Autosomal Dominant Retinitis Pigmentosa: No Evidence for Nonallelic Genetic Heterogeneity on 3q

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Summary

Since the initial report of linkage of autosomal dominant retinitis pigmentosa (adRP) to the long arm of chromosome 3, several mutations in the gene encoding rhodopsin, which also maps to 3q, have been reported in adRP pedigrees. However, there has been some discussion as to the possibility of a second adRP locus on 3q. This suggestion has important diagnostic and research implications and must raise doubts about the usefulness of linked markers for reliable diagnosis of RP patients. In order to address this issue we have performed an admixture test (A-test) on 10 D3S47-linked adRP pedigrees and have found a likelihood ratio of heterogeneity versus homogeneity of 4.90. We performed a second A-test, combining the data from all families with known rhodopsin mutations. In this test we obtained a reduced likelihood ratio of heterogeneity versus homogeneity, of 1.0. On the basis of these statistical analyses we have found no significant support for two adRP loci on chromosome 3q. Furthermore, using 40 CEPH families, we have localized the rhodopsin gene to the D3S47-D3S20 interval, with a maximum lod score (Z_m) of 20 and have found that the order qter-D3S47-rhodopsin-D3S20-cen is significantly more likely than any other order. In addition, we have mapped (Z_m = 30) the microsatellite marker D3S621 relative to other loci in this region of the genome.

Introduction

Recent technological developments in the field of clinical genetics have enabled us to begin to elucidate the complexities of a heterogeneous group of retinal degenerative disorders collectively termed “retinitis pigmentosa” (RP). Patients with RP report problems with night and peripheral vision, which typically lead to total loss of sight. Clinical examination reveals a wide variety of signs, including degeneration of the photoreceptors, pigment deposits on the retina, attenuated retinal vessels, abnormal electroretinograms, and optic-disk pallor (Heckenlively 1988). Prevalence estimates of RP range from approximately .02% to .03% of human populations (Boughman et al. 1980; Bundey and Crews 1984), making RP the most common inherited disorder of the eye. Inheritance of RP may occur in either an autosomal dominant (adRP), autosomal recessive (arRP), or X-linked (xRP) fashion.

Previously there has been a report of the first localization of an adRP gene on the long arm of chromosome 3 (McWilliam et al. 1989), close to the gene encoding the photoreceptor-specific protein rhodopsin (Farrar et al. 1990). The results of this linkage study prompted investigators to sequence the rhodopsin gene in RP patients, and, to date, at least 60 mutations in rhodopsin have been shown to cosegregate with RP (reviewed in Humphries et al. 1992), implicating these mutations as causative elements in this group of disorders. In addition, mutations in rhodopsin have now been implicated in the most common form of RP, i.e., arRP (Rosenfeld et al. 1992).

The localization of the first adRP gene was the result of almost 3 years of exclusion work using RFLP-based techniques. The advent of the PCR, in conjunction with the identification of a new set of highly polymorphic markers known as microsatellites, enabled investigators to rapidly identify two further adRP loci within the past 2 years—one to the short arm of chromosome 6 (Farrar et al. 1991a) and a second to the pericentric
region of chromosome 8 (Blanton et al. 1991). These studies identified peripherin/RDS—a homologue of the retinal degeneration slow gene in the mouse, as carrying mutations that cosegregate with the disease phenotype in a number of adRP families (Farrar et al. 1991b; Kajiwara et al. 1991). Because of the lack of obvious candidate genes for RP in the region, the adRP gene in the pericentric region of chromosome 8 has not been characterized to date. Evidence now exists for still further genetic heterogeneity in adRP (Bashir et al. 1992; Kumar-Singh et al., in press).

Previous to these studies, an xIRP locus had been identified on Xp (Bhattacharya 1984). Homogeneity tests on the pooled data from nine different laboratories indicated that there were two xIRP loci on Xp, approximately 28 cM apart (Ott et al. 1990), with the likelihood ratio being $6.4 \times 10^8$ in favor of two xIRP loci versus a single xIRP locus. In addition, tentative evidence has been provided for the existence of a third xIRP locus, distal to the two already identified (Musarella et al. 1990; Ott et al. 1990), supported by a likelihood ratio of 293:1 for three xIRP loci versus two xIRP loci.

Recently, it has been suggested in a number of reports that there may be two adRP genes on chromosome 3q (Olsson et al. 1990; Sammans et al. 1990; Inglehearn et al. 1992). In the study by Inglehearn et al. this hypothesis was based on two lines of evidence. In the original pedigree (TCDM1) in which adRP mapped to 3q, no recombination events were observed between D3S47 (probe C17) and adRP, with a lod score of 16.5 (McWilliam et al. 1989). Similarly in a British adRP pedigree (adRP3), a distance of only $\theta = .05$ was estimated between D3S47 and adRP, with a maximum lod score ($Z_m$) of 6.08 (Lester et al. 1990). In contrast to this, the use of rhodopsin mutations in adRP pedigrees as intragenic markers resulted in a larger estimated distance, $\theta = .12$, between rhodopsin and D3S47 (Inglehearn et al. 1992). These pieces of data together with the absence of rhodopsin mutations in both TCDM1 and adRP3 lead Inglehearn et al. (1992) to suggest the possible involvement of a second adRP locus on 3q, one allelic with rhodopsin and one in the vicinity of D3S47.

This ongoing discussion on nonallelic genetic heterogeneity on 3q, in conjunction with the recent observation of a codon 207 mutation resulting in the replacement of the amino acid methionine by arginine in the rhodopsin gene in TCDM1 (G. J. Farrar, J. Findlay, R. Kumar-Singh, P. Kenna, M. M. Humphries, E. M. Sharp, D. Shiels, and P. Humphries, unpublished observations), has stimulated us to perform an admixture test (A-test) on the available data in 10 D3S47-linked adRP families to formally test this hypothesis. In this way, we provide statistical data suggesting that there is no significant support for two adRP loci on 3q. Furthermore, we provide a more refined genetic map of the region in question, with an accurate location for the rhodopsin gene and the microsatellite marker D3S621.

**Material and Methods**

**Homogeneity Testing**

To test whether one or two loci are involved in 10 D3S47-linked adRP families, an A-test was performed using the program HOMOG2 (Ott et al. 1986). In this test, heterogeneity is allowed for under a model of a mixture of two family types, both with linkage, one with $\theta_1$, the other with $\theta_2$, and the proportion of families of one type being denoted by $\alpha$. On input of two-point lod scores from the 10 families (table 1), over a shared range of map positions, HOMOG2 calculates a lod-score matrix giving combined log likelihoods over stepped values of $\alpha$ and all values of $\theta_1$ and $\theta_2$ that are quoted. In this analysis, given the number of families involved and the data available, a value of $\alpha = .1$ and $\theta = 0.001, .01, .05, .1, .2, .3, .4$ were chosen. The likelihood ratio (LR) in favor of heterogeneity over homogeneity is reported by calculating the ratio between the maximum likelihood under each hypothesis. By convention, if the maximum likelihood when two loci are allowed is 50–100 times greater than that gained under the constraint of a single locus, then the conclusion of heterogeneity is considered statistically significant (Ott et al. 1990). The LR was also computed when all families known to have rhodopsin mutations (families AD1, AD10, AD14, AD25, AD38, and TCDM1) were combined and used as a single family. Given the number of families involved in this second test—i.e., $S = \alpha$ was set at .2. To assess the power of the data to detect a difference $d$ in map location between the two hypothesized disease loci, we conducted a support interval for $d$ (Mérette et al. 1991), as follows: For a given recombination fraction $\theta$ between a disease locus and the marker, the disease is either to the left or to the right of the marker at map distance $-x$ or $x$ from marker to disease, where $x$ is the (Kosambi) map distance obtained from $\theta$. Therefore, given $\theta_1$ and $\theta_2$ between the two disease loci and the marker locus, the absolute distance between the disease loci is either $d = |X_1 + X_2|$ or $d = |X_1 - X_2|$. The support (in likelihood) for $d$ is then defined as
\[
\ln[L(d)] = \max_{\theta_1, \theta_2} \ln[L(\theta_1, \theta_2; d = |X_1 \pm X_2|)]
\] (1)

A 2-unit support interval for \(d\) approximately corresponds to a 95% confidence interval.

**Linkage Analysis**

Two microsatellite markers were typed in 40 families of the Centre d'Étude du Polymorphism Humain (CEPH) panel in this study. D3S621 (primers 5'GTG AAT CGT GCA AAA GTT CC3' and 5'TAT GGG TAG AAG TGA CGT GG3') has previously been localized to this linkage group by typing two adRP pedigrees (Kumar-Singh et al. 1991). The (CA)n microsatellite present in intron 1 of the rhodopsin gene has been described elsewhere (Weber and May 1989). PCR was carried out in a 20-μl volume containing 200 ng of genomic DNA; 200 μM each dATP, dGTP, and dGTP; 2.5 μM dCTP; 1 μCi α²³dCTP; 50 mM KCl; 10 mM Tris-HCl (pH 8.3); 1.5 mM MgCl₂; 0.01% gelatin (w/v); 0.1% Triton X-100; 20 pmol of each primer; and 0.75 units of Taq polymerase. Samples were denatured at 94°C for 4 min prior to the addition of the Taq polymerase and were processed through 32 cycles of 30 s at 94°C, 30 s at 55°C, and 40 s at 72°C. Aliquots of the amplified DNA were mixed with an equal volume of formamide buffer and electrophoresed on 8% denaturing polyacrylamide gels.

Mapping data were compiled with the CEPH database version 5.3.2, and calculations were performed with the LINKAGE version 4.9 (Lathrop et al. 1984) package of programs, on a 6230 VAX and a 640-K PC. Male and female recombination rates were taken to be equal except where indicated, and the Kosambi mapping function was used to convert recombination fraction to map distance, in all analyses.

FA-76 is a previously undescribed four-generation Spanish pedigree with RP segregating in an autosomal dominant manner. Data generated with the probe C17 (D3S47) from three affected and six unaffected members of this family show no recombination (\(\theta = 0\))

<table>
<thead>
<tr>
<th>FAMILY</th>
<th>LOD SCORE AT θ</th>
<th>DATA SOURCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCDM1</td>
<td>16.4 16.4 16.1 15.0 13.7 10.7 4.99 2.19</td>
<td>Present study</td>
</tr>
<tr>
<td>adRP3</td>
<td>-99.9 4.73 5.70 6.08 5.81 4.70 3.23 1.54</td>
<td>Inglehearn et al. 1992</td>
</tr>
<tr>
<td>P20</td>
<td>-99.9 1.17 3.04 4.59 4.77 4.13 2.97 1.55</td>
<td>A. Gal (personal communication)</td>
</tr>
<tr>
<td>AD1</td>
<td>-99.9 -5.02 -2.09 -2.3 -3.6 6.2 50 25</td>
<td>Inglehearn et al. 1992</td>
</tr>
<tr>
<td>AD10</td>
<td>-99.9 -90.07 .64 .77 .72 .54 .29</td>
<td>Inglehearn et al. 1992</td>
</tr>
<tr>
<td>S</td>
<td>-99.9 .01 1.26 1.72 1.72 1.35 .79 .22</td>
<td>A. Gal (personal communication)</td>
</tr>
<tr>
<td>AD14</td>
<td>-99.9 .22 1.17 1.66 1.69 1.34 .88 .33</td>
<td>Inglehearn et al. 1992</td>
</tr>
<tr>
<td>AD25</td>
<td>-99.9 -1.18 .78 1.30 1.37 1.19 .84 .43</td>
<td>Inglehearn et al. 1992</td>
</tr>
<tr>
<td>AD38</td>
<td>.37 .37 .36 .30 .23 .12 .05 .01</td>
<td>Inglehearn et al. 1992</td>
</tr>
<tr>
<td>FA-76</td>
<td>1.20 1.20 1.18 1.09 .98 .72 .44 .17</td>
<td>J. Benitez (personal communication)</td>
</tr>
</tbody>
</table>

**Figure 1** Distributions of the deviation \(d\) between \(X_1\) and \(X_2\), and their associated max \(\text{InLs}\), i.e., the support for \(d\) (eq. [1]). The 2-unit support intervals corresponding to 95% confidence encompass the range 0–43 cM, for the first A-test (10 families), and 0–63 cM, for the second A-test (5 families).
between D3S47 and adRP, with $Z_m = 1.2$. Pedigrees P20 (Olsson et al. 1990) and S (Sammans et al. 1990) have been described elsewhere, and updated lod scores between RP and D3S47, for both these pedigrees, were obtained by courtesy of Dr. Andreas Gal. We have described family TCDM1 elsewhere (McWilliam et al. 1989), and updated lod scores with D3S47 and RP are presented in table 1. Data of D3S47 and RP from all other families used in this study have been reviewed elsewhere (Inglehearn et al. 1992)

### Results

Two-point lod scores between D3S47 and adRP from 10 3q-linked adRP families are summarized in table 1. An A-test on this data set was performed using HOMOG2. The maximum log likelihood (max lnL) under the hypothesis of heterogeneity and homogeneity, at increments of $\alpha = .1$, was 75.618 and 74.028, respectively. These values result in an LR of 4.90, well below the requirement of 50–100 that is required for statistical significance. Hence, from this result alone, we can conclude that, on the basis of linkage analysis, there is no statistical evidence supporting two adRP loci on 3q. Furthermore, when all families with known rhodopsin mutations were combined, equal max lnLs were obtained for heterogeneity and homogeneity, maximizing at a value of 74.028, thereby resulting in an LR of 1.0 and hence indicating a reduced support for heterogeneity. The power of each A-test was assessed from the distribution of the deviations between $\theta_1$ and $\theta_2$ and from their associated max lnLs. The corresponding 2-unit support interval constructed from the first test includes 0 cM, where $\theta_1 = \theta_2$ (i.e., $d = 0$) the position of homogeneity, and also the region between 0 cM and 43 cM (fig. 1). The support interval from the second test is also shown in figure 1. Similarly, it includes $d = 0$, the position of homogeneity, and the region from 0 cM to 63 cM.

Results of two-point analyses of rhodopsin and D3S621, using other markers in this region of the genome—i.e., D3S20 (L1169), D3S47 (C17), D3S14 (R208), and D3S19 (U1)—and the CEPH data base (version 4.5), are presented in table 2. Multipoint analyses of rhodopsin, D3S47, and D3S20, using CMAP, are presented in figure 2. A $Z_m$ of 20.25 is achieved when rhodopsin is placed 14.5 cM proximal to D3S47 and 7 cM distal to D3S20. Relative odds against this order are presented in table 3.

Multipoint analyses of D3S621, D3S14, and D3S47 result in this most likely order, with a lod score of 30.23. Odds against this order are presented in table 3. Multipoint analyses of the combined data from D3S621, D3S14, D3S47, rhodopsin, D3S20, and D3S19 were used to generate a male, female, and sex-averaged map of this region (fig. 3).

### Discussion

The adRP gene segregating in a number of families has previously been shown to be linked to the 3q marker D3S47 (McWilliam et al. 1989; Lester et al. 1990; Olsson et al. 1990; Sammans et al. 1991). However, the degree of linkage of adRP to D3S47 in adRP families has been variable. For example, for families TCDM1, adRP3, and P20, linkage between adRP and D3S47 maximizes at $\theta = 0$, .05, and .1, respectively.

Recently, Inglehearn et al. (1992) have estimated that

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### Table 2

**Maximum Two-Point Lod Scores of the Rhodopsin Gene and D3S621 between Other Markers in This Linkage Group, as Calculated by LODSCORE**

<table>
<thead>
<tr>
<th>LOCUS</th>
<th>PROBE</th>
<th>$\theta_m$</th>
<th>$Z_m$</th>
<th>1-Lod Confidence Interval</th>
<th>$\theta_m$</th>
<th>$Z_m$</th>
<th>1-Lod Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>D3S20</td>
<td>L1169</td>
<td>.092</td>
<td>13.7</td>
<td>.06-.11</td>
<td>.228</td>
<td>9.4</td>
<td>.19-.25</td>
</tr>
<tr>
<td>D3S621</td>
<td>PCR</td>
<td>.180</td>
<td>15.9</td>
<td>.16-.2</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>D3S19</td>
<td>U1</td>
<td>.161</td>
<td>4.5</td>
<td>.1-.3</td>
<td>.189</td>
<td>4.4</td>
<td>.1-.3</td>
</tr>
<tr>
<td>D3S47</td>
<td>C17</td>
<td>.151</td>
<td>9.9</td>
<td>.1-.2</td>
<td>.102</td>
<td>19.6</td>
<td>.06-.14</td>
</tr>
<tr>
<td>D3S14</td>
<td>R208</td>
<td>.161</td>
<td>8.7</td>
<td>.14-.2</td>
<td>.092</td>
<td>22.6</td>
<td>.05-.14</td>
</tr>
<tr>
<td>Rhodopsin gene</td>
<td>PCR</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>.180</td>
<td>15.9</td>
<td>.16-.2</td>
</tr>
</tbody>
</table>
the distance between rhodopsin and D3S47 is approximately 12 cM. These observations, in conjunction with the absence of rhodopsin mutations in the families tightly linked to D3S47, lead them to speculate that the data would be consistent with the hypotheses of a second adRP locus on 3q. Other investigators have also speculated that there are two adRP loci on 3q (Olsson et al. 1990; Sammans et al. 1991); however, in each case, no formal statistical test for the evidence available has been presented. In all these studies the authors indicated that the confidence intervals for the map positions of rhodopsin and the adRP gene in the families being studied do overlap. On the basis of all these observations, two adRP loci have been assigned to the D3S47-D3S20 region by the chromosome 3 committee (Naylor and Carritt 1990): one allelic with rhodopsin (i.e., RP4) and one (i.e., RP5) in the vicinity of D3S47.

In the present study, we have undertaken a formal investigation of the two-locus hypothesis. Hence, we have performed an A-test on the data previously available, with the addition of one more D3S47-linked Spanish family (a total of 10 pedigrees). The results of this homogeneity test indicate that there is no statistically significant argument for the existence of two adRP loci on 3q. The LR of heterogeneity versus homogeneity is 4.90—well below the 50–100 required for

**Figure 2** Localization of rhodopsin between D3S47 and D3S20, by CMAP. D3S47 was arbitrarily placed at 0.0 cM, and D3S20 was positioned 21.37 cM proximal from it. Distance between D3S47 and D3S20 was calculated from a multipoint involving D3S47, rhodopsin, D3S20, and D3S19. This data set is superimposed on the location of the adRP gene in family P20, by LINKMAP. Note that the position for the adRP gene in P20 maximizes at the same point as the most likely position for the rhodopsin gene. Male and female recombination rates were taken to be equal, and the Kosambi mapping function was used to convert recombination fraction to map distance. Since the submission of this paper, a mutation in the rhodopsin gene has been identified in family P20 (A. Gal, personal communication), hence verifying the conclusions of the above analyses.

### Table 3

<table>
<thead>
<tr>
<th>Order</th>
<th>Probability Relative to Most Likely Order</th>
</tr>
</thead>
<tbody>
<tr>
<td>D3S47–rhodopsin–D3S20</td>
<td>1:1</td>
</tr>
<tr>
<td>D3S47–D3S20–rhodopsin</td>
<td>1:5.6 × 10^6</td>
</tr>
<tr>
<td>rhodopsin–D3S47–D3S20</td>
<td>1:1.4 × 10^6</td>
</tr>
<tr>
<td>D3S621–D3S14–D3S47</td>
<td>1:1</td>
</tr>
<tr>
<td>D3S14–D3S47–D3S621</td>
<td>1:2.1 × 10^4</td>
</tr>
<tr>
<td>D3S14–D3S621–D3S47</td>
<td>1:1.9 × 10^16</td>
</tr>
</tbody>
</table>
statistical significance (Ott et al. 1990). To test the power of the data available, we have constructed a 2-unit support interval (fig. 1). This support interval includes the value $d = 0$ (where $\theta_1 = \theta_2$) and also the region where $d$ is in the range of 0–43 cM, indicating that the loci may be either identical (homogeneity) or 0–43 cM apart. The second A-test, in which all families carrying rhodopsin mutations have been combined, produces less substantial support in favor of heterogeneity. In this test the LR is 1.0—i.e., the likelihood for homogeneity and that for heterogeneity are equal—and therefore well below the value of 50–100 required for support of heterogeneity. It is never possible to prove that $\theta_1$ and $\theta_2$ are the same, i.e., that there is homogeneity. As the data size increases, the support interval for the deviation between $\theta_1$ and $\theta_2$ will narrow if there is homogeneity. The support interval for the second A-test includes $d = 0$—i.e., the position of homogeneity—and an interval of 0–63 cM, indicating that only differences ($\theta_2 \pm \theta_1$) greater than 63 cM would be detected with this data set. The reduced likelihood of heterogeneity when the data from families known to have rhodopsin mutations are combined emphasizes the probability that the variable linkage data observed may be a result of statistical fluctuation, rather than a real difference between families. This suggestion is supported by the recent observation of a codon 207 mutation resulting in the replacement of the amino acid methionine by arginine, in the rhodopsin gene in TCDM1 (G. J. Farrar, J. Findlay, R. Kumar-Singh, P. Kenna, M. M. Humphries, E. M. Sharp, D. Shiels, and P. Humphries, unpublished observations). Observation of the support intervals from the two tests (fig. 1) indicates that the power of the test is quite weak. However, we can conclude that it is not possible to use the available linkage data for 3q-linked adRP families to support the hypothesis of nonallelic genetic heterogeneity in 3q-linked adRP. Nevertheless, these same data have previously been used to assign two adRP loci to 3q. While the presence of a second adRP locus close to rhodopsin cannot be excluded, at present there is no significant evidence arising from the available linkage data that supports the assignment of two adRP loci on 3q.

To further investigate the two-locus hypothesis, we have localized ($Z_{m} = 20$) the rhodopsin gene in the D3S47-D3S20 linkage group. Using the intragenic polymorphism in rhodopsin, we have typed 40 families of the CEPH panel (fig. 2). In a multipoint analysis of D3S47, rhodopsin, and D3S20, we have found that the order qter-D3S47-rhodopsin-D3S20-cen is significantly more likely than any other order. Odds against this order are presented in table 3. We have also mapped the highly polymorphic marker D3S621 (PIC = .78) by using 40 CEPH families. Multipoint analyses of D3S621, D3S14, and D3S47 result in the order qter-D3S621-D3S14-D3S47-cen as being the most likely order, with a lod score of 30. Odds against this order

**Figure 3** Male, female, and sex-averaged maps of the region of the rhodopsin gene, as determined by CILINK. Map distances are in centimorgans and were calculated using the Kosambi mapping function.
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are presented in table 3. A \( Z_m \) of 15.92 was obtained at \( \theta = 0.18 \) between D3S621 and rhodopsin (table 2). Hence this marker will be very useful for linkage studies of this region of the genome. A map of the region comprising the markers D3S621, D3S14, D3S47, rhodopsin, D3S20, and D3S19 is presented in figure 3.

Olsson et al. (1990) have reported linkage of adRP in P20 to D3S47, with \( \theta = 0.08 \), lod score 4.78, and no recombinations with D3S20 (Sammans et al. 1991). The authors suggested that these data, in view of the closer linkage between adRP and D3S47 in other families, would be consistent with a two-locus hypothesis. However, they stated that the 1-lod confidence intervals of the lod-score distributions involving D3S47 in each of these families fall just within each other. Using our refined genetic map of this 3q region, we have compared the location for the rhodopsin gene and the adRP gene in family P20 (fig. 2) and have found that both genes map to the same approximate location. These data again indicate that the interfamilial difference in linkage results between these families may be a consequence of statistical fluctuation, rather than of biological dissimilarity.

In summary, stimulated by previous reports of possible locus heterogeneity in 3q-linked adRP families, we have performed two A-tests—the first on 10 D3S47-linked adRP pedigrees and the second on 5 families—by combining the data from all families with rhodopsin mutations into a single family. For these two groups, we have obtained LRs of heterogeneity versus homogeneity that are 4.90 and 1.0, respectively, well below the 50–100 value required for statistical significance. Hence we find no evidence, based on linkage data, for the involvement of a second adRP locus on 3q. In addition, we have refined the genetic localization of the rhodopsin gene on 3q and have obtained a significant order of D3S47–rhodopsin–D3S20. Furthermore, we have localized the highly polymorphic marker D3S621 in this linkage group and have constructed a CEPH-based map of six loci in the region of the proposed second adRP gene. We have used this refined map together with previous linkage data for RP families, to show that the data do not support the hypothesis of nonallelic genetic heterogeneity, on 3q, for adRP. On the basis of these observations, we propose that the assignment of a second adRP locus (RP5) to 3q (Naylor and Carritt 1990), in the D3S47-D3S20 region, should be reconsidered until more direct evidence for the existence of two adRP loci on 3q is available—e.g., a mutation in a gene other than rhodopsin. The resolution of the question of nonallelic genetic heterogeneity is of great importance, in view of the serious implications that such heterogeneity would have on the use of 3q-linked markers in the diagnosis of adRP.

Note added in proof.—Since the submission of the manuscript of this paper, mutations in the rhodopsin gene in families P20 and S (A. Gal, personal communication) and adRP3 (Bell et al. 1992) have been identified. These new data support the view expressed in this paper—that at present there is no evidence for locus heterogeneity on 3q in adRP.

Acknowledgments

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