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Linkage analysis of five pedigrees affected with typical autosomal dominant retinitis pigmentosa

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SUMMARY Five pedigrees (including an expanded version of a previously reported pedigree) exhibiting typical autosomal dominant retinitis pigmentosa were analysed for linkage of RP to 29 genetic markers. No significant lod scores resulted. The largest lod score is +1·51 and suggests linkage between RP and Rh blood group at an estimated recombination fraction of 20% in males and 40% in females. Further studies are needed to confirm or refute this suggested linkage.

Retinitis pigmentosa (RP) is the generic name given to a group of retinopathies sharing similar clinical manifestations but having a variety of aetiologies. The disease may be inherited as a simple Mendelian trait with autosomal dominant, autosomal recessive, or X linked transmission. It can also occur sporadically or as a component of several syndromes.[1 2]

We have previously reported the results of linkage analysis on a large pedigree (RP01) with typical autosomal dominant RP.[3] Although some of the findings were modified when the computer analysis was revised,[4] the lod score for RP with Rh blood group was unaltered and suggested linkage (maximum Z=+2·50 at 10% recombination). It therefore appeared worthwhile to extend the linkage analysis by collecting data from additional members of RP01 as well as from other pedigrees exhibiting typical autosomal dominant RP. We present the results of this effort here.

Materials and methods

The original study of RP01[3] consisted of 54 people examined for genetic markers. Another 35 members have now been typed and one child in the original analysis whose RP status was uncertain has been deleted from this analysis. In addition to these 88 subjects, the linkage analysis included 40 people not available for blood studies but necessary in the pedigree as the parent of, or link between, typed members. The pedigree is shown (figs 1, 2) as it was analysed, in two parts called RP01B and RP01C. The affected subjects of the earliest generations are second cousins once removed. Members of the second pedigree, RP01A (fig 3), live in the same rural neighbourhood as RP01B and C, but no genealogical connection could be found. Five of six RP01A members were typed. In the remaining three pedigrees (figs 4, 5, 6), the number of people studied for genetic markers were: RP02, 15 of 19; RP05, 47 of

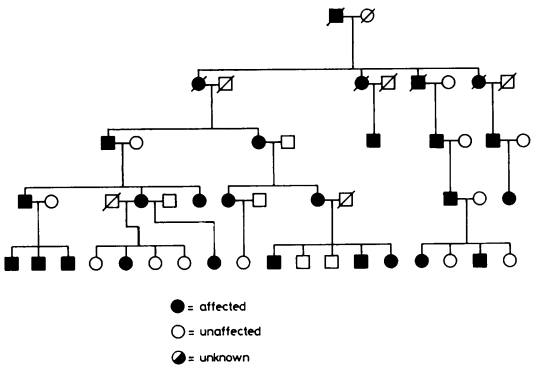

FIG 1 *Kindred RP01B*

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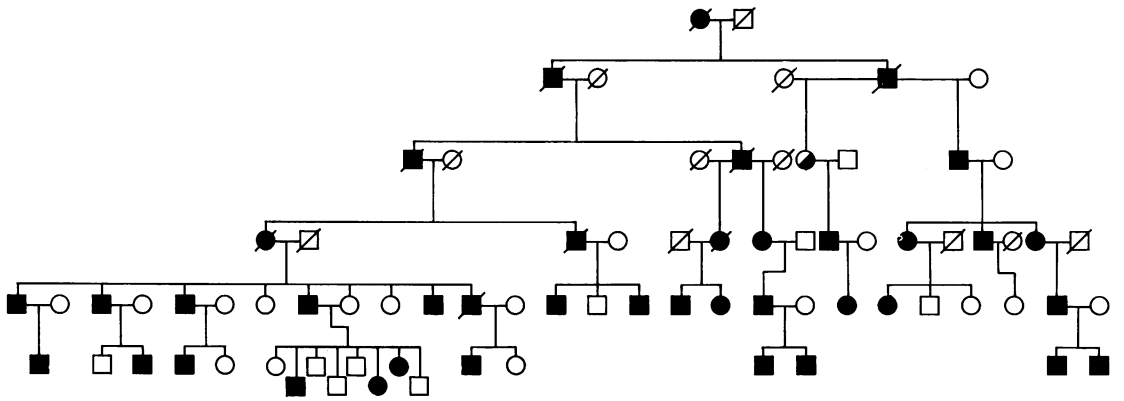

FIG 2 *Kindred RP01C*

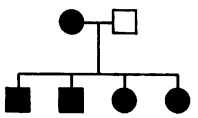

FIG 3 *Kindred RP01A*

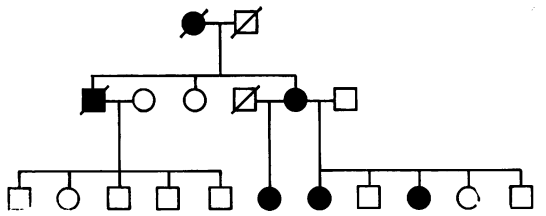

FIG 4 *Kindred RP02*

55; and RP06, 68 of 77. Thus, the analysis included 285 people, 223 of whom were typed for genetic markers.

All pedigrees are segregating typical autosomal dominant RP, which is characterised by chronic progressive degeneration of the retinal neuroepithelium (especially the rods), widespread pigmentary changes including 'bone spicule' pigment deposits, and optic nerve atrophy. The common symptoms are night blindness and gradual reduction of the peripheral visual field, which may terminate in the loss of central vision. We use the term 'typical' to distinguish this form from autosomal dominant cone-rod dystrophy, which, unlike 'typical' RP, exhibits early involvement of the cones. RP status of all members was determined by medical history and (for those whose blood was taken) also by direct examination.

Phenotypes were determined for PTC tasting

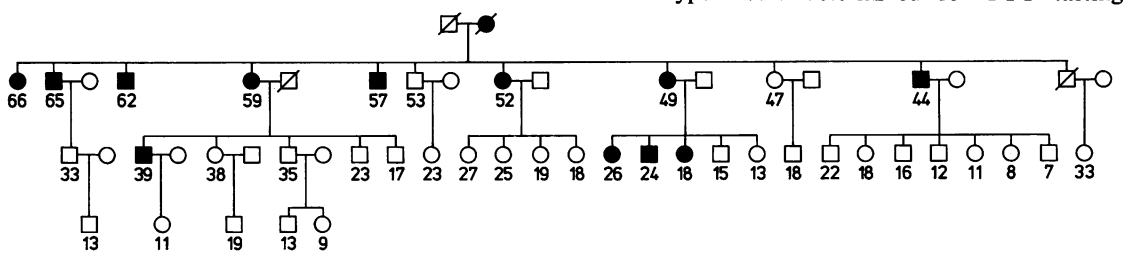

FIG 5 *Kindred RP05 with ages of affected and at risk members*

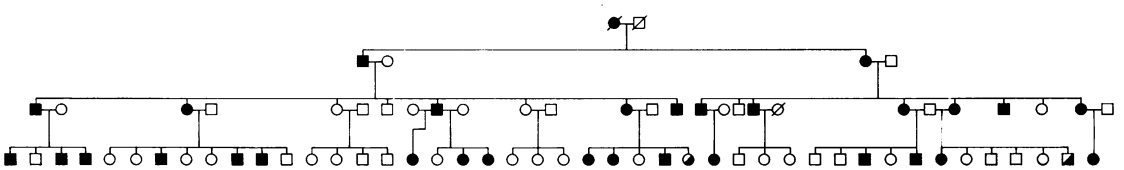

FIG 6 *Kindred RP06*

ability and 28 blood markers (ABO, Le, Rh, MNSs, Fy, Lu, K, Jk, P, Ak_1, PGD, ADA, PGM_1, PGP, ACP_1, GALT, GPT, EsD, GLO_1, HPA, TF, GC, CHE_1, CHE_2, AMY_2, BF, PGM_2, GOT_1)* using standard laboratory procedures. The programme LIPED[5] was used to calculate lod scores at 36 combinations of θ_{male}, θ_{female} (recombination fraction θ=0·01, 0·05, 0·10, 0·20, 0·30, and 0·40) for the 16 to 23 markers that were informative in the five pedigrees. Lod scores were then summed across pedigrees. The Rhesus blood group locus (Rh) was analysed assuming the presence of the four most common alleles: R_1(CDe), r(cde), R_2(cDE), and R_0(cDe). The distribution of Rh antigens in each pedigree did not indicate the presence of other alleles.

When the genotype of a person marrying into the pedigree is not known exactly and cannot be inferred from progeny, LIPED computes probabilities of possible parental genotypes from the population gene frequencies supplied by the user. All pedigrees were analysed using gene frequencies estimated from large samples of people of European origin, except RP06 which is Navajo Indian. For the analysis of this pedigree, we located Navajo gene frequency estimates for nine of the informative markers (including Rh), south-west Amerindian frequencies for another four, and were forced to use Caucasian frequencies for the remaining ten informative markers.

Examination of the age of onset range within each pedigree revealed that RP05 and RP06 had members unaffected but at risk. Since the onset range for RP06 was narrow (age 6 to 8), two members less than 8 years old were simply called 'unknown' for RP phenotype. On the other hand, RP05 had a wide onset range (age 10 to 25) and there were 20 unaffected members less than 25 years old (see figure 5). For this pedigree, we applied a sub-routine to LIPED developed by Hodge *et al*[6] which adjusts the penetrance of the RP gene according to age.

*Gene symbols are those used by the Human Gene Mapping Conference, Edinburgh, 1979 (*Cytogenet Cell Genet* 1979:25).

Results

For simplicity, we report lod scores calculated at $\theta_{male}=\theta_{female}$ (table 1). The maximum calculated score is marked with an asterisk or is given in the last column if it occurred at $\theta_m \neq \theta_f$. No statistically significant lod score (lod$\geqslant$3·0) was produced, the largest score being +1·51 for RP–Rh at θ_m=0·20,

TABLE 1 *Lod scores between RP and genetic markers* ($\theta_m=\theta_f$)†

Marker	*Chromosome*	θ=0·01	0·05	0·10	0·20	0·30	0·40	*Maximum if at* $\theta_m \neq \theta_f$:		
								Z	θ_m	θ_f
PGD	1	−0·98	−0·33	−0·10	0·04	0·06	0·04	0·07	0·40	0·30
Rh	1	−21·33	−8·12	−3·18	0·42	1·27	0·96	1·51	0·20	0·40
PGM_1	1	−21·01	−9·53	−5·01	−1·30	0·03	0·31	0·40	0·30	0·40
AMY_2	1	−3·21	−1·85	−1·28	−0·67	−0·29	−0·08*			
Fy	1	−27·30	−12·90	−7·17	−2·42	−0·59	0·01*			
ACP_1	2	−39·99	−19·43	−11·37	−4·61	−1·78	−0·53*			
MNSs	4	−36·85	−16·99	−9·21	−2·88	−0·49	0·25	0·29	0·40	0·30
GC	4	−16·63	−6·40	−2·60	0·04	0·55	0·29	0·56	0·30	0·40
BF	6	−1·18	−0·57	−0·36	−0·19	−0·10	−0·04*			
GLO_1	6	−24·61	−12·27	−7·30	−3·06	−1·26	−0·43*			
ABO	9	−34·61	−17·11	−9·95	−3·83	−1·20	−0·11*			
GALT	9	−5·25	−2·58	−1·52	−0·61	−0·19	0·00	0·02	0·20	0·40
EsD	13	−4·36	−1·68	−0·35	0·66	0·78	0·46	1·07	0·40	0·20
HPA	16	−14·80	−5·51	−2·11	0·25	0·71	0·42	0·77	0·30	0·40
PGP	16	−2·19	−1·10	−0·58	−0·14	0·02	0·04	0·06	0·30	0·40
ADA	20	−9·76	−4·92	−2·91	−1·11	−0·32	−0·00*			
GPT	?	−31·94	−15·72	−9·08	−3·30	−0·91	−0·07	0·06	0·30	0·40
Jk	?	−18·90	−9·77	−6·03	−2·82	−1·40	−0·58*			
P	?	−14·90	−7·09	−3·85	−1·20	−0·24	0·05*			
TF	?	−8·48	−4·61	−3·07	−1·78	−1·09	−0·45*			
CHE_1	?	−0·79	−0·15	0·08	0·22	0·22	0·14	0·22	0·30	0·01
CHE_2	?	−0·22	−0·21	−0·18	−0·12	−0·06	−0·02*			
PTC	?	−0·45	0·07	0·16	0·11	0·03	−0·00	0·35	0·20	0·01
Le	?	−4·31	−1·93	−0·94	−0·19	0·01	0·03	0·05	0·40	0·30
K	?	−8·08	−4·29	−2·69	−1·26	−0·54	−0·14*			

†The maximum calculated lod score is marked with an asterisk, unless it occurred at $\theta_m \neq \theta_f$, in which case it is given in the last column of the table. Scores $\leqslant -2·0$ (linkage excluded at that θ) are underlined. All lod scores for AK_1 and GOT_1 were less than absolute value 0·01.

TABLE 2 *Lod scores with Rh and nearby chromosome 1 markers for the pedigrees separately* ($\theta_m=\theta$)†

	$\theta=0.01$	0.05	0.10	0.20	0.30	0.40	*Maximum if at* $\theta_m \neq \theta_f$:		
							Z	θ_m	θ_f
RP–PGD									
RP06	−0·98	−0·33	−0·10	0·04	0·06	0·04	0·07	0·40	0·30
RP–Rh									
RP01B+C	−7·07	−1·90	−0·90	0·97*	0·95	0·54			
RP02	0·31*	0·28	0·25	0·17	0·09	0·03			
RP05	−5·85	−3·08	−1·92	−0·84	−0·33	−0·08*			
RP06	−8·71	−3·43	−1·42	0·12	0·56	0·47	0·92	0·10	0·40
RP–PGM_1									
RP01B+C	−12·98	−5·58	−2·72	−0·49	0·25	0·33	0·36	0·30	0·40
RP01A	−0·57	−0·56	−0·47	−0·27	−0·11	−0·03*			
RP02	−0·51	0·10	0·28	0·31*	0·21	0·07			
RP05	−2·47	−1·14	−1·64	−0·23	−0·07	−0·01*			
RP06	−4·47	−2·35	−1·45	−0·62	−0·24	−0·05*			

†The maximum calculated lod score is marked with an asterisk, unless it occurred at $\theta_m \neq \theta_f$, in which case it is given in the last column of the table. Scores for uninformative pedigrees (lods=0·00) are omitted.

TABLE 3 *Rh data by pedigree*†

RP01B
I 0,0
II 0,0,0,0,0,0,0,0
III 3,3,3,2,6,6,3,3,1
IV 3,5,0,3,0,3,1,3,3,0,6,2,3
V 2,5,6,3,3,1,1,3,1,3,1,1,3,3,5,3,3,3

RP01C
I 0,0
II 0,0,0,0,0
III 0,0,0,0,0,0,0,0,0
IV 0,0,0,2,0,0,5,3,3,3,5,0,5,0,0,0
V 1,0,6,5,6,7,3,6,3,3,6,0,5,3,3,3,6,3,2,3,3,2,3,2,6,3,1
VI 1,5,5,6,7,6,3,6,3,3,6,6,3,5,6,5,5,1,3

RP01A
I 6,0
II 5,6,5,5

RP02
I 0,0
II 0,3,3,0,6,2
III 6,3,3,6,6,3,3,5,3,5,3

RP05
I 0,0
II 4,6,3,5,5,0,5,5,2,5,3,5,2,4,0,4,6,0,0
III 6,6,5,0,5,0,5,3,4,5,4,3,5,6,6,5,2,3,5,3,5,5,5,5,5,5,5,5,5
IV 6,3,3,5,2

RP06
I 0,0
II 0,0,1,5
III 2,4,2,2,2,0,2,2,2,2,0,0,0,4,2,2,2,3,2,0,2,2,3,3,3,3,0
IV 2,4,0,2,0,1,0,4,1,2,1,2,0,2,2,1,2,4,1,2,2,2,2,2,4,4,2,4,2,4,1,2,4,1,2,2,4,3,2,5,3,3,3,2

Code	*Phenotype (Rh antigens present):* *D*	*C*	*c*	*E*	*e*	*Genotype assuming existence of 4 alleles:* R_1 (*CDe*), *r*(*cde*), R_2 (*cDE*), R_0 (*cDe*)
0	not tested					
1	+	+	−	−	+	R_1/R_1
2	+	+	+	+	+	R_1/R_2
3	+	+	+	−	+	R_1/r or R_1/R_0
4	+	−	+	+	−	R_2/R_2
5	+	−	+	+	+	R_2/r or R_2/R_0
6	−	−	+	−	+	r/r
7	+	−	+	−	+	r/R_0 or R_0/R_0

†The Rh phenotype codes for every subject in figs 1 to 6 are listed by generation, from left to right. The phenotype represented by each code, and the genotype interpretation used in the linkage analysis, is given at the bottom of the table.

$\theta_f=0.40$. The Rh locus has been mapped to the short arm of chromosome 1.[7] Scores with other chromosome 1 markers are maximal at θ values indicative of loose or no linkage. Other lod scores greater than +0·50 are: +1·07 for RP–EsD, +0·77 for RP–HPA, and +0·56 for RP–GC. Scores of $\leqslant -2.0$ are underlined in table 1; they are evidence against linkage of RP to the marker at that and smaller θ values.

Table 2 presents lod scores of RP with Rh for the pedigrees separately, since it may be inappropriate to sum across pedigrees if more than one RP locus is involved. Scores for RP with chromosome 1 markers that are within mapable distance of Rh are also given. Table 3 gives the Rh phenotype data for all pedigrees.

Discussion

The lod score of +1·51 suggests loose linkage of RP with the Rh blood group locus. In summing lod scores across pedigrees, we are assuming that the same RP locus is involved in all cases. Clinically, there is no basis for predicting otherwise. Although

the age of onset range differed between pedigrees, this may reflect differences in efforts at early diagnosis. Thus, the narrow onset range in the Navajo family could result from their being regularly examined by an ophthalmologist. The three larger pedigrees (RP01B+C, RP05, and RP06) all had at least some members diagnosed by the age of 10.

In the absence of biological evidence of heterogeneity, one can search for evidence of heterogeneity in the recombination fraction. Morton[8] proposed a test for linkage heterogeneity such as might result from involvement of more than one disease locus: the quantity $4{\cdot}605\ (\Sigma\hat{z}_i - \hat{Z})$ approximates a χ^2 distribution with n–1 degrees of freedom, where $\hat{z}_i$ is the maximum score at $\theta_m=\theta_f$ for i^{th} pedigree, $\hat{Z}$ is the maximum summed score at $\theta_m=\theta_f$ for the combined pedigrees, and n is the number of pedigrees. We performed this test for RP–Rh (interpolating for $\hat{Z}$ and $\hat{z}_i$) and did not find significant heterogeneity ($p=0{\cdot}67$).

If RP is linked to Rh, it would also show linkage to PGD on the pter side of Rh (recombination fraction $\theta_m=0{\cdot}17$, $\theta_f=0{\cdot}27$)[7] or to PGM_1 on the qter side of Rh (recombination fraction $\theta_m=0{\cdot}25$, $\theta_f=0{\cdot}38$).[7] Our present estimate of recombination fraction for RP–Rh would place the RP locus close to the PGM_1 locus if it were on the qter side. Since close linkage of RP–PGM_1 has been excluded by our data, the more likely location of the RP locus is on the pter side of Rh. Our scores with PGD are not inconsistent with this location; however they provide almost no information on the matter.

Hussels-Maumenee *et al*[9] examined three pedigrees for linkage relations of autosomal RP to 15 markers. No lod score greater than $+0{\cdot}50$ was obtained. Scores with Rh were negative and when these are summed to our results, the lod scores at $\theta_m=\theta_f=0{\cdot}10$, $0{\cdot}20$, $0{\cdot}30$, and $0{\cdot}40$ become $-6{\cdot}50$, $-1{\cdot}04$, $+0{\cdot}71$, and $+0{\cdot}83$, respectively. Since the maximum score we calculated for RP–Rh occurs at loose recombination fractions, a large number of informative matings will be needed to bring this score to $+3{\cdot}0$ or $-2{\cdot}0$ and thereby establish or reject linkage.

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