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Recombination between Rhodopsin and Locus D3S47 (C17) in Rhodopsin Retinitis Pigmentosa Families

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Summary

Autosomal dominant retinitis pigmentosa (adRP) has shown linkage to the chromosome 3q marker C17 (D3S47) in two large adRP pedigrees known as TCDM1 and adRP3. On the basis of this evidence the rhodopsin gene, which also maps to 3q, was screened for mutations which segregated with the disease in adRP patients, and several have now been identified. However, we report that, as yet, no rhodopsin mutation has been found in the families first linked to C17. Since no highly informative marker system is available in the rhodopsin gene, it has not been possible to measure the genetic distance between rhodopsin and D3S47 accurately. We now present a linkage analysis between D3S47 and the rhodopsin locus (RHO) in five proven rhodopsin–retinitis pigmentosa (rhodopsin-RP) families, using the causative mutations as highly informative polymorphic markers. The distance, between RHO and D3S47, obtained by this analysis is $\theta = .12$, with a lod score of 4.5. This contrasts with peak lod scores between D3S47 and adRP of 6.1 at $\theta = .05$ and 16.5 at $\theta = 0$ in families adRP3 and TCDM1, respectively. These data would be consistent with the hypothesis that TCDM1 and ADRP3 represent a second adRP locus on chromosome 3q, closer to D3S47 than is the rhodopsin locus. This result shows that care must be taken when interpreting adRP exclusion data generated with probe C17 and that it is probably not a suitable marker for predictive genetic testing in all chromosome 3q–linked adRP families.

Introduction

Retinitis pigmentosa (RP) is one of the most common human inherited eye disorders. The RP disorders are a heterogeneous group of retinal degenerations characterized by progressive visual field loss, night blindness, and pigmentary retinopathy. Some 36%–48% of RP patients are isolated cases and are therefore unclassifiable into either a genetic or nongenetic RP category, while the remainder show autosomal dominant (~20%), autosomal recessive (~20%), or X-linked (~13%) modes of inheritance (reviewed by Kaplan et al. 1990).

Within the autosomal dominant category of RP (adRP), different patterns of receptor-cell dysfunction have been reported by Massof and Finkelstein (1979), 1981). They showed that in some cases there was loss of rod function before loss of cone function (type 1 families), while in other families both rod and cone function degenerated simultaneously (type 2 families). In support of this classification, a separate study by Lyness et al. (1985) found that in some adRP families all affected members lost rod sensitivity throughout the visual field, in the presence of relatively normal cone thresholds. Onset in these families was consistently early, usually in the first decade of life. This form of RP was termed "diffuse" or "D-type" adRP. In other adRP families a simultaneous loss of function of both rods and cones, in a patchy fashion, was ob-

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served, with wide variation in age at onset. This was thus named "regional" or "R-type" adRP.

The first confirmed linkage in adRP was observed in a single large Irish D-type family which showed no recombination to locus D3S47 (probe C17) on chromosome 3q (McWilliam et al. 1989; Farrar et al. 1990). The gene encoding rhodopsin, the rod photoreceptor pigment, maps to 3q21-24 (Nathans et al. 1986), close to the D3S47 locus (3q21–qter; Naylor and Bishop 1989), and was therefore a candidate gene in adRP. Subsequently, four different single-base substitutions in the rhodopsin gene, affecting three different amino acids, were identified in unrelated U.S. adRP patients (Dryja et al. 1990*a*, 1990*b*), confirming that mutations in this gene are the cause of adRP in a proportion of patients.

Our laboratory demonstrated close linkage between locus D3S47 and adRP in two British D-type adRP families (Lester et al. 1990; Inglehearn et al. 1991). On sequencing the rhodopsin exons of these families, a 3-bp deletion was identified in one, which resulted in the loss of a single isoleucine residue at codon 255 (Inglehearn et al. 1991). However, no mutation was found in the remaining C17 linked D-type family. Subsequently, using a rapid screening method developed in our laboratory, we screened a further 37 adRP families and have found rhodopsin mutations in a further 11 of them. Eight of the 12 proven rhodopsin-RP families have been classified as having either D-type adRP or disease with altitudinal distribution of pigmentation (sometimes known as "sectorial" or "sector" RP), while the remainder are unclassified (Keen et al. 1991*b*; Inglehearn et al., in press). Further phenotypic differences between families with particular rhodopsin mutations have been described elsewhere (Fitzke et al. 1991). Meanwhile, a total of six type 2/R families have now shown significant exclusion of linkage in the immediate vicinity of the D3S47 locus (Blanton et al. 1990; Farrar et al. 1990; Inglehearn et al. 1990; Lester et al. 1990; Kaplan et al. 1991). Thus it seems increasingly likely that the gene(s) transmitting type 1/D adRP or disease with altitudinal distribution map to chromosome 3q, while type 2/R adRP has a different genetic location.

A number of questions remain about the adRP locus on chromosome 3q. Family TCDM1, the first pedigree linked to marker C17, has a peak lod score of 16.5 with no recombination, one of the highest linkage results ever recorded in a single family (Farrar et al. 1990). Yet, to date, no rhodopsin mutation has been reported in this family. Meanwhile an unusual family with type 2 adRP but consistently early onset, has been reported by Olsson et al. (1990), showing linkage to D3S47 with a peak lod score of 4.8 at θ = .08. adRP in this family showed three crossovers with C17, contrasting with the extremely tight linkage in family TCDM1. On the basis of these results two adRP loci have been assigned to chromosome 3q (Naylor and Carritt 1990). RP4 is allelic with rhodopsin, while RP5 represents a hypothetical second gene in the vicinity of D3S47. However, since no accurate estimate for the distance between D3S47 and the rhodopsin locus (RHO) is available, it has not been possible either to prove the presence of the second locus or to determine which family falls into which category. In a multipoint analysis between D3S47, adRP, RHO, and a number of flanking markers, using the relatively uninformative rhodopsin microsatellite, Farrar et al. (1990) saw no crossovers between these three loci in TCDM1. This analysis placed RHO at θ = .015 from C17 but with a 99% (2 lod) confidence interval with a θ of .00–.30.

We now present a linkage analysis between C17 (D3S47) and RHO, using the mutations found in rhodopsin-RP families as highly informative polymorphisms. Data are presented from the five such families which proved informative for C17, together with updated lod scores in families adRP3 (C17 linked D-type) and adRP5 (C17 linked R-type). We also report that extensive sequence analysis of the rhodopsin-coding sequence has failed to reveal a mutation in either adRP3 or TCDM1, the families first linked to locus D3S47.

Patients and Methods

All of the families used in the present study have been described previously. The rhodopsin-RP families used for the determination of genetic distance between RHO and D3S47 are as follows: adRP1 (codon 347; Keen et al. 1991*b*); adRP14 (deletion of codon 255; Inglehearn et al. 1991); and adRP10, adRP25, and adRP38 (codons 296, 190, and 211, respectively; Keen et al. 1991*a*). adRP1, adRP10, and adRP14 are D-type, while adRP25 and adRP38 are unclassified. Methods used for detecting and sequencing of each mutation and also for confirming segregation of the mutations with the adRP phenotype are described elsewhere (Keen et al. 1991*a*). Since linkage analysis in these families was performed against the mutation and not the phenotype, no correction for age at onset was required. Families adRP3 and TCDM1 are large D-type

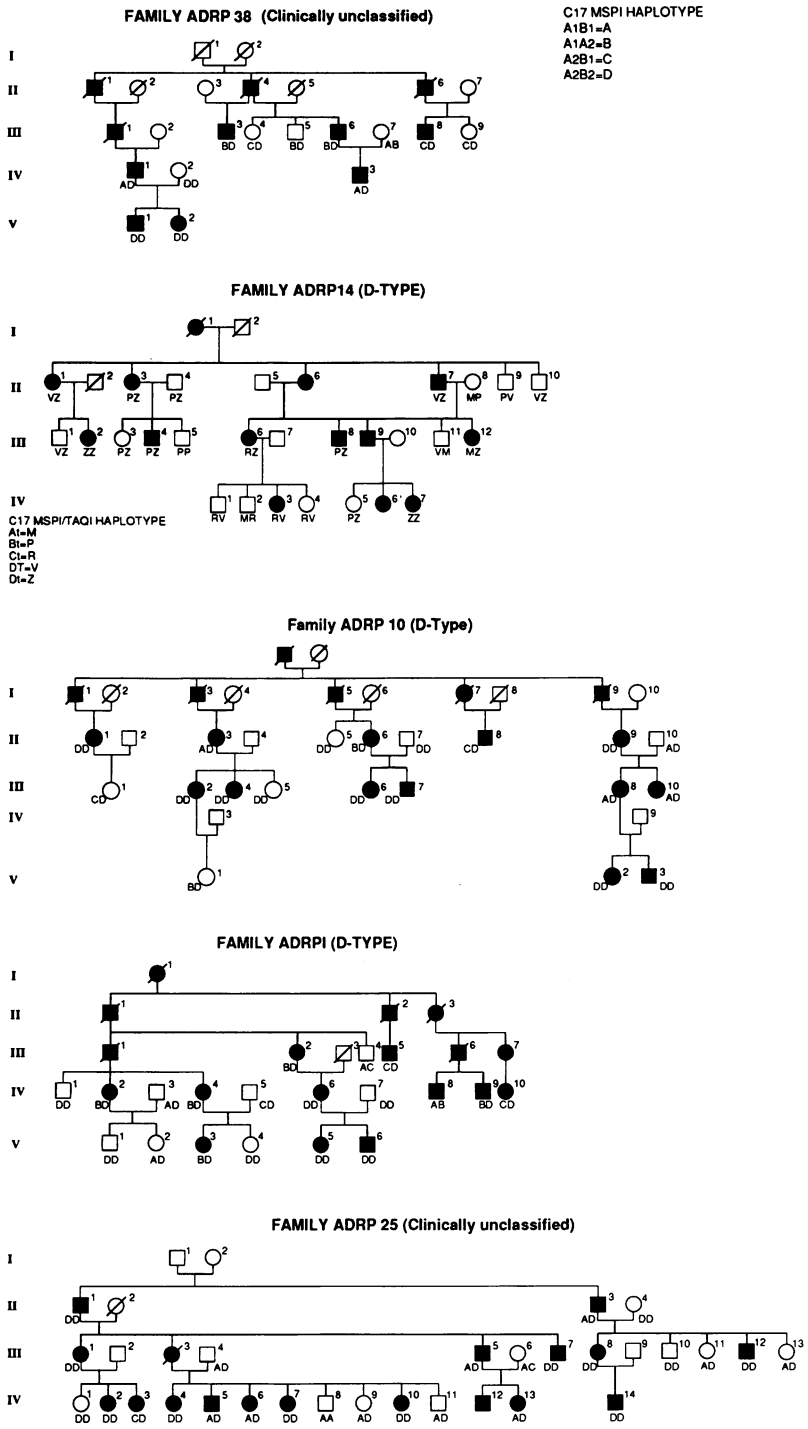

Figure 1 Pedigrees for five rhodopsin-RP families used to estimate genetic distance between D3S47 and rhodopsin. adRP status in each patient has been diagnosed by clinicians and then has been confirmed at the molecular level by detection of a rhodopsin mutation. Mutations segregated with the phenotype in all cases. The letters below each individual in the pedigrees indicate the C17 haplotype observed. The allele systems for C17 have been described elsewhere (Lester et al. 1990). Haplotype combinations for the *Msp*I allele systems are given in the key to the top right of the figure. In the case of adRP14, C17 was rendered maximally informative by further haplotyping the *Taq*I polymorphic system with the *Msp*I systems. Haplotype combinations for the analysis are given in a key immediately adjacent to the adRP14 pedigree. An unblackened square (□) denotes a normal male; an unblackened circle (○) denotes a normal female; a blackened square (■) denotes a male affected with adRP; and a blackened circle (●) denote a female affected with adRP. A slash (/) through the symbol denotes that individual is deceased.

families which were previously reported to be C17 linked with no recombination (Lester et al. 1990, McWilliam et al. 1989). In these families age at onset is consistently early, with night blindness usually within the first or second decade. No instances of obligate nonexpressing carriers, such as exist in other adRP pedigrees (e.g., see Inglehearn et al. 1990), have been observed in these families, and the ratios of affected to normal offspring approximately correspond in each generation. Penetrance was therefore assumed to be 100% after the age of 25 years.

Patients' genomic DNAs were obtained from peripheral blood lymphocytes. Probe C17 was purchased from Collaborative Research Inc. (Bedford, MA). Restriction-enzyme digestions were carried out in buffer supplied by the manufacturer, for 4–16 h. *Msp*I digests were found to be most successful when carried out at room temperature. Samples were then size-fractionated on 1% agarose gels and blotted onto hybond-N membranes (Amersham). Filters were hybridized with P-32-labeled C17 which had been precompeted with sheared human placental DNA to reduce lane background due to repeats in the probe (Sealey et al. 1985). More detailed protocols for hybridization and competing have been described elsewhere (Inglehearn et al. 1990).

Linkage analysis was carried out using the data-management package LINKSYS (Attwood and Bryant 1988), in conjunction with the program LIPED (Ott 1974). Two allele systems are detectable with C17 in *Msp*I digests (e.g., see Lester et al. 1990). These are referred to as the "A" system (A1 = 14 kb; and A2 = 12.3 kb) and "B" system (B1 = 5.2 kb; and B2 = 3.5 kb). Haplotype frequencies for these systems, on the basis of a sample of 44 unrelated Caucasian individuals, are as follows: A = A1B1 (.0875); B = A1B2 (.2625); C = A2B1 (.1625); and D = A2B2 (.4875). To further increase the informativeness of adRP14, a *Taq*I polymorphism was also haplotyped with the above systems, as shown in figure 1. This system has alleles T (7.2 kb) and t(6.8 kb) at frequencies of .17 and .83, respectively, on the basis of a sample of 45 unrelated Caucasians.

Results

Rhodopsin mutations have been described in families adRP1, adRP10, adRP14, and adRP38. Segregation of each mutation with the adRP phenotype was confirmed in each family either by heteroduplex detection or, where appropriate, restriction-enzyme digestion of PCR-amplified rhodopsin exons (Inglehearn et al. 1991; Keen et al. 1991*a*, 1991*b*; author's unpublished data). Thus there is no possibility of error by misdiagnosis in the following analysis, since linkage was performed using the mutation as a marker, not the phenotype. DNA from each family was *Msp*I digested, Southern blotted, and probed with precompeted C17. The pedigrees and allele systems observed are shown in figure 1. Lod scores between rhodopsin and C17 in each family are shown in table 1. Single crossovers are detected in families adRP10, adRP14, and adRP25, while at least two crossovers would be required to explain segregation in adRP1. The pooled data from these families suggests that rhodopsin and locus D3S47 map at a distance of $\theta = .12$ apart, with a peak lod score of 4.5.

adRP3 and TCDM1 are D-type families in which adRP has already been reported to be linked to marker C17 (McWilliam et al. 1989; Lester et al. 1990). The D3S47-adRP lod score for adRP3 has been updated subsequently to include a new branch which reveals

Table 1

Lod Scores between C17 (D3S47) and Rhodopsin in Rhodopsin-RP Families

	Lod Score at θ of											
	.00	.001	.01	.05	.1	.11	.12	.13	.15	.2	.3	.4
AD1	−99.99	−5.02	−2.09	−.23	.36	.42	.47	.51	.57	.62	.50	.25
AD10	−99.99	−.90	.07	.64	.77	.77	.78	.78	.77	.72	.54	.29
AD14	−99.99	.22	1.17	1.66	1.69	1.67	1.65	1.62	1.56	1.34	.88	.33
AD25	−99.99	−.18	.78	1.3	1.37	1.37	1.36	1.34	1.31	1.19	.84	.43
AD38	.37	.37	.36	.30	.23	.22	.21	.19	.17	.12	.05	.01
Pooled		−5.51	.29	3.68	4.42	4.45	4.47	4.44	4.38	3.99	2.81	1.31

Note.—Causative mutations were used as markers.

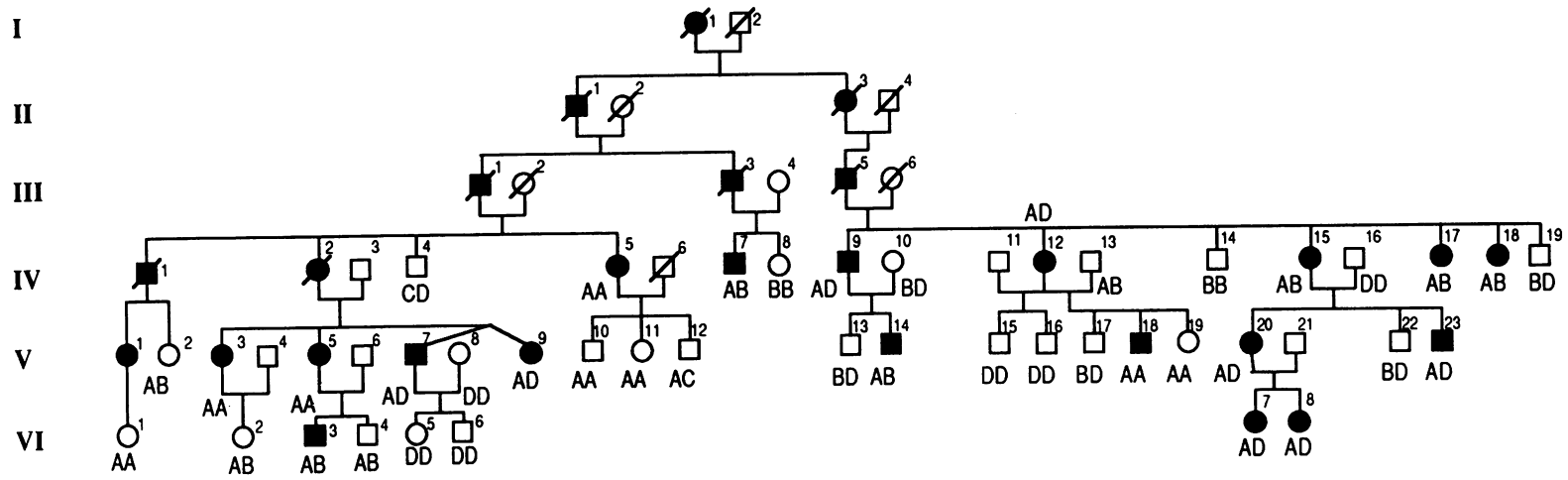

Figure 2 Pedigree for family adRP3, including previously unreported branch comprising offspring of individual IV-12. C17 haplotypes for the *MspI* allele systems are shown below each individual and are as described in the key to fig. 1. Status in this case is established only at the clinical level, since the causative mutation in this family has not been established. However, the phenotype in this family is one of consistent early onset with no known incidence of partial penetrance, so that the analysis is unlikely to be flawed by misdiagnosis. Symbols are as in fig. 1.

a single recombination event. Paternities have been confirmed in the new branch by using a variety of multilocus and single-locus VNTR probes. This results in a peak lod score between adRP and C17 of 6.1 at $\theta = .05$. The complete pedigree and C17 genotypes are shown in figure 2, while the new lod scores are shown in table 2. These data are plotted graphically in figure 3, along with the pooled RHO-RP/D3S47 lod scores. Table 2 also shows the updated C17 lod score in TCDM1 (from Farrar et al. 1990).

In order to search for a rhodopsin mutation in adRP3, the exons and 10–100 bp of the surrounding introns have been sequenced from PCR-amplified patient DNA. More than 80% of the exon sequences have been observed on both strands, while the remainder has been clearly read on one strand. As a further check, exons were PCR amplified and run on hydrolink gels to test for heteroduplexed DNA. In our hands, this technique has successfully detected nine rhodopsin mutations. No mutation was detected by either of these methods. It is therefore unlikely that adRP in this family is caused by a mutation in the coding sequence of rhodopsin. A causative mutation may exist in an intron or regulatory sequences. Also, any PCR-based mutation-detection system has the weakness that a deletion or insertion involving part or all of a primer would cause selective amplification of the normal sequence only. However, Southern blot analysis of patient's genomic DNA cut with frequent cutting enzymes has revealed no evidence of a substantial deletion. We therefore cannot rule out the hypothesis that adRP in this family may result from a mutation in another gene in the region of locus D3S47.

Similarly, the rhodopsin exons in family TCDM1 have also been extensively searched, by sequencing alone. It too has revealed no mutation to date, placing

Table 2

Lod Scores between C17 and adRP Phenotype

	Lod Score at θ of								
	.000	.001	.01	.05	.10	.20	.30	.40	Reference(s)
Group 1:[a]									
RHO-RP	−∞	−5.51	.29	3.68	4.42	3.99	2.81	1.31	Present study
Group 2:[b]									
adRP3	−∞	4.73	5.70	6.08	5.81	4.70	3.23	1.54	Lester et al. 1990
TCDM1	16.5	16.50		14.90	13.20	9.44	4.99	2.19	McWilliam et al. 1989; Farrar et al. 1990
Group 3:[c]									
Family 20	−∞		3.05	4.59	4.78	4.14	2.98	1.55	Olsson et al. 1990
Group 4:[d]									
adRP5	−∞	−18.10	−10.10	−5.28	−3.15	−1.27	−.44	−.07	Inglehearn et al. 1990
adRP7	−∞	−6.87	−3.88	−1.83	−1.04	−.42	−.18	−.07	Lester et al. 1990
UCLA-RP01	−∞	−19.70		−5.76	−3.50	−1.63	−.78	−.27	Blanton et al. 1990
Family D	−∞	−6.86	−3.92	−1.91	−1.13	−.48	−.22	−.10	Jiménez et al. 1991
Family 1	−∞	−4.5	−2.51	−1.16	−.63	−.18	−.005		Kaplan et al. 1991
Family 2	−∞	−4.96	−2.96	−1.57	−.99	−.44	−.17		Kaplan et al. 1991
TCDG1	Significant exclusion of C17 – Rho region by multipoint analysis, log likelihood less than −2.0								Farrar et al. 1990
Group 5:[e]									
Family B	−∞	−4.18	−2.20	−.90	−.42	−.06	.04	.04	Jiménez et al. 1991
Family T	−∞	−3.26	−1.30	−.07	.31	.44	.30	.10	Jiménez et al. 1991

[a] Data are pooled lod scores of C17 vs. rhodopsin mutation in proven rhodopsin RP families. Thus the peak value is an estimate of the actual distance between C17 and rhodopsin.

[b] D-type phenotype and tight linkage to D3S47; but, to date, no rhodopsin mutation has been found in these families, in spite of an extensive search in both.

[c] Type 2 in phenotype but has early onset and shows less tight linkage to D3S47. No mutation has been reported in this family.

[d] Described as type 2 or R type. All families show exclusion of linkage to marker C17 (D3S47), with varying significance (family D is described as unclassified but has unaffected obligate carriers, a symptom normally associated with type 2/R adRP).

[e] Phenotypically unclassified.

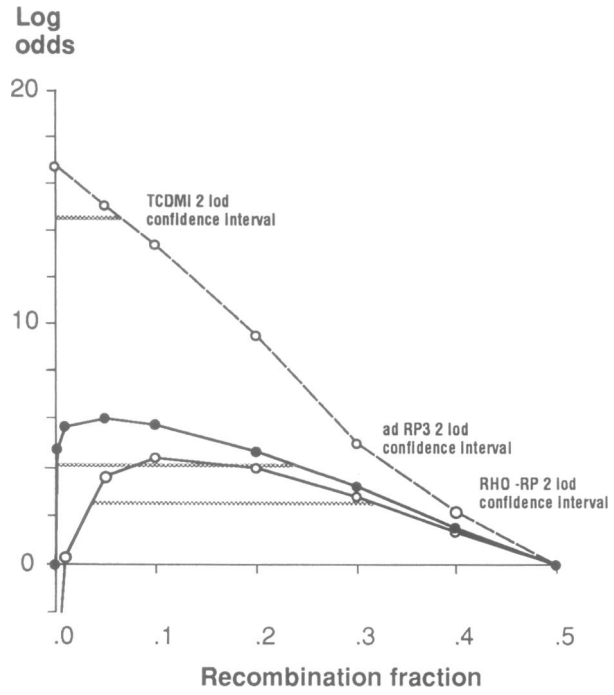

Figure 3 Graph showing lod scores between adRP and D3S47 in TCDM1 (O - - O) and adRP3 (● - - ●) and between rhodopsin and D3S47 in rhodopsin-RP (RHO-RP) families (O———O). Hatched lines under the curve for each plot denote the area bounded by a 99% confidence interval, outside of which the lod score has dropped more than 2 lod units from the peak.

it provisionally in the same category as adRP3 in this respect.

Table 2 reviews the linkage results presented in the present study and compares these with C17 linkage results obtained in a number of families in our and other laboratories. The result shown for family adRP5, an R-type family for which C17 linkage has been excluded in this laboratory, has been updated by haplotyping alleles of the C17 *Taq*I system with those of the *Msp*I A and B systems, to gain an exclusion at increased significance.

Discussion

The evidence reviewed in table 2 suggests that, as a general rule, type 1/D and sectorial adRP families map to chromosome 3q, while type 2/R families map elsewhere in the genome (see footnotes to table 2). However, data presented in the present study and in other studies now imply that there may be two categories of adRP family which map to 3q. D-type families adRP3 (present study) and TCDM1 (McWilliams et al. 1989; Farrar et al. 1990) show close linkage between adRP and C17 (lod score 6.1 at $\theta = .05$ and lod score 16.5 at $\theta = 0$, respectively). Yet, to date, these families have not revealed any rhodopsin mutation. On the other hand, D-type families adRP1, adRP10, and adRP14 and unclassified families adRP25 and adRP38 have all been shown to have rhodopsin mutations. When these are used as sequence polymorphisms, these families reveal linkage between rhodopsin and C17—but with a rather higher level of recombination (lod score 4.5 at $\theta = .12$). These lod-score data are shown graphically in figure 3. The 99% confidence intervals for each family are drawn onto each curve, as bars indicating the point at which lod scores drop by 2 from the peak. Thus it can be seen that the confidence intervals even for RhoRP and TCDM1 overlap, while adRP3 cannot be said to be significantly different from either of these. Therefore lod scores alone cannot be said to prove the two-locus hypothesis. However, these data, considered with the failure to find mutations in the coding sequences of adRP3 and TCDM1, nevertheless constitute further evidence suggestive of a second locus. If this is indeed the case, then, on the basis of the results presented here, it seems likely that the rhodopsin locus (RP4) maps some distance from locus D3S47, while the putative RP5 locus maps much closer to D3S47.

These results have implications both for research and for diagnosis in adRP. First, it is necessary to note that a family cannot be said to be excluded from the D3S47 region unless the exclusion is significant (i.e., the lod score is less than -2) to a considerable genetic distance from the locus. Thus adRP in family T reported by Jiménez et al. (1991) can no more be said to be excluded from the vicinity of the D3S47 locus than can that in adRP1, which subsequently proved to have a rhodopsin mutation. On this basis, only three families—adRP5, TCDG1, and UCLA-RP01—all of which are type 2/R, could be said to be conclusively excluded from linkage to D3S47, though other type 2/R families show highly suggestive results. Second, C17 is not a suitable probe for predictive testing in all chromosome 3–linked adRP families. Given that in the majority of cases each rhodopsin family has a different mutation, it may be tempting, in order to assess risk in such families, to use D3S47 linkage instead of directly testing for rhodopsin mutations. However, until the question of a second 3q RP locus has been resolved, this approach seems unlikely to be accurate except in large families with proven tight linkage.

Acknowledgments

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