Autosomal dominant retinitis pigmentosa mapping to chromosome 7p exhibits variable expression

R Y Kim, F W Fitzke, A T Moore, M Jay, C Inglehearn, G B Arden, S S Bhattacharya, A C Bird

Abstract

The genetic locus causing autosomal dominant retinitis pigmentosa (adRP) has recently been mapped in a large English family to chromosome 7p. Eight affected members of this family were studied electrophysiologically and psychophysically with dark adapted static threshold perimetry and dark adaptometry. The phenotypes observed fell into three categories: minimally affected with no symptoms, and normal (or near normal) electrophysiology and psychophysics; moderately affected with mild symptoms, abnormal electroretinograms, and equal loss of rod and cone function in affected areas of the retina; and severely affected with extinguished electroretinograms and barely detectable dark adapted static threshold sensitivities. The mutation in the gene on 7p causing adRP in this family causes regional retinal dysfunction with greatly variable expressivity ranging from normal to profoundly abnormal in a manner not explained by age.

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Institute of Ophthalmology and Moorfields Eye Hospital, London
R Y Kim
F W Fitzke
A T Moore
M Jay
C Inglehearn
G B Arden
S S Bhattacharya
A C Bird

Correspondence to:
Professor A C Bird, Professorial Unit, Moorfields Eye Hospital, City Road, London EC1V 2PD.

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Inherited disorders causing photoreceptor degeneration with nightblindness, reduced peripheral vision, and preservation of central vision until late are known collectively as retinitis pigmentosa (RP).[1] RP may be inherited in an autosomal dominant (adRP), autosomal recessive, or X linked manner. The incidence of RP in the United Kingdom is approximately 1 in 5000, with adRP accounting for 24% of families and 38% of cases.[2]

In adRP both allelic and non-allelic genetic heterogeneity exist.[3–11] Mutations in the rhodopsin gene (RHO) on chromosome 3 account for approximately 30% of adRP,[12] with over 50 mutations having been reported.[13] Mutations in the gene encoding RDS-peripherin on chromosome 6 have also been implicated in adRP.[9 14–18] A third locus has been provisionally mapped to chromosome 8[8] and a fourth to chromosome 7q.[10] Recently, our group has mapped a fifth adRP genetic locus to chromosome 7p.[11]

In this report, we describe the electrophysiological and psychophysical features of retinal dysfunction in chromosome 7p-adRP[11] in affected family members different from those described in a previous study which used older generation instrumentation.[19] We expand the known range of phenotype expression observed in chromosome 7p-adRP.

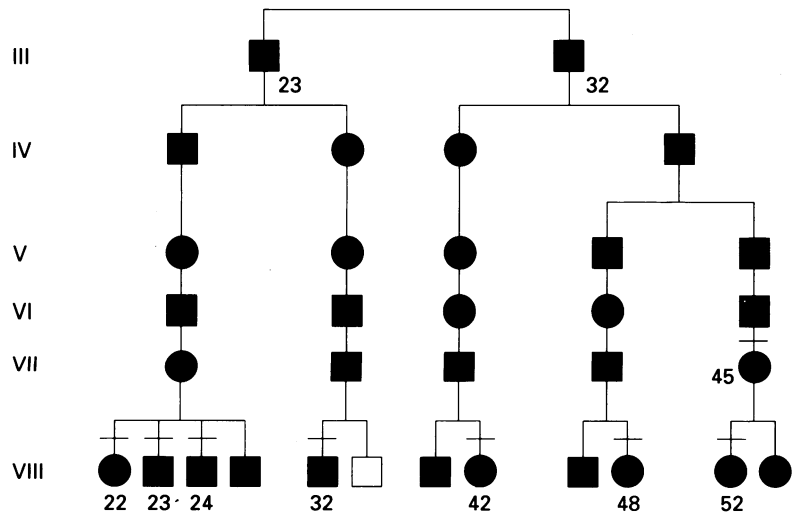

Figure 1 Abbreviated family pedigree (see Inglehearn et al,[11] *Moore* et al,[19] *and Jay* et al,[20] *for more details of this nine-generation family). Solid boxes or circles indicate affected males and females, respectively. Horizontal notches indicate individuals studied in this report. Roman and arabic numerals indicated respectively, generation and position numbers in refs 19 and 20.*

Methods

Some details of this large, nine generation English family have been described previously.[11 19 20] The severity of disease varied widely between affected members. We studied eight patients (Fig 1) with the haplotype on chromosome 7p linked with adRP[11] who were not studied previously.[19] They were selected on the basis of having sufficient visual function to warrant documentation using electrophysiological and psychophysical techniques. The right eye of each patient was studied. Patient details are summarised in Table 1. Patients VIII-22, VIII-23, and VIII-24 are siblings. Patient VII-45 is the mother of VIII-52.

Subjects underwent dark adapted electroretinographic testing (ERG) using a standard protocol.[21] Blue flashes were used for eliciting rod dominant responses, red flashes for resolving cone responses from rod responses, and white for mixed cone and rod responses as well as cone flicker responses. In contrast with our previous study in which dark adapted static threshold testing was performed at only 22 points without dark adaptometry,[19] in this study both dark adapted static threshold perimetry and dark adaptometry were performed using a newer

Table 1 Patient characteristics

				Subjective symptoms	
Patient	*Sex*	*Age*	*VA*	*Night blind*	*Field constriction*
VIII-23	M	43	6/6	No	No
VIII-24	M	45	6/6	No	No
VIII-48	F	25	6/6	No	No
VIII-22	F	46	6/6	Yes	No
VII-45	F	51	6/6	Yes	No
VIII-52	F	26	6/6	Yes	No
VIII-42	F	38	6/12	Yes	Yes
VII-32	M	49	6/6	Yes	Yes

Table 2 Flash electroretinographic results

	Blue run 12* b Wave		Red run 18* b Wave		White run 20* a Wave		White run 20* b Wave		30 Hz flicker* b Wave	
Subject	*Amp*	*Imp*	*Amp*	*Imp*	*Amp*	*Imp*	*Amp*	*Imp*	*Amp*	*Imp*
Normal mean	319	57	91	48	132	22	384	45	43	29
Normal limit	141	69	16	56	41	25	208	49	10	32
VIII-23	220	58	150	48	200	22	240	46	35	29
VIII-24	260	58	225	54	100	22	280	49	45	29
VIII-48	145	60	75	56	40	27	150	56	30	29
VIII-22	40	56	25	50	Flat		40	46	12	32
VII-45	Flat		Flat		Flat		Flat		Flat	
VIII-52	Flat		Flat		Flat		Flat		Flat	
VIII-42	Flat		Flat		Flat		Flat		Flat	
VIII-32	Flat		Flat		Flat		Flat		Flat	

*Refers to runs 12, 18, 20, and 30 (flicker) in Jay *et al*[20]. In run 18, only the cone b wave was measured.
Amp=amplitude in μV; Imp=implicit time in ms.
Normal limit=normal mean −2 SD for amplitude and normal mean +2 SD for implicit time.

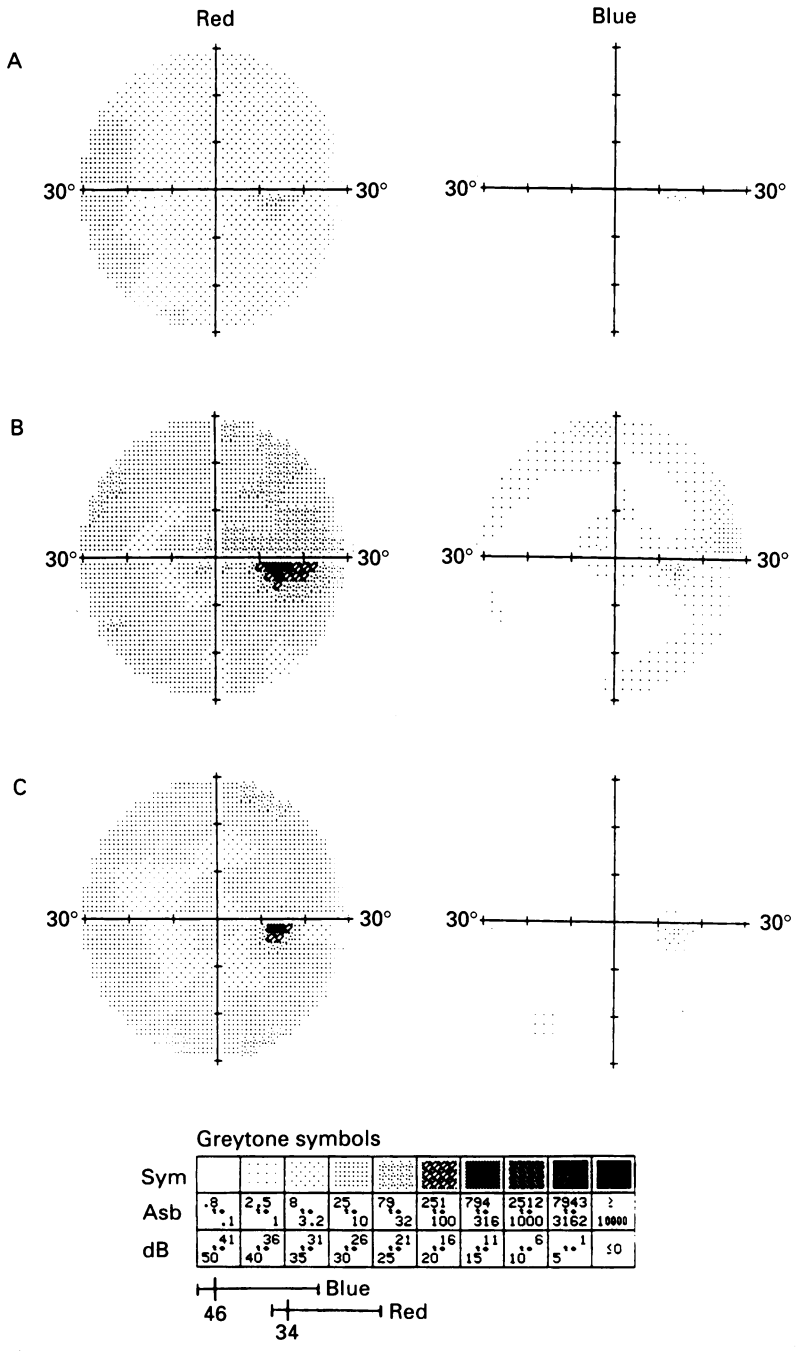

Figure 2 Dark adapted static threshold perimetry for patients VIII-23 (A), VIII-24 (B), and VIII-48 (C). Average sensitivities in decibels (dB) with bars indicating range for normal individuals are indicated on the greyscale at the bottom.

generation, modified Humphrey automated perimeter.[22 23] Under dark adapted conditions with dilated pupils, cone and rod sensitivities were determined in an unlit bowl with size 5 red and blue test stimuli, respectively, using a standard 30-2 program. Two points were then selected for dark adaptometry. Following exposure to bright white light sufficient to bleach 95% of rhodopsin, the recovery of sensitivity to size 5 blue test stimuli was followed over time.

Results

Patients VIII-23, VIII-24, and VIII-48 were all asymptomatic. In one (VIII-48), the only abnormality was a delayed and reduced ERG amplitude to bright white flashes (Table 2), her other ERG responses and sensitivities (Fig 2C and Fig 4A) being normal. In the other two, the results of all functional tests were within normal limits (Table 2, Fig 2A and 2B). These patients all had scattered intraretinal bone spicule pigmentation and the haplotype linked with chromosome 7p-adRP.

Patients VIII-22, VII-45, and VIII-52 were symptomatic with reduced ERG responses (Table 2). Dark adapted static threshold perimetry revealed peripheral depression in cone and rod mediated sensitivities which were affected in the same areas to a similar degree with preservation of sensitivities centrally (Fig 3). These individuals demonstrate regional[24] or class 2[25] functional loss. While the final thresholds for the cone and rod components of the dark adaptation curve were elevated, the rates of dark adaptation were normal (Fig 4B, C, and D).

Patients VIII-42 and VII-32 were severely affected with symptoms of early onset, extinguished ERG responses, and barely detectable dark adapted static perimetric sensitivities (Fig 5). These individuals were too severely affected to undergo dark adaptometry testing.

There is no recognisable pattern of severity of disease in the families. There is no correlation of the degree of functional loss between siblings or between children and their parents or the sex of the affected parent.

Discussion

By history alone, this family seems to exhibit incomplete penetrance, with RP appearing to 'skip' generations.[20] Assessment of penetrance, however, varies with the level of ascertainment and the sensitivity of testing systems in the detection of retinal functional losses. In our previous survey of different members of this family,[19] we studied one asymptomatic obligate carrier (VII-41) who exhibited reduced amplitude electroretinographic responses and peripheral constriction on Goldmann perimetry. On this basis it was considered that there was variable expressivity rather than incomplete penetrance. Patients VIII-23, VIII-24, and VIII-48 had minimal fundus changes; two of the three lacked any delay in cone implicit times and none had elevated dark adapted static perimetric rod thresholds, both of which have reported as being sensitive indicators of mild retinal dysfunction.[19 26 27] It is possible that these individuals

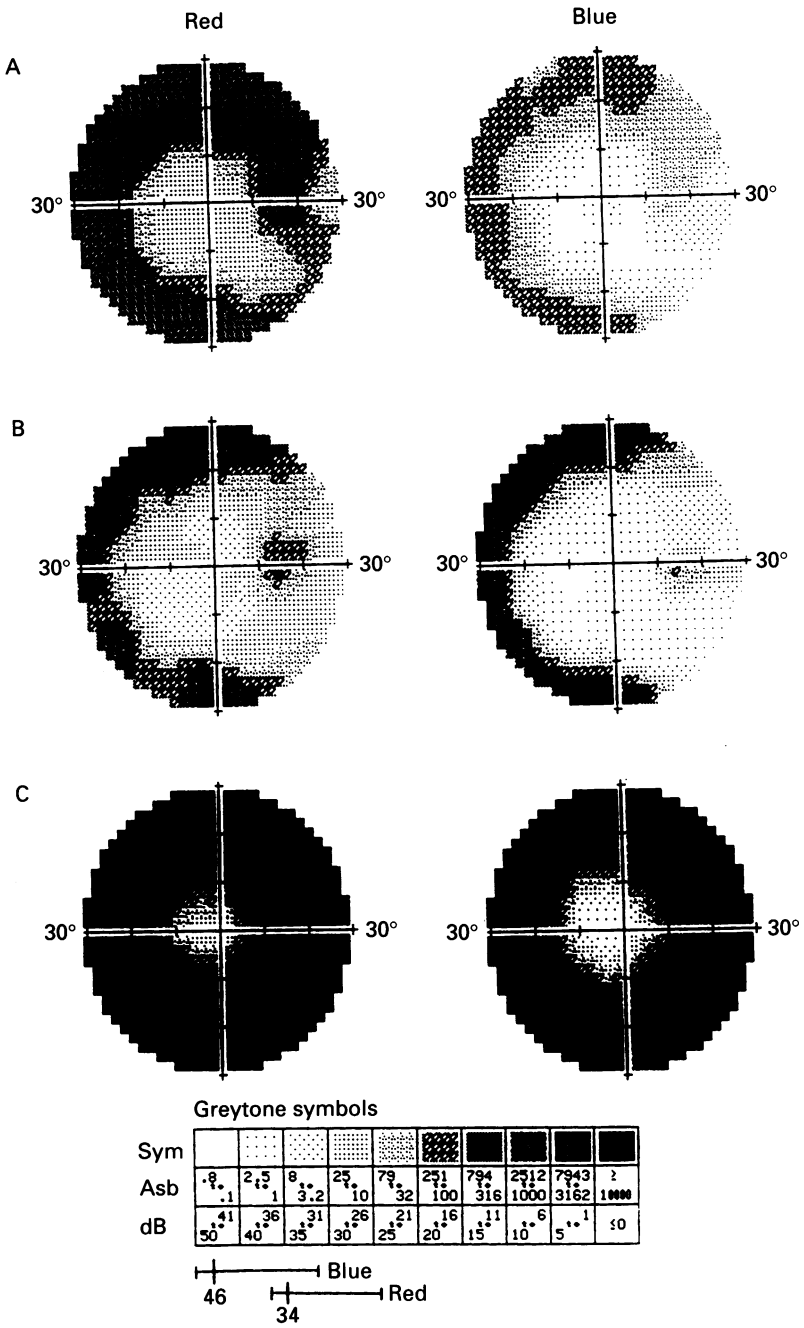

Figure 3 Dark adapted static threshold perimetry for patients VIII-22 (A), VII-45 (B), and VIII-52 (C). Average sensitivities in decibels (dB) with bars indicating range for normal individuals are indicated on the greyscale at the bottom.

would have been indistinguishable from normal using currently available examination techniques had they been seen in the second or third decade of life at a time when genetic counselling is most important. Thus, this family highlights the potential difficulty in distinguishing between incomplete penetrance (an all or none phenomenon) and variable expressivity (a graded phenomenon).

The degree of retinal degeneration was variable in a manner not explained by age. The eight patients studied varied from minimally affected and asymptomatic with only scattered intraretinal bone spicules but normal ERG responses and dark adapted psychophysics to severely affected with extinguished electroretinograms and barely detectable dark adapted static perimetric sensitivities. Between these two extremes were moderately affected members with recent symptoms, reduced electroretinographic responses, and psychophysical evidence of regional[24] or class 2[25] retinal functional loss, as opposed to diffuse[24] or class 1[25] functional loss.

The pattern of concentric, regional retinal functional loss (Fig 3) differs from the regional patterns seen in adRP associated with mutations in the RHO gene.[23 28-37] In all but one patient with a rhodopsin mutation,[23] the inferior retina was preferentially compromised in an altitudinal distribution. The one exception was a RHO gene insertion causing retinal functional loss greater inferiorly but not in an altitudinal distribution.[23] In addition to regional[24] or class 2[25] retinal functional loss, allelic mutations in the RHO gene can cause diffuse[24] or class 1[25] functional loss.[13] Since many of the functional attributes of rhodopsin are known,[38] it is possible to formulate hypotheses concerning the pathogenesis of disease. Although the genetic locus responsible for adRP in this family has been mapped to the short arm of chromosome 7,[11] the responsible gene has yet to be identified.

These families present a particular challenge in genetic counselling since at a time at which members are having children the phenotype may not be recognisable. For this reason, it is not possible to exclude the possibility of their having affected children or of excluding genetic risk in a member whose parents are apparently normal. This is all the more important since mild disease or a lack of disease in the parent does not preclude severe disease in the children. Knowledge of the locus of the causative gene allows accurate counselling if the family is informative for the available genetic markers. Once the mutation is determined the genetic status could be identified with certainty.

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1 Heckenlively JR, ed. *Retinitis pigmentosa*. Philadelphia: Lippincott, 1988.
2 Jay M. On the heredity of retinitis pigmentosa. *Br J Ophthalmol* 1982; **66**: 405–16.
3 McWilliam P, Farrar GJ, Kenna P, Bradley DG, Humphries MM, Sharp EM, *et al*. Autosomal dominant retinitis pigmentosa (ADRP). Localization of an ADRP gene to the long arm of chromosome 3. *Genomics* 1989; **5**: 619–22.
4 Dryja TP, McGee TL, Reichel E, Hahn LB, Cowley GS, Yandell DW, *et al*. A point mutation of the rhodopsin gene in one form of retinitis pigmentosa. *Nature* 1990; **343**: 364–6.
5 Farrar GJ, McWilliam P, Bradley DG, Kenna P, Lawler M, Sharp EM, *et al*. Autosomal dominant retinitis pigmentosa: linkage to rhodopsin and evidence for genetic heterogeneity. *Genomics* 1990; **8**: 35–40.
6 Lester DH, Inglehearn CF, Bashir R, Ackford H, Easkowitz L, Jay M, *et al*. Linkage to D3S47 (C17) in one large autosomal dominant retinitis pigmentosa family and exclusion in another: confirmation of genetic heterogeneity. *Am J Hum Genet* 1990; **47**: 536–41.
7 Kaplan J, Bonneau D, Frezal J, Munnich A, Dufier J-L. Clinical and genetic heterogeneity in retinitis pigmentosa. *Hum Genet* 1990; **85**: 635–42.
8 Blanton SH, Heckenlively JR, Cottingham AW, Friedman J, Sadler LA, Wagner M, *et al*. Linkage mapping of autosomal dominant retinitis pigmentosa (RP1) to the pericentric region of human chromosome 8. *Genomics* 1991; **11**: 856–69.
9 Farrar GJ, Kenna P, Jordan SA, Kumar-Singh R, Humphries MM, Sharp EM, *et al*. A three-base pair deletion in the peripherin-RDS gene in one form of retinitis pigmentosa. *Nature* 1991; **354**: 478–80.
10 Jordan SA, Farrar GJ, Kenna P, Humphries MM, Sheils DM, Kumar-Singh R, *et al*. Localization of an autosomal dominant retinitis pigmentosa gene to chromosome 7q. *Nature Genet* 1993; **4**: 54–7.

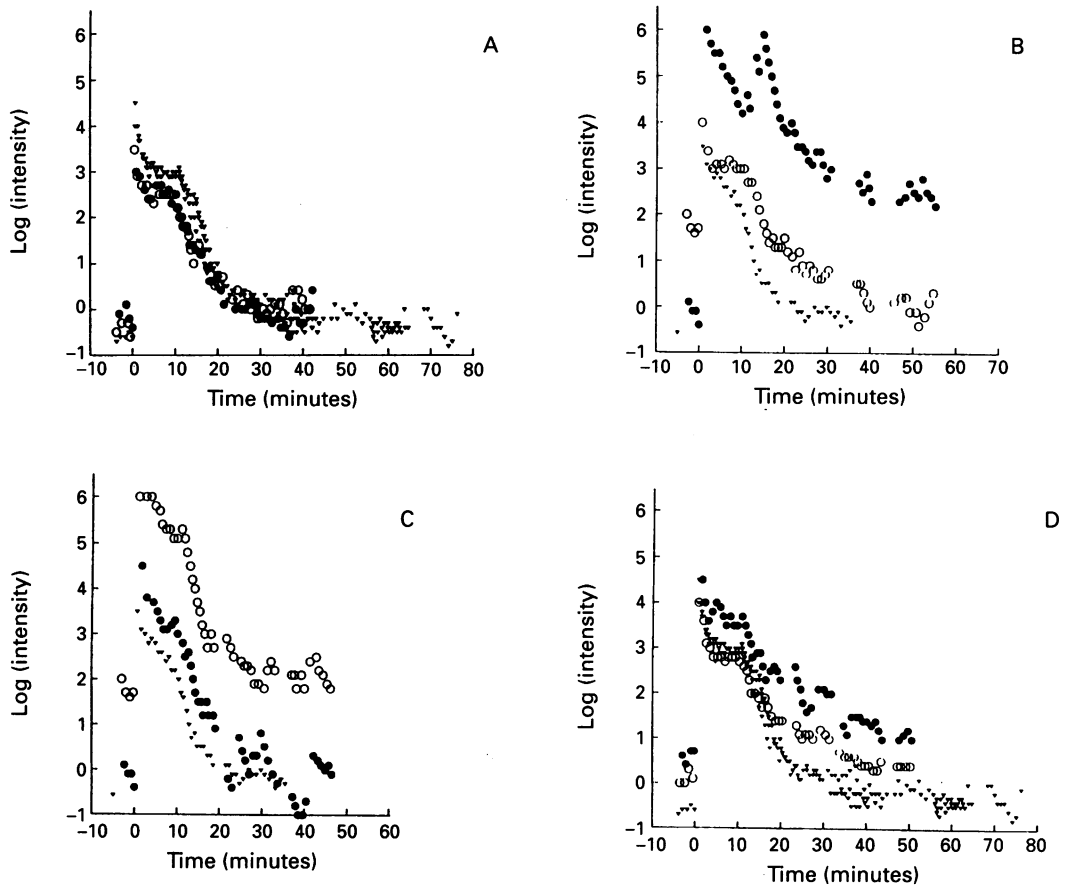

Figure 4 Dark adaptometry. Large circles indicate patient responses; small circles for age-matched normals. Prebleach measurements were made before time 0. Two points were evaluated based upon the results of dark adapted static threshold perimetry (Figs 1–3). (A) Patient VIII-48 was studied at positions +9°, +9° (solid circles) and −9°, −9° (open circles); (B) patient VIII-22 was studied at positions −9°, +15° (solid circles) and +9°, −15° (open circles); (C) patient VII-45 was studied at positions +15°, −15° (solid circles) and −15°, +15° (open circles); (D) patient VIII-52 was studied at positions −3°, +9° (solid circles) and −9°, 0° (open circles).

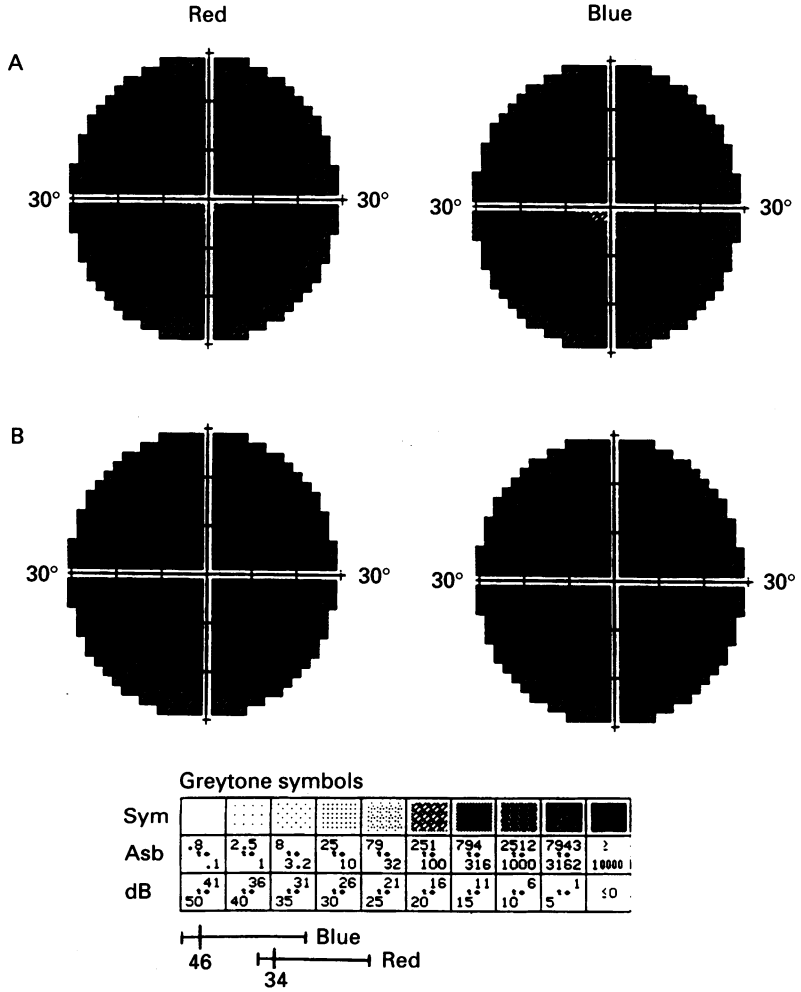

Figure 5 Dark adapted static threshold perimetry for patients VIII-42 (A) and VII-32 (B). Average sensitivities in decibels (dB) with bars indicating range for normal individuals are indicated on the greyscale at the bottom.

11 Inglehearn CF, Carter SA, Keen TJ, Lindsey J, Stephenson AM, Bashir R, *et al.* A new locus for autosomal dominant retinitis pigmentosa on chromosome 7p. *Nature Genet* 1993; **4**: 51–3.

12 Dryja TP. Doyne Lecture. Rhodopsin and autosomal dominant retinitis pigmentosa. *Eye* 1992; **6**: 1–10.

13 Al-Maghtheh M, Gregory C, Inglehearn C, Bhattacharya S. Rhodopsin mutations in autosomal dominant retinitis pigmentosa. *Human Mutation* (in press).

14 Kajiwara K, Hahn LB, Mukai S, Travis GH, Berson EL, Dryja TP. Mutations in the human retinal degeneration slow gene in autosomal dominant retinitis pigmentosa. *Nature* 1991; **354**: 480–3.

15 Farrar GJ, Kenna P, Jordan SA, Kumar-Singh R, Humphries MM, Sharp EM, *et al.* Autosomal dominant retinitis pigmentosa: a novel mutation at the peripherin/RDS locus in the original 6p-linked pedigree. *Genomics* 1992; **14**: 805–7.

16 Kajiwara K, Sandberg MA, Berson EL, Dryja TP. A null mutation in the human peripherin/RDS gene in a family with autosomal dominant retinitis punctate albescens. *Nature Genet* 1993; **3**: 208–12.

17 Wells J, Wroblewski J, Keen J, Inglehearn C, Jubb C, Eckstein A, *et al.* Mutations in the human retinal degeneration slow (RDS) gene can cause either retinitis pigmentosa or macular dystrophy. *Nature Genet* 1993; **3**: 213–8.

18 Weleber RG, Carr RE, Murphey WH, Sheffield VC, Stone EM. Phenotypic variation including retinitis pigmentosa, pattern dystrophy, and fundus flavimaculatus in a single family with a deletion of codon 153 or 154 of the peripherin/RDS gene. *Arch Ophthalmol* 1993; **111**: 1531–42.

19 Moore AT, Fitzke F, Jay M, Arden GB, Inglehearn CF, Keen TJ, *et al.* Autosomal dominant retinitis pigmentosa with apparent incomplete penetrance: a clinical, electrophysiological, psychophysical, and molecular genetic study. *Br J Ophthalmol* 1993; **77**: 473–9.

20 Jay M, Jay B, Moore AT, Bird AC. Nine generations of a family with autosomal dominant retinitis pigmentosa and evidence of variable expressivity from census records. *J Med Genet* 1992; **29**: 906–10.

21 Arden GB, Carter RM, Hogg CR, Powell DJ, Ernst WJK, Clover GM, *et al.* A modified ERG technique and the results obtained in X-linked retinitis pigmentosa. *Br J Ophthalmol* 1981; **67**: 419–30.

22 Chen J, Fitzke F, Pauliekhoff D, Bird AC. Functional loss in age-related Bruch's membrane change with choroidal perfusion defect. *Invest Ophthalmol Vis Sci* 1992; **33**: 334–40.

23 Kim RY, Al-Maghtheh M, Fitzke FW, Arden GB, Jay M, Bhattacharya SS, *et al.* Dominant retinitis pigmentosa associated with two rhodopsin gene mutations: Leu-40-Arg and an insertion disrupting the 5′-splice junction of exon 5. *Arch Ophthalmol* 1993; **111**: 1518–24.

24 Lyness AL, Ernst W, Quinlan MP, Clover GM, Arden GB, Carter RM, *et al.* A clinical, psychophysical, and electroretinographic survey of patients with autosomal dominant retinitis pigmentosa. *Br J Ophthalmol* 1985; **69**: 326–39.

25 Massof RW, Finkelstein D. Two forms of autosomal dominant primary retinitis pigmentosa. *Doc Ophthalmol* 1979; **51**: 289–346.
26 Berson EL, Gouras P, Gunkel RD, Myrianthopoulos NC. Dominant retinitis pigmentosa with reduced penetrance. *Arch Ophthalmol* 1969; **81**: 226–34.
27 Berson EL, Simonoff EA. Dominant retinitis pigmentosa with reduced penetrance. Further studies of the electroretinogram. *Arch Ophthalmol* 1979; **97**: 1286–91.
28 Heckenlively JR, Rodriquez JA, Daiger SP. Autosomal dominant sectoral retinitis pigmentosa: two families with transversion mutation in codon 23 of rhodopsin. *Arch Ophthalmol* 1991; **109**: 84–91.
29 Jacobson SG, Kemp CM, Sung C-H, Nathans J. Retinal function and rhodopsin levels in autosomal dominant retinitis pigmentosa with rhodopsin mutations. *Am J Ophthalmol* 1991; **112**: 256–71.
30 Fishman GF, Stone EM, Gilbert LD, Kenna P, Sheffield VC. Ocular findings associated with a rhodopsin gene codon 58 transversion mutation in autosomal dominant retinitis pigmentosa. *Arch Ophthalmol* 1991; **109**: 1387–93.
31 Fishman GA, Stone EM, Sheffield VC, Gilbert LD, Kimura AE. Ocular findings associated with rhodopsin gene codon 17 and codon 182 transition mutations in dominant retinitis pigmentosa. *Arch Ophthalmol* 1992; **110**: 54–62.
32 Kemp CM, Jacobson SG, Roman AJ, Sung C-H, Nathans J. Abnormal rod dark adaptation in autosomal dominant retinitis pigmentosa with proline-23-histidine rhodopsin mutation. *Am J Ophthalmol* 1992; **113**: 165–74.
33 Hayakawa M, Hotta Y, Imai Y, Fujiki K, Nakamura A, Yamashima K, *et al*. Clinical features of autosomal dominant retinitis pigmentosa with rhodopsin gene codon 17 mutation and retinal neovascularization in a Japanese patient. *Am J Ophthalmol* 1993; **115**: 168–73.
34 Moore AT, Fitzke FW, Kemp CM, Arden GB, Keen TJ, Inglehearn CF, *et al*. Abnormal dark adaptation kinetics in autosomal dominant sector retinitis pigmentosa due to rod opsin mutation. *Br J Ophthalmol* 1992; **76**: 465–9.
35 Fishman GA, Stone EM, Gilbert LD, Sheffield VC. Ocular findings associated with a rhodopsin gene codon 106 mutation. *Arch Ophthalmol* 1992; **110**: 646–53.
36 Kranich H, Barkowski S, Denton MJ, Krey S, Dickinson P, Duvigneau C, *et al*. Autosomal dominant 'sector' retinitis pigmentosa due to a point mutation predicting an Asn-15-Ser substitution of rhodopsin. *Hum Mol Genet* 1993; **2**: 813–4.
37 Sullivan LJ, Makris GS, Dickinson P, Mullhall LEM, Forrest S, Cotton RGH, *et al*. A new codon 15 rhodopsin gene mutation in autosomal dominant retinitis pigmentosa is associated with sectorial disease. *Arch Ophthalmol* 1993; **111**: 1512–7.
38 Khorana HG. Minireview: rhodopsin, photoreceptor of the rod cell. *J Biol Chem* 1992; **267**: 1–4.