosylated rhodopsin molecules are not incorporated into rod outer segments.²⁵ Similar functional abnormalities have been observed for several mutant rhodopsins classified as type II mutants by Sung *et al.*²⁶ Class II mutants affect residues in the transmembrane and extracellular domains of the rhodopsin protein²⁷ and result in defective rhodopsin proteins, which accumulate inappropriately in the endoplasmic reticulum instead of being transported to the plasma membrane. Both affected individuals presented with a tigroid pattern of the posterior pole and a predilection for pigmentary changes in the inferior retina. Peripheral visual field loss was predominant in the superior hemisphere, confluent with a parafoveal sensitivity loss. In the 30° dark adapted threshold perimetry, rod function was diffusely affected, in patient III-1 even more than in patient II-4. On electroretinographic testing, however, rod responses seemed relatively well preserved, especially in case III-1. This can only be explained when these rod responses were evoked by more peripheral photoreceptors. The fact that the implicit times of the cone ERG response and the cone dark adaptation time were prolonged, suggests that a major part of the cones must be involved in the disease process. According to the electroretinographic findings, the RP in this family might be considered of the cone-rod type as defined by Heckenlively,²⁸ a diagnosis based primarily on ERG responses. Case II-4 was in a more advanced stage of the disease, in which both cone and rod responses are significantly reduced, a phenomenon also observed in patients with cone-rod dystrophy.²⁸ The tigroid aspect of the posterior pole together with the progressive peripheral visual field loss and the fact that the first complaint was not night blindness, are also in accordance with this diagnosis.²⁸ Altitudinal visual field loss has been described in cone-rod degenerations,²⁹ but is more specific for type 2 or regional adRP, especially in combination with the degenerative changes in the inferior part of the retina. Cases with sectoral RP can have prolonged cone-implicit times like our cases,³ but show rod-cone function loss rather than a cone-rod one in the ERG. Regional and sector RP have been observed in cases with rhodopsin mutations at codon 15,^{14,15} 17,¹⁰ 58,^{5,7} 106,¹¹ 182,¹⁰ 190,¹³ 267,¹³ and in some cases with codon 23^{3,8} mutations. Cases with codon 46,¹⁶ 345⁹ and 347^{6,12} mutations or sometimes with codon 23⁴ seemed to have a diffuse form of RP. None of these mutations presented with a cone-rod pattern in the ERG. Both, type 2 adRP patients and RP patients with cone-rod degeneration, with substantial ERG responses, are supposed to have a disease of milder progression than that seen in type 1 or typical rod-cone adRP.^{17,28} Since intrafamilial variability has been reported in families with rhodopsin mutations,^{4,6,7,9} our sample of only two cases is too small to draw any definite conclusions.

Since rhodopsin is expressed only in rod photoreceptors, the substantial loss of cone function in our two patients is remarkable. One explanation would be that from the mid periphery, where rods are at their maximum concentration, the loss progressed more rapidly towards the central part of the retina than to the periphery, through which cones got involved at an early stage of the degenerative process. Whether or not this assumption is true remains to be clarified.

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