Ocular manifestations in autosomal dominant retinitis pigmentosa with a Lys-296-Glu rhodopsin mutation at the retinal binding site

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Abstract

A lysine to glutamic acid substitution at codon 296 in the rhodopsin gene has been reported in a family with autosomal dominant retinitis pigmentosa. This mutation is of particular functional interest as this lysine molecule is the binding site of 11-*cis*-retinal. The clinical features of a family with this mutation have not been reported previously. We examined 14 patients with autosomal dominant retinitis pigmentosa and a lysine-296-glutamic acid rhodopsin mutation. Four had detailed psychophysical and electrophysiological testing. Most affected subjects had severe disease with poor night vision from early life, and marked reduction of visual acuity and visual field by their early forties. Psychophysical testing showed no demonstrable rod function and severely reduced cone function in all patients tested.

(*Br J Ophthalmol* 1994; 78: 353–358)

process. Predictions are possible concerning the effect of such a mutation on photoreceptor metabolism.

In this report, the ocular features and results of detailed psychophysical and electrophysiological tests in patients with this disorder are described.

Materials and methods

SUBJECTS

The proband IV-7 was identified by a British Retinitis Pigmentosa Society questionnaire. The complete kindred is shown in Figure 1. Six generations were documented with approximately 50% of those at risk of having the abnormal gene being affected in each generation, males and females were affected equally, and there was male to male transmission. These findings implied autosomal dominant inheritance with complete penetrance.

In August 1990 all available family members were reviewed (Table 1). Each affected family member had an ocular examination including visual acuity, confrontation visual fields, and indirect ophthalmoscopy. All affected members had typical fundus features of retinitis pigmentosa: optic nerve pallor, retinal vascular attenuation, and peripheral neurosensory retinal pigmentation with macular sparing. After the examinations were completed, 10 ml of peripheral blood were taken from each person and placed in potassium ethylenediaminetetra-acetic acid. Blood samples were taken from 10 affected and five unaffected family members, as well as one spouse. Details of the DNA analysis have been published in a separate report.⁷

The functional loss was characterised in four affected family members with a visual acuity of 6/60 or better using the following techniques:

(1) *Photopic visual fields*. Kinetic Goldmann visual fields or Humphrey visual fields were performed in the standard fashion.

(2) *Dark adapted visual fields*. The pupil was dilated with phenylephrine 2.5% and cyclopentolate 1.0%, and the patient was dark adapted for at least 45 minutes. The Humphrey field analyser (Allergan Humphrey, Hertfordshire) was modified for use in dark adapted conditions.¹⁹ An infrared source illuminated the bowl, and an infrared monitor (Phillips, Eindhoven, Holland) was used to detect eye movements. Fields were recorded using programs central 30–2, peripheral 30/60–2, macula, and custom macula 49.

The target size corresponded to Goldmann size V for peripheral testing and to Goldmann size III for macular programs. Each program was per-

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Accepted for publication
21 December 1993

Figure 1 Kindred – Moorfields RP959. Circles: females. Squares: males. Filled symbols: affected members. Arrow indicates proband. Single diagonal indicates death. Cross indicates death in infancy. Lozenge indicates miscarriage. V-6 has the abnormal genotype.

Table 1 Historical information

Patient	Onset night blindness (years)	Onset decreased side vision (years)	Onset decreased reading vision (years)	Age at cataract extraction (years)
III-5	Birth	Unknown	Unknown	Unknown
III-13	Birth	Birth	33	54
III-21*	Birth	15	15	56
IV-2*	Birth	37	37	40
IV-4	Birth	30	33	39
IV-5	Birth	5	33	33
III-18	Birth	Birth	Unknown	Unknown
IV-7	Birth	25	25	28
IV-8	Birth	40	—	—
III-19	Birth	Unknown	Unknown	Unknown
III-23	Birth	Unknown	47	51
IV-9	Birth	37	37	40
IV-10	Birth	25	25	27
V-6	Birth	—	—	—
V-7	Birth	—	—	—
IV-11	Birth	25	26	—
IV-12	Birth	17	17	—

*Information from telephone interview.

formed with both a red (predominant wavelength 650 nm) and blue (predominant wavelength 450 nm) filter in the stimulus beam.

(3) *Dark adaptometry*. Results of the dark adapted blue central 30–2 fields were reviewed to determine the most informative locations of dark adapted visual sensitivity. Ideally, test locations were outside the central 9° with sensitivities higher than 20 dB. If no such point fulfilled these criteria, a location inside 9° was used. The Humphrey field analyser was used for dark adaptometry, and it was controlled by a custom program on an IBM PS/2 model 50 computer as described.^{20,21} Fully dark adapted rod thresholds were measured at two coordinates with the blue filter in the stimulus beam.

(4) *Fundus reflectometry*. Fundus reflectometry was used to measure reflectance levels of the light adapted eye compared with the dark adapted eye using published methods.²² This provided a quantitative estimate of rhodopsin regeneration.

(5) *Electroretinography*. In patients IV-8, IV-11, and IV-12, the electroretinogram was obtained with silver-silver chloride reference and ground electrodes, a gold foil electrode placed in the lower fornix, and a stroboscopic flash

stimulus.²³ Patient V-7's electroretinogram was obtained with a Ganzfeld stimulator lined with green (550 nm) and red (660 nm) light emitting diodes.²⁴

(6) *Colour vision testing*. This was performed using a television stimulator and computer graphics system.^{25,26}

(7) *Fundus photography*. Colour fundus photography of the disc, macula, and periphery was performed with a Zeiss fundus camera.

Results

The majority of patients in this family had severe visual compromise at an early age. However, there were exceptions to this. Two family members (V-6 and V-7) denied that they were affected initially since they had less visual difficulty than other family members with the disease. However, on repeated questioning it was evident that their night vision was poor from early life but they had little trouble by day. Another family member was reported to have sufficient vision to repaint his house at the age of 62 years.

No patient remembered having good vision at night. They noticed decreased side vision and decreased daytime or reading vision at about the age of 30 years. Most had cataract extractions in their thirties, but there was little if any post-operative improvement in visual acuity. Severe reduction in central vision (count fingers, hand motions, light perception level) was typical in their early forties (Tables 1 and 2).

Four patients were evaluated at Moorfields Eye Hospital. Testing revealed similar results in all four cases (Tables 3–4). Cases 3 and 4 are representative and are presented in detail.

CASE 3

Family member IV-12, age 22, never had night vision. Loss of side vision was noticed by the age of 17 years, associated with a mild decrease in reading vision. She had worn spectacle correction since the age of 5 years.

Table 2 Results of ocular examination

Patient	Age (years)	Sex	Visual acuity	Visual fields	Pigment deposits	Central choroidal atrophy
III-5	70	Female	LP	0	++	+++
III-13	70	Female	NLP	0	+++	+
IV-4	43	Female	CF	0	++	—
IV-5	39	Female	CF	5	+	—
III-18	65	Female	6/24	2	+++	—
IV-7	45	Female	HM	0	+++	+++
IV-8	44	Male	6/12	25	+	—
III-19	69	Male	6/60	2	++	+
III-23	68	Female	6/18	0	+	—
IV-9	42	Female	6/12	2	+	—
IV-10	40	Female	6/6	2	(*)+	—
V-6§	21	Female	6/9	—	—	—
V-7	18	Male	6/9	75	(*)+	—
IV-11	27	Female	6/12	25	+	—
IV-12	22	Female	6/18	25	—	—

+++ = severe.

++ = moderate.

+ = mild.

— = absent.

NLP = no light perception.

LP = light perception.

CF = count fingers.

HM = hand movements.

(*) = additional white subretinal deposits.

§ = Subject V-6 has declined to be examined further.

Table 3 Light adapted visual field size and dark adapted sensitivities in decibels using Humphrey visual fields, central 30–2. Normal values: red, 25–35 dB; blue, 42–53 dB

	Sensitivities					
	Visual field	Red 3°	Red 9°	Blue 3°	Blue 9°	Blue >9°
IV-8	25°	10	0	4	0	0
IV-11	25°	15	0	13	0	0
IV-12	25°	26	13	13	3	0
V-7	40°	20	8	10	0	0

Table 4 Dark adaptometry

Patient	Prebleach log intensity V target (dB)			Cone duration (min)	Comments
	Point one	Point two	Rod break		
IV-8	31	32	No	30	Rapid decline to prebleach levels
IV-12	24	25	No	30	Typical contour of cone dark adaptation
V-7	45	45	No	40	Rapid decline to prebleach levels

Figure 2 Dark adaptation curve of patient IV-12 (large symbols) after strong light adaptation showing normal cone adaptation but absence of any recorded rod adaptation. Small symbols represent a normal recovery. The time constant, c , was determined to be 2.3 minutes indicating a normal time course of cone recovery.¹⁷

With +3.50 correction visual acuity was 6/18 with the right eye and 6/9 with the left. The lenses were clear, and there were few vitreous cells. There was mild optic nerve pallor and retinal vascular attenuation. The peripheral retinal pigment epithelium had a mottled appearance without pigment migration into the retina. Cystoid macular oedema was present, which was greater in the right eye than the left. There was no choroidal atrophy.

Goldmann visual fields showed marked generalised constriction and measured 25° with the V4e target (Table 3).

Dark adapted sensitivities to red and blue in the left eye central 30-2 program showed mean values of 26 dB and 13 dB, respectively, at the 3° locations. (Normal values for red, 25–35 dB, and for blue, 42–53 dB.) The 9° locations revealed mean values of 13 dB red, and 3 dB blue. Dark adapted red fields showed few functioning locations outside 21°. On dark adapted blue field testing the target was not seen outside 9° (up to and including 60°) at all standard points tested. There were no fixation losses, false positives, or false negatives (excellent reliability indices) (Table 3).

Dark adaptometry was tested at coordinates 3,3 and 3,-3. Prebleach thresholds to the V

target were elevated to 24 dB and 25 dB, respectively. A normal cone portion of the dark adaptometry curve was found; prebleach thresholds were reached in 10 minutes (Fig 2). Dark adaptometry was continued for 30 minutes. There was no cone-rod break and no identifiable rod portion (Table 3).

The ERG showed no recordable response.

CASE 4

Family member V-7, aged 18 years, was of particular interest to us. At the time of the family survey, he denied symptoms. On repeat questioning he reported some difficulty at night but to a lesser degree than the rest of his family. He denied loss of side vision or daytime visual difficulty. He had worn hyperopic spectacle correction since the age of 6 years, and amblyopia of the left eye was diagnosed aged 6 years which had been treated by patching of the right eye.

On examination, visual acuity with +4.50 spectacles was 6/6 with the right eye and 6/9 with the left. There was a variable 8° to 12° left esotropia. No cataracts were present. There were many vitreous cells. The fundus showed mild optic nerve pallor and retinal vascular attenuation. There was limited pigment migration into the retina and widespread white subretinal deposits (Fig 3). No cystoid macular oedema or central choroidal atrophy was seen.

Light adapted central 30-2 and peripheral 30/60-2 fields were performed in the right eye with the V white target. They were relatively full except for nasal depression between 40° and 60° (Fig 4 A-D, Table 3).

Right eye central 30-2 dark adapted red fields showed wide-spread diffuse depression. Mean sensitivity values obtained were 20 dB at 3° and 8 dB at 9° (Fig 4 E, F). Central 30-2 and peripheral 30/60-2 dark adapted blue field showed no response throughout, with the exception of the central 3° which showed a mean value of 10 dB (Fig 4 G H, Table 3). Reliability indices were excellent.

Pre-bleach dark adaptometry thresholds to the V target at points 3,-3 and -9,-9 were 45 dB at

Fig 3A

Fig 3B

Figure 3 Fundus photographs, left eye, patient V-7 showing attenuation of blood vessels (A) and pigment migration into the retina in the midperiphery (B).

Fig 4A

Fig 4B

Fig 4C

Fig 4D

Figure 4 Humphrey visual fields, right eye, patient V-7. (A, B) Light adapted central 30-2. (C, D) Light adapted peripheral 30/60-2. (E, F) Dark adapted central 30-2 red. (G, H) Dark adapted central 30-2 blue. (A, C, E, G show grey scale; B, D, F, H show numerical sensitivity values.)

both locations. Post-bleach values returned to prebleach levels in 10 minutes. Dark adaptometry was continued for 40 minutes but there was no identifiable rod portion (Table 3).

Fundus reflectometry showed no measurable rhodopsin; however, small amplitude nystagmus hindered measurement.

The ERG showed very attenuated responses (Fig 5). With the green flashes, there was a response peaking at about 175 ms, with an amplitude graded with light intensity. The minimum response of 3 μ V was obtained with an intensity 300 times greater than that which evokes a minimal b-wave in a normal eye. No a-wave was seen. The red flash responses show a small cornea negative response, beginning about 75 ms following the flash, and the size of this response is also graded with light intensity. The negativity is analogous to the threshold response for rods (the scotopic threshold response).²⁷ With red flashes, a cone generated response can be recorded, the photopic threshold response.²⁴ The flash intensity required to evoke this response was about 10 times greater than in normal subjects. The most intense flash evoked a small cone b-wave but this peaked at 150 ms, a very

delayed cone response. With a background light, no responses were recorded.

Colour vision testing of the right eye showed normal thresholds within the central 1°; outside 1° the thresholds were elevated. Testing at 10° showed absent tritan colour vision and gross changes along other colour confusion lines.

Discussion

The lysine-296-glutamic acid mutation in the rhodopsin gene causes a severe form of retinitis pigmentosa. All patients had a lifetime of poor night vision. There was relative sparing of daytime vision early in the disease, a feature characteristic of type I or diffuse retinitis pigmentosa.²⁸⁻³⁰ By the fourth decade of life there was reduction of central vision, severe visual field constriction, and lens opacification. Although the visual prognosis was universally poor, some variability of disease expression was detected as is common in autosomal dominant disease. The disease is more severe than that seen with the mutations glutamic acid-344-stop, arginine-135-leucine and arginine-135-tryptophan, and lacks the altitudinal distribution of disease seen with

Fig 4E

Fig 4F

Fig 4G

Fig 4H

threonine-58-arginine, glycine-106-arginine, threonine-17-methionine, and glycine-182-serine.¹³⁻¹⁷

Psychophysical and electrophysiological tests corroborated the severity of disease. Dark adapted Humphrey visual fields with the blue target, a test specific for rod function, showed threshold elevations of more than 4 log units and no measurable rod function even in the patient who claimed some residual night vision. Cone thresholds were also elevated in all patients except in the central 3°. Patient V-7 had a nearly normal central light adapted cone sensitivity, but with dark adaptation the cone thresholds were elevated 1-2 log units. This is explained by persistence of cone mediated contrast detection in the light adapted state, but a loss of absolute cone sensitivity in the dark adapted state. The electroretinogram showed no rod or cone response in three patients, and a severely attenuated and delayed cone and rod response in the fourth. Despite the severity of rod and cone photoreceptor dysfunction in this disease, there is some evidence in case 4 that rods are affected primarily.

The metabolic disturbance at the cellular level caused by the presence of a mutant gene may be due to two possible mechanisms. If the abnormal protein does not pass through the rough endoplasmic reticulum to the outer segment, any loss

of function of rhodopsin would be caused by reduced availability of rhodopsin during disc membrane formation. If the mutant rhodopsin does not reach the outer segment, the consequent disease is likely to be identical, regardless of the specific rhodopsin mutation. A second mechanism of cellular dysfunction would be consequent upon the abnormal rhodopsin passing into the outer segment, its presence disrupting outer segment metabolism.³¹ In general, the latter appears to be a much more likely given the variability of disease from one family to another with different mutations in the rhodopsin gene.

If the abnormal protein were incorporated into the outer segment disc membrane it would be possible to construct a hypothesis concerning the effect this may have on cell function. In the heterozygous state, the outer segment would contain two different rhodopsin populations: normal rhodopsin from the normal gene and mutant rhodopsin. It might be assumed that a rhodopsin mutation involving the 11-*cis*-retinal binding site might effectively stop transduction. However, an experimental membrane assay with the lysine-296-glutamic acid rhodopsin mutation has shown that abnormal protein will not bind 11-*cis*-retinal, and that it reacts constantly with transducin [D Oprian, personal communication]. If the mutant rhodopsin behaved in this way in the outer segment, it is predictable that

Fig 5A

Fig 5B

Figure 5 (A) Electrorretinogram, right eye, patient V-7 using green flash showing progressive increase in b-wave with increase flash intensity. B-wave is small compared with normal, and is markedly delayed. Lowest trace: 0.1; second trace: 0.3; third trace: 1.0; fourth trace: 3.3; fifth trace: 33.0 quanta absorbed/receptor/flash. Vertical divisions equal 10 μ V; horizontal divisions equal 25 ms. (B) Electrorretinogram using red flash, the photopic and scotopic threshold responses are seen at high intensity implying marked desensitisation to red light. Lowest trace: 0.47; second trace: 2.83; third trace: 8.50 quanta absorbed/receptor/flash. Vertical divisions equal 5 μ V; horizontal divisions equal to 25 ms.²⁴

the retina would act as if it were in constant light and would not dark adapt. This would result in a markedly reduced scotopic sensitivity owing to the presence of the mutant protein, and yet the normal rhodopsin would bleach and regenerate. This would be measurable if there were not extensive loss of rod outer segment volume or massive photoreceptor cell death.

Fundus reflectometry, an indirect assessment of rhodopsin levels, showed no measurable rhodopsin in one patient. This may have been due to the confounding factors of reduced reflectance and the small amplitude nystagmus hindering measurement. Examination of a less severely affected individual may resolve the question of functional implications of the Lys-296-Glu mutation.

Supported in part of grants from British Retinitis Pigmentosa Society, National Retinitis Pigmentosa Foundation Fighting Blindness USA, and Wellcome Trust. Dr Owens was supported as a Wolfson fellow.

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