

ORIGINAL ARTICLES – Clinical science

Autosomal dominant retinitis pigmentosa with apparent incomplete penetrance: a clinical, electrophysiological, psychophysical, and molecular genetic study

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Abstract

Twenty five symptomatic individuals and six asymptomatic obligate gene carriers from four families with autosomal dominant retinitis pigmentosa (adRP) showing apparent incomplete penetrance have been studied. Symptomatic individuals from three families showed early onset of night blindness, non-recordable rod electroretinograms, and marked elevation of both rod and cone thresholds in all subjects tested. In the fourth family, there was more variation in the age of onset of night blindness and some symptomatic individuals showed well preserved rod and cone function in some retinal areas. All asymptomatic individuals tested had evidence of mild abnormalities of rod and cone function, indicating that these families show marked variation in expressivity rather than true non-penetrance of the adRP gene. No mutations of the rhodopsin or RDS genes were found in these families and the precise genetic mutation(s) remain to be identified.

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Clinical and psychophysical studies in autosomal dominant retinitis pigmentosa (adRP) have suggested that there may be genetic heterogeneity within the disorder.¹⁻⁵ This has been confirmed by the finding of mutations in the rhodopsin gene on chromosome 3^{6,7} and the retinal degeneration slow (RDS) gene on chromosome 6⁸⁻¹⁰ in some families with adRP. Some forms of adRP do not show linkage to or mutations of either the rhodopsin gene or the RDS gene and additional genetic mutations remain to be identified.

Most families, including those with known mutations, show complete penetrance of the adRP gene. In a few families incomplete penetrance is a notable feature¹¹⁻¹⁵ and it has been suggested on the basis of the electroretinographic findings that this may be a distinct form of adRP.^{11,12}

We have studied both symptomatic individuals and asymptomatic obligate gene carriers from four families showing apparent incomplete penetrance in order to characterise the pattern of

retinal disease in affected family members and to investigate rod and cone function in those obligate gene carriers who remain asymptomatic in the fourth or fifth decade of life. We have also investigated whether any of the families show mutations of the rhodopsin or RDS genes, or linkage to chromosomes 3 or 6.

Patients and methods

Twenty five symptomatic individuals (mean age 32 years; range 13-58 years) and six asymptomatic obligate gene carriers (mean age 46 years; range 39-60 years) from four families with apparent incomplete penetrance took part in the study. In each family there was transmission of the disease through at least three generations (Fig 1), and in three there was evidence of male to male transmission. In the fourth, although there was no male to male transmission, all the affected females had severe disease, suggesting autosomal dominant inheritance.

Each subject underwent a full clinical evaluation. A variety of investigations including an electroretinography (ERG), electro-oculography (EOG), Goldmann perimetry, and detailed dark adapted static perimetry were performed in the majority of subjects (subjects with advanced RP with extensive field loss did not undergo psychophysical testing). In addition, photopic flicker testing was performed on each of the six asymptomatic obligate gene carriers. Detailed Goldmann perimetry was performed on each eye using the IV 4e and I 4e targets. The ERG was

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Family 1

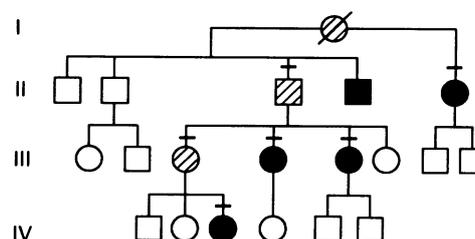


Figure 1

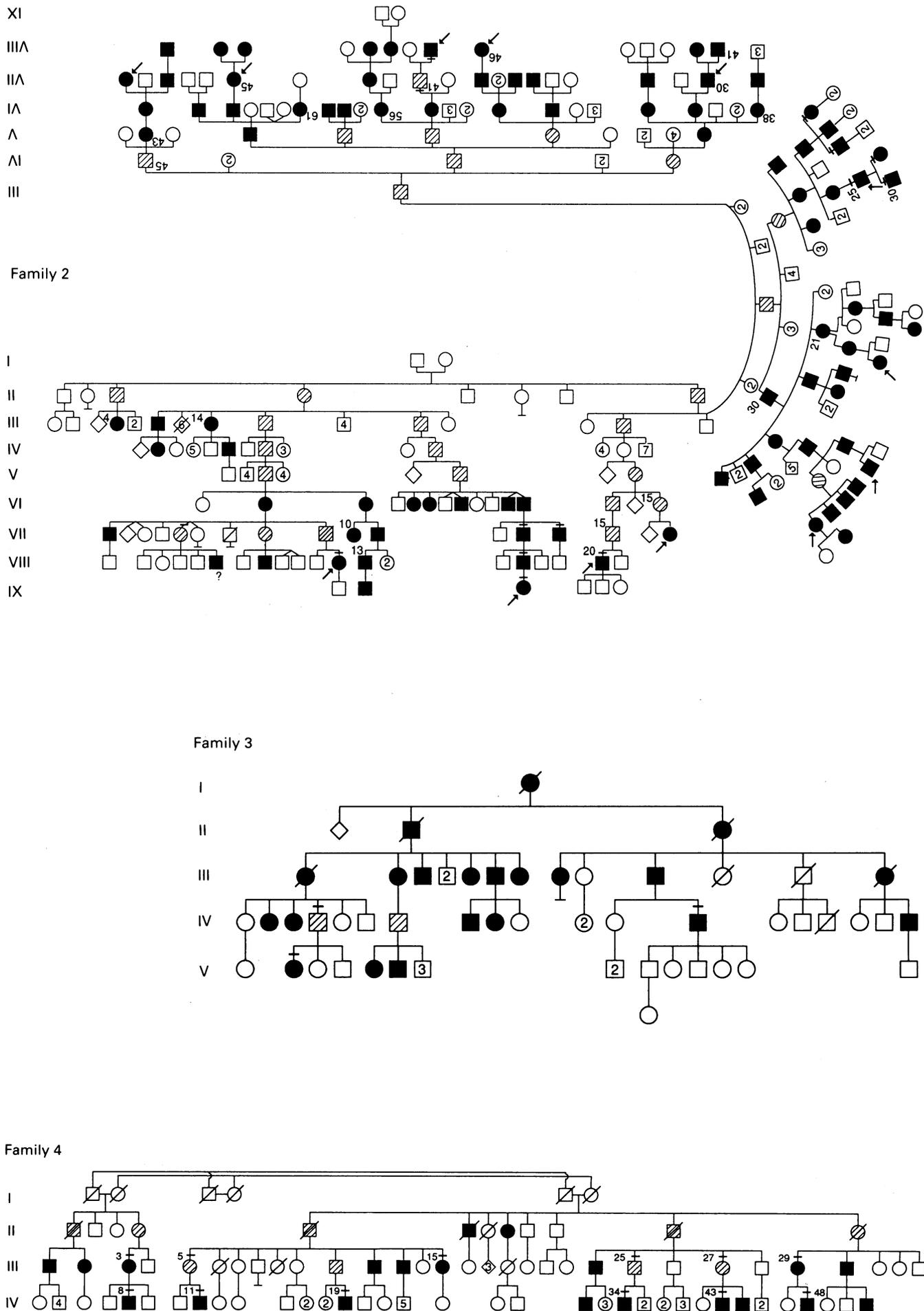


Figure 1 Pedigrees of families 1, 2, 3, and 4. ●■: symptomatic individual; ◐◑: asymptomatic obligate gene carrier; ↗: proband; +: examined by the authors.

Table 1 Age of onset of night blindness

Family	Onset of night blindness			No of patients examined
	<10 years	11-20 years	>21 years	
1	4	0	0	4
2	2	3	5	10
3	2	0	0	2
4	4	4	0	9*

*One patient denied any night blindness.

performed in accordance with the protocol described in Arden *et al.*¹⁶ and the details of the method used for photopic flicker are given in Tyler *et al.*¹⁷ Dark adapted perimetry was performed on one eye (which showed least field loss on Goldmann perimetry) of each subject using red (dominant wavelength 660 nm, subtending 0.9°) and green (dominant wavelength 530 nm, subtending 0.9°) targets. The pupil was dilated with 1% cyclopentolate and the eye dark adapted for 40 minutes before starting the test. At least 17 points at different retinal locations in both upper and lower fields were tested in each case. The apparatus and method for the dark adapted static perimetry have been described previously.¹⁸

Symptomatic members from each family were screened for mutations in the rhodopsin and RDS genes. Exon sequences were amplified by the polymerase chain reaction using primers flanking the exons.^{9,19,20} Amplified fragments were run on hydrolink gels in order to detect mutations as heteroduplexed fragments of normal and mutated DNA sequences.²¹ This method has successfully detected 13 different mutations in the rhodopsin and RDS genes in 17 different families with retinal dystrophies^{10,20} and appears to detect the same proportion of mutations in screening of RP families as single strand conformation polymorphism (SSCP)²² and denaturing gradient gel electrophoresis (DGGE).⁷

Linkage analysis was performed on markers

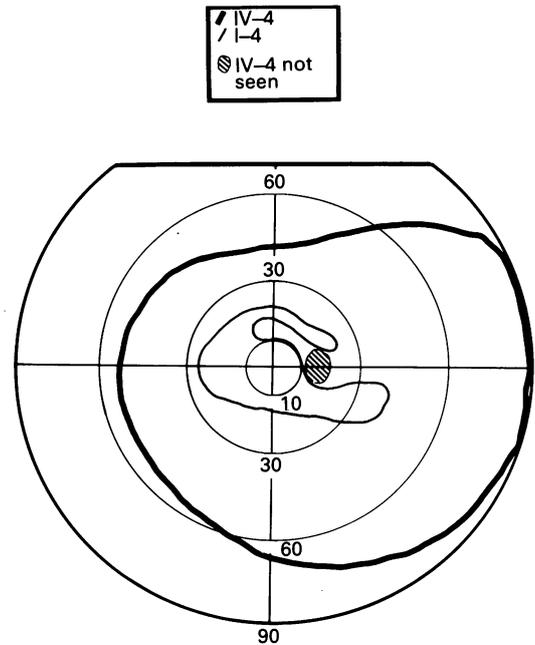


Figure 2 Goldmann field performed on the right eye of subject IV-34 from family 4.

within the rhodopsin and RDS genes in the families. The rhodopsin poly-CA tract²³ and the RDS gene poly-T tract²⁴ were amplified by the polymerase chain reaction in symptomatic family members. One primer in each amplification was kinase end labelled with ³²P-γ ATP, then samples were run on denaturing acrylamide gels. The gels were dried and exposed to autoradiographic film overnight. Inheritance of alleles relative to the disease was analysed using the program LINKAGE, from the LINKAGE package version 5.10.²⁵

Informed consent was obtained after the nature of the procedures had been fully explained.

Table 2 Affected patients: clinical findings

Family	Subject	Age	Acuity (R:L)	Cataract	Maculae	Goldmann fields (IV 4e target)	Electroretinogram
1	III-5	34	6/18;6/18	Yes	MO	10 degrees	Non-recordable
1	IV-3	18	6/18;6/12	No	MH	20 degrees	Non-recordable
1	III-4	30	6/36;6/36	Yes	MA	10 degrees	Non-recordable
1	II-5	42	6/18;6/24	Yes	MO	10 degrees	Non-recordable
2	VIII-12	39	6/12;6/12	Yes	MO	10 degrees	Not performed
2	VIII-47	13	6/5;6/5	No	Normal	10 degrees	Absent rod, minimal cone responses
2	VII-25	58	6/36;NPL	Yes	MA	5 degrees	Not performed
2	VIII-30	19	6/9;6/9	No	Normal	40 degrees	Rod and cone responses
2	VIII-31	22	6/6;6/6	No	Normal	40 degrees	Rod and cone responses
2	VII-28	33	6/18;6/12	Yes	MO	5 degrees	Non-recordable
2	VII-26	42	6/18;6/18	Yes	MA	5 degrees	Not performed
2	VII-14	46	6/18;6/18	Yes	MO	40 degrees	Absent rod, reduced cone responses
2	VII-13	56	6/12;6/12	No	MO	5 degrees	Non-recordable
2	VII-17	24	6/5;6/5	No	Normal	Full*	Non-recordable
3	IV-14	53	6/36;6/36	Yes	MA	15 degrees	Non-recordable
3	V-2	22	6/6;6/5	No	Normal	60 degrees	Non-recordable
4	IV-11	37	6/18;6/18	Yes	MO	10 degrees	Non-recordable
4	III-15	45	6/9;6/9	Yes	Normal	5 degrees	Not performed
4	IV-48	19	6/9;6/6	No	Normal	Full*	Absent rod, reduced cone responses
4	IV-34	16	6/6;6/6	No	Normal	Full*	Absent rod, reduced cone responses
4	IV-8	20	6/12;6/12	Yes	MO	10 degrees	Non-recordable
4	III-3	45	6/18;6/9	Yes	MO	10 degrees	Non-recordable
4	III-29	40	LP;LP	Yes	MA	<5 degrees	Not performed
4	III-19	18	LP†;6/5	No	Normal	Full*	Absent rod, reduced cone responses
4	IV-43	21	6/6;6/6	No	Normal	Full*	Non-recordable

MO=macular oedema.

MA=macular atrophy.

MH=macular hole.

*Field loss evident with smaller targets.

†Right optic nerve hypoplasia.

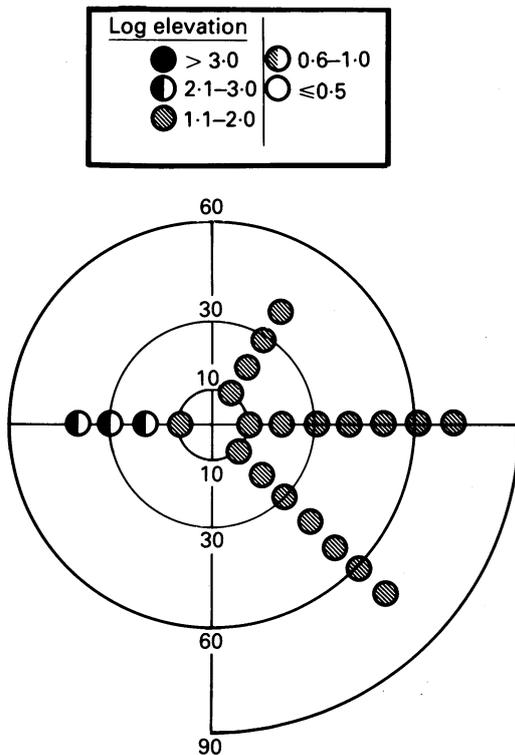


Figure 3 Static perimetry with red (dominant wavelength 660 nm, subtending 0.9 degrees) target, performed on the dark adapted right eye of subject IV-34 from family 4. The symbols represent the extent of threshold elevation relative to normal in log units. Visual angle in degrees is indicated on the vertical axis.

Results

SYMPTOMATIC FAMILY MEMBERS

Clinical features

In three families (1, 3, 4) all symptomatic members had early onset of night blindness and evidence of severe disease. Of the 15 patients from these families 10 had onset of night blind-

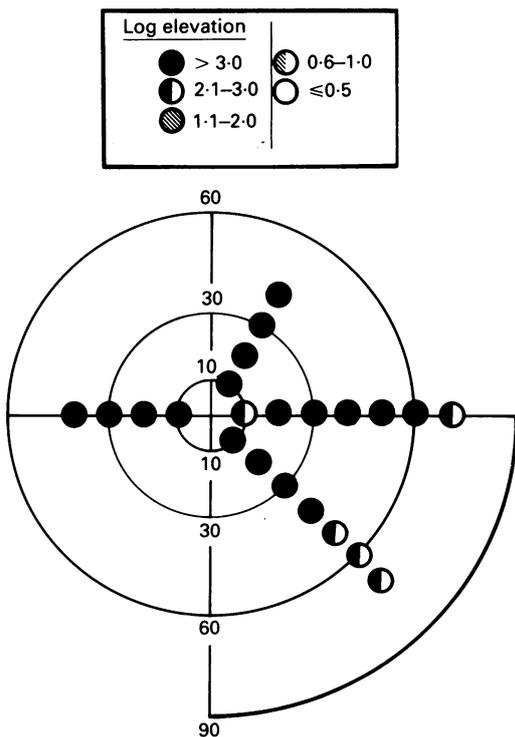


Figure 4 Static perimetry with green/blue (dominant wavelength 530 nm, subtending 0.9 degrees) target, performed on the dark adapted right eye of subject IV-34 from family 4. The symbols represent the extent of threshold elevation relative to normal in log units. Visual angle in degrees is indicated on the vertical axis.

ness before the age of 10 years and in four the onset was before the age of 20 years. One denied symptoms of night blindness. In the fourth family (family 2) there was a more variable onset of symptoms with half the patients developing night blindness after the age of 20 years (Table 1). The results of the clinical examination are shown in Table 2. In the majority of patients with reduced acuity, this was due to posterior subcapsular lens opacities or macular oedema or atrophy or a combination of these three factors. Macular oedema was present in 17 eyes, 26 of the 50 eyes had posterior subcapsular lens opacities, and one eye was aphakic. The typical fundus features of RP were seen in all 50 eyes.

Psychophysical testing and electroretinography

Scotopic and photopic visual field testing showed extensive loss of rod and cone function in most subjects tested. Only one affected individual over the age of 25 had a visual field greater than 20 degrees to the larger target (IV 4e) of the Goldmann perimeter. Although field loss was greater with increasing age, severe field loss was also seen in young family members (Table 2). There were interfamilial and intrafamilial differences in severity. In family 1 all affected family members tested, including one 18 year old subject, had extensive field loss and this pattern of severe disease was also seen in family 4. Dark adapted static perimetry performed in four members of family 1 and eight members of family 4, similarly showed widespread elevation of rod and cone thresholds throughout the retina even in young family members (Figs 2, 3, 4).

The threshold elevations were such that classification into diffuse (type 1) or regional (type 2) disease^{1,2} was not possible. In family 3 only one affected individual underwent dark adapted static perimetry and this again showed widespread and marked rod and cone threshold elevations. In these three families no subject had rod or cone thresholds within 1 log unit of normal in any area of the visual field tested. In contrast, in family 2, there was more variation in the severity of disease. One 13 year old boy had visual fields, on Goldmann perimetry (IV 4e target) reduced to 10 degrees whereas other older symptomatic family members had well preserved fields to the same target (Table 2). Similarly scotopic perimetry showed widespread and severe rod and cone threshold elevations in some subjects while in others there were some areas of the visual field with normal or only mildly elevated rod and cone thresholds. In subjects with mild disease there was patchy loss of rod and cone function consistent with the regional pattern of disease described by Lyness *et al.*²

Electroretinography showed similar interfamilial variation (Table 2). In families 1, 3, and 4 there were no identifiable rod responses in any subject and most showed non-recordable cone responses. Two subjects from family 4 had delayed cone implicit times. In family 2 the ERG responses were consistent with the findings on psychophysical testing. Two subjects with mild disease showed well preserved rod and cone responses, and all subjects with recordable cone responses had normal cone b wave implicit times.

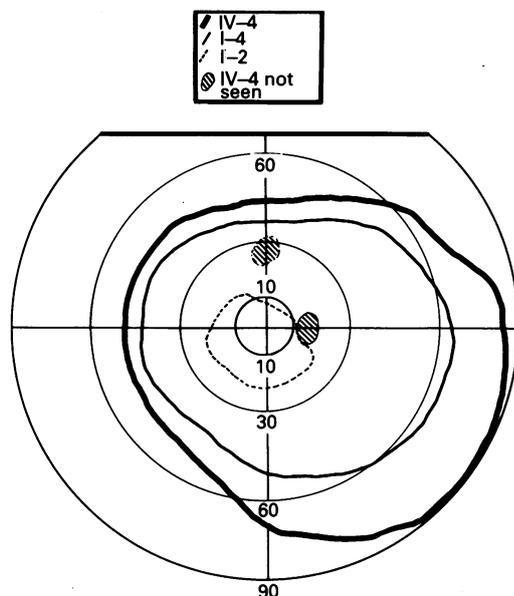


Figure 5 Goldmann field performed on the right eye of subject III-25 from family 4.

ASYMPTOMATIC OBLIGATE GENE CARRIERS

Clinical findings

All six subjects had normal visual acuity, normal fundus examination, and normal Goldmann fields to the larger target (IV 4e) used (Fig 5). Three subjects showed mild peripheral constriction and in two there were small mid peripheral scotomas to smaller targets (Table 3).

Electrophysiological and psychophysical testing

The light rise of the EOG showed a mild reduction in one or both eyes in three subjects (Table 3). The amplitudes of flash ERG were normal in five subjects and in one both scotopic and photopic responses were just below 2 SD from normal. Cone b wave implicit times were prolonged in two subjects (Table 4). Dark adapted perimetry showed normal rod and cone responses at most of the retinal locations studied but in each subject there were mild rod threshold elevations (maximum threshold elevation 1.2–1.9 log units) in at least one location. The results from a typical subject are shown in Figures 6 and 7, which can be compared with those of his 16 year old affected son (Figs 3 and 4). Flicker sensitivity was reduced in three subjects particularly at high frequencies (Table 4).

Table 3 Asymptomatic obligate gene carriers: results of perimetry, photopic flicker, and electro-oculography (EOG)

Family	Subject	Age	Goldmann perimetry	EOG(R/L)	Photopic flicker
1	II-3	60	Scotoma I-2e isoptre	241/161	Normal*
1	III-3	39	Peripheral constriction I-4e isoptre	250/271	Relative high frequency loss >2 SD
2	VII-41	40	Peripheral constriction I-2e isoptre	180/157	Normal*
3	IV-4	49	Normal	258/235	Normal*
4	III-25	41	Small scotoma I-4e target	150/170	Relative high frequency loss >2 SD
4	III-27	49	Peripheral constriction I-2e target	200/218	Relative high frequency loss >2 SD

*Although photopic flicker was within 2 SD of normal it was selectively reduced at the higher frequencies beyond 1 SD from normal.

MOLECULAR GENETICS OF THE FAMILIES

No mutations of the rhodopsin or RDS genes were found in any of the four families using the hydrolysis heteroduplex method. In families 2, 3, and 4 crossovers occurred between intragenic markers within the rhodopsin gene and all four families showed crossovers with markers within the RDS gene, providing further evidence for the exclusion of these genes as the disease locus. Family 2 provided data excluding linkage (lod score < -2.0) to rhodopsin and RDS at genetic distances of 3 and 4 cM respectively. Families 3 and 4 proved less informative, but did show one and two crossovers respectively with the rhodopsin marker and two crossovers each with the RDS marker, significantly excluding the immediate genetic loci. Similarly, in family 1 one crossover was observed with the RDS marker; the rhodopsin polymorphism was uninformative in this family.

Discussion

In some autosomal dominant disorders individuals known to be carrying the abnormal gene, because of the presence of an affected offspring and parent, may show no evidence of the disease. This non-penetrance may be complete but often subtle signs of the disease may be apparent on careful examination and investigation or may develop with increasing age. The borderline between mild expression of a gene and non-penetrance may therefore be difficult to define, especially in a disease such as adRP which may show a wide range of expression which is usually age dependent. Although non-penetrance has been described in adRP, there have been few

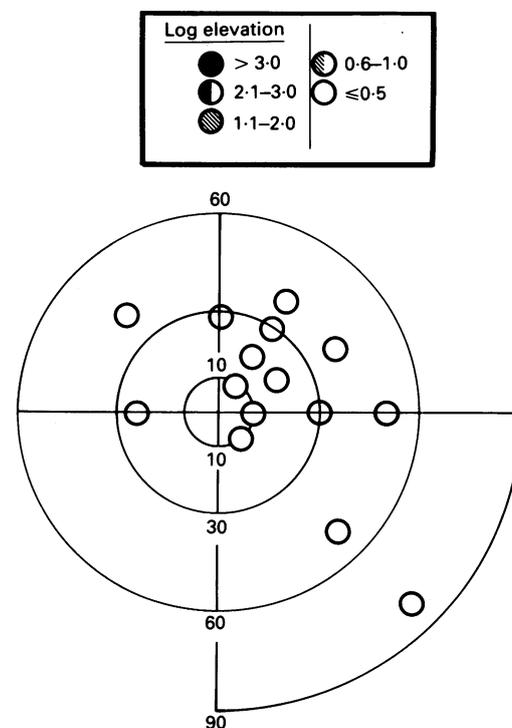


Figure 6 Static perimetry with red (dominant wavelength 660 nm, subtending 0.9 degrees) target, performed on the dark adapted right eye of subject III-25 from family 4. The symbols represent the extent of threshold elevation relative to normal in log units. Visual angle in degrees is indicated on the vertical axis.

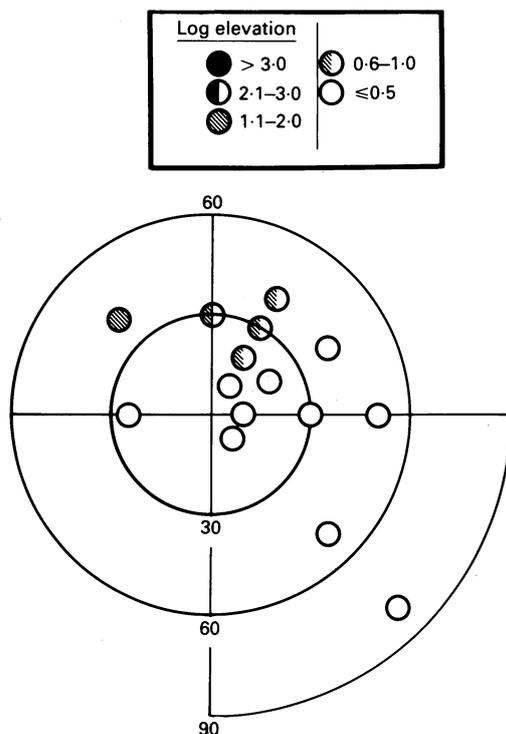


Figure 7 Static perimetry with green/blue (dominant wavelength 530 nm, subtending 0.9 degrees) target, performed on the dark adapted right eye of subject III-25 from family 4. The symbols represent the extent of threshold elevation relative to normal in log units. Visual angle in degrees is indicated on the vertical axis.

systematic studies of such families. Berson *et al*¹¹ studied one family with incomplete penetrance and suggested on the basis of the electroretinographic findings that this was distinct from other forms of adRP showing complete penetrance. In their family and two others reported subsequently¹² young symptomatic individuals showed substantially delayed cone implicit times. Two asymptomatic individuals age 42 and 75 years with the abnormal gene had a normal ERG and normal rod thresholds at the one location tested suggesting that they showed true non-penetrance of the gene. The younger patient tested 10 years later retained a normal full field ERG.¹² The families we have studied are similar to those reported by Berson and Simonoff¹² in

that some family members with the abnormal gene are asymptomatic and have a normal fundus appearance at an age when they would be expected to show clear signs of the disease. Although these 'skipped individuals' were normal on the basis of routine clinical testing, in contrast to the subjects reported by Berson *et al*¹¹ and Berson and Simonoff¹² we have been able to show that all six subjects show mild electrophysiological or psychophysical abnormalities of retinal function in some retinal locations. The most consistent abnormality was elevated rod thresholds on dark adapted perimetry. The finding of abnormal cone implicit times on electroretinography and elevated photopic flicker thresholds in some subjects is consistent with the suggestion of Berson and Simonoff¹² that there may be early peripheral cone involvement in this form of adRP.

In our families we have shown functional abnormalities in all members known to have the abnormal gene indicating that there is variable expression of the mutant gene rather than true non-penetrance. The question arises whether or not such families represent one or more distinct subtypes of adRP. On the basis of the findings in the asymptomatic obligate gene carriers they can be classified as type II or regional (R) type adRP¹² but differ from other R type families we have studied both in the severity of disease seen in young symptomatic family members and in the wide range of disease severity. Although there is some interfamilial variability in the pedigrees reported here, they share many similarities, and it is possible that they may be caused by mutations at a single locus. Variations in the pattern of retinal dysfunction have been shown to be common with different mutations in the rhodopsin gene²⁶⁻³² and similar allelic heterogeneity may be seen in other genetic disorders.³³ We have demonstrated that our families do not have mutations of the rhodopsin or RDS genes but this does not exclude the possibility that mutations of gene promoters or other related regulatory regions may be responsible. However, in three families we have excluded linkage to known loci on chromosomes 3 and 6 indicating that other genetic loci are involved. Whether or not such a wide range of expressions are caused by mutations at a single locus will depend upon the demonstration of the genetic defects.

One might expect families showing apparent incomplete penetrance to be those with mild disease of late onset, with the 'skipped individuals' being at the milder end of the disease spectrum. However, we have shown that symptomatic individuals have severe disease often of early onset. There must therefore be other factors, either genetic or environmental, that influence expression of the mutant gene. The extreme intrafamilial variation, with younger individuals often being severely affected, seen in our families make an environmental influence unlikely. Examination of the pedigree structure provides no evidence for anticipation³⁴ or genomic imprinting effects³⁵ and it seems more likely that other 'modifying' loci are responsible for influencing expression of the primary mutant gene. The identification of these genetic interactions remains a major challenge.

Table 4 Asymptomatic obligate gene carriers: amplitude and implicit times of the flash ERG

Family	Subject eye		Scotopic blue		Bright flash white				Flicker (30 Hz)	
			b amp	b imp	a amp	a imp	b amp	b imp	b amp	b imp
1	II-3	R	190	70	180	15	200	55	38	33
		L	160	80	160	15	200	55	16	33
1	III-3	R	270	60	160	15	260	55	32	31
		L	250	60	120	15	360	55	32	31
2	VII-41	R	60	60	120	16	80	50	30	35
		L	50	60	120	16	80	50	30	35
3	IV-4	R	260	70	140	15	330	50	35	31
		L	225	68	140	16	360	52	40	31
4	III-25	R	260	66	200	15	240	50	25	32
		L	230	66	200	14	360	48	30	30
4	III-27	R	180	60	240	15	240	50	25	32
		L	140	60	200	15	360	48	30	30
Normal mean			319	57	262	15	404	50	43	29
Normal -2 SD			141	69	133	20	227	56	10	32

R=right eye.

L=left eye.

a amp=amplitude a wave in microvolts.

a imp=implicit time a wave in milliseconds.

b amp=amplitude b wave in microvolts.

b imp=implicit time b wave in milliseconds.

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Note added on proof:

Since acceptance of this paper the disease locus in family 2 has been identified on chromosome 7p (Inglehearn CF, Carter SA, Keen TJ, Lindsey J, Stephenson AM, Bashir R, et al. A new locus for autosomal dominant retinitis pigmentosa (adRP) on chromosome 7p. *Nature Genetics* 1993, in press).