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 RP013 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
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All pedigrees are segregating typical autosomal dominant RP, which is characterised by chronic progressive degeneration of the retinal neuro-epithelium (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...
ability and 28 blood markers (ABO, Le, Rh, MNSs, Fy, Lu, K, Jk, P, Ak, PGD, ADA, PGM1, GPG, ACP1, GALT, GPT, EsD, GLO1, HPA, TF, GC, CHE1, CHE2, AMY2, BF, PGM2, GOT1)* using standard laboratory procedures. The programme LIPEDE 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: R1(CDe), r(cde), R2(cDE), and R0(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, LIPEDE 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 LIPEDE developed by Hodge et al which adjusts the penetrance of the RP gene according to age.

### Results

For simplicity, we report lod scores calculated at θ male = θ female (table 1). The maximum calculated score is marked with an asterisk or is given in the last column if it occurred at θ m ≠ θ f. No statistically significant lod score (lod>3·0) was produced, the largest score being +1·51 for RP-Rh at θ m = 0·20,
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TABLE 2 Lod scores with Rh and nearby chromosome 1 markers for the pedigrees separately ($\theta_m = 0$)†

<table>
<thead>
<tr>
<th>$\theta_m$</th>
<th>$\theta_f$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z</td>
<td>0.0</td>
</tr>
<tr>
<td>0.0</td>
<td>-0.98</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RP-PGD</th>
</tr>
</thead>
<tbody>
<tr>
<td>RP06</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RP-Rh</th>
</tr>
</thead>
<tbody>
<tr>
<td>RP01B+C</td>
</tr>
<tr>
<td>RP02</td>
</tr>
<tr>
<td>RP05</td>
</tr>
<tr>
<td>RP06</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RP-PGM</th>
</tr>
</thead>
<tbody>
<tr>
<td>RP01B+C</td>
</tr>
<tr>
<td>RP01A</td>
</tr>
<tr>
<td>RP02</td>
</tr>
<tr>
<td>RP05</td>
</tr>
<tr>
<td>RP06</td>
</tr>
</tbody>
</table>

†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 (lod = 0.00) are omitted.

TABLE 3 Rh data by pedigree†

<table>
<thead>
<tr>
<th>Code</th>
<th>Phenotype (Rh antigens present):</th>
<th>Genotype assuming existence of 4 alleles:</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>C</td>
<td>c</td>
</tr>
<tr>
<td>0</td>
<td>not tested</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>+</td>
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<tr>
<td>3</td>
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</tr>
<tr>
<td>4</td>
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<td>-</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

†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 $\theta$ 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 $\leq-2.0$ are underlined in table 1; they are evidence against linkage of RP to the marker at that and smaller $\theta$ 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 diag-
nosis. 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 hetero-
genity, one can search for evidence of heterogeneity 
in the recombination fraction. Morton\(^4\) proposed a 
test for linkage heterogeneity such as might result 
from involvement of more than one disease locus: 
the quantity \(4\cdot 605 (\sum z_i - \bar{Z})\) approximates a \(\chi^2\) 
distribution with \(n-1\) degrees of freedom, where \(z_i\) 
is the maximum score at \(\theta_m=\theta_i\) for \(i\)th pedigree, 
\(\bar{Z}\) is the maximum summed score at \(\theta_m=\theta_i\) for 
the combined pedigrees, and \(n\) is the number of 
pedigrees. We performed this test for RP-Rh 
(interpolating for \(\bar{Z}\) and \(z_i\)) and did not find sig-
nificant heterogeneity (p=0.67).

If RP is linked to Rh, it would also show linkage 
to PGD on the pter side of Rh (recombination 
fraction \(\theta_m=0.17, \theta_i=0.27\))\(^7\) or to \(\text{PGM}_1\) on the 
pter side of Rh (recombination fraction \(\theta_m=0.25, \theta_i=0.38\)).\(^7\) Our present estimate of recombination 
fraction for RP-Rh would place the RP locus close 
to the \(\text{PGM}_1\) locus if it were on the qter side. Since 
close linkage of RP-\(\text{PGM}_1\) 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 \(et\ a1\)^\(^8\) examined three pedigrees 
for linkage relations of autosomal RP to 15 markers. 
No lod score greater than \(+0.50\) was obtained. 
Scores with Rh were negative and when these 
are summed to our results, the lod scores at \(\theta_m=\theta_i= 
0.10, 0.20, 0.30, \text{ and } 0.40 \text{ become } -6.50, -1.04, 
+0.71, \text{ and } +0.83, \text{ respectively. Since the maximum} 
\text{score we calculated for RP-Rh occurs at loose} 
\text{recombination fractions, a large number of informa-}

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tion in memory of Margaret Helen Weston.

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