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Evidence for a Major Retinitis Pigmentosa Locus on 19q13.4 (RP11), and Association with a Unique Bimodal Expressivity Phenotype

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Summary

Retinitis pigmentosa (RP) is the name given to a heterogeneous group of retinal degenerations mapping to at least 16 loci. The autosomal dominant form (adRP), accounting for ~25% of cases, can be caused by mutations in two genes, rhodopsin and peripherin/RDS, and by at least six other loci identified by linkage analysis. The RP11 locus for adRP has previously been mapped to chromosome 19q13.4 in a large English family. This linkage has been independently confirmed in a Japanese family, and we now report three additional unrelated linked U.K. families, suggesting that this is a major locus for RP. Linkage analysis in the U.K. families refines the RP11 interval to 5 cM between markers D19S180 and AFMc001yb1. All linked families exhibit incomplete penetrance; some obligate gene carriers remain asymptomatic throughout their lives, whereas symptomatic individuals experience night blindness and visual field loss in their teens and are generally registered as blind by their 30s. This "bimodal expressivity" contrasts with the variable-expressivity RP mapping to chromosome 7p (RP9) in another family, which has implications for diagnosis and counseling of RP11 families. These results may also imply that a proportion of sporadic RP, previously assumed to be recessive, might result from mutations at this locus.

Introduction

Retinitis pigmentosa (RP) is a heterogeneous form of inherited retinal degeneration characterized by night blindness (nyctalopia) and constricted visual fields in the early stages, often progressing to registrable blindness. RP affects 1–2 in every 5,000 births in the Western world (Boughman et al. 1980). Clinical manifestations include pigment deposition in the retina and attenuation of retinal blood vessels, with later depigmentation or atrophy of the retinal pigment epithelium. Electroretinogram (ERG) abnormalities are recordable in the early stages, with reduced amplitude of rods and, in some cases, cones. In advanced RP both rod and cone ERG responses are extinguished.

RP can be inherited in an autosomal dominant, autosomal recessive, or X-linked fashion, and the effects of the mutant gene may be confined to the eye or may be part of a multisystem disorder such as Usher or Bardet Biedl syndrome. So far, at least 16 different loci have been implicated in nonsyndromic RP (reviewed by Inglehearn and Hardcastle 1996). The autosomal dominant form (adRP), which accounts for ~25% of patients (Jay 1982), is itself both genetically and clinically heterogeneous. It can be caused by mutations in the rhodopsin (Dryja et al. 1990) and peripherin/RDS (Farrar et al. 1991; Kajiwara et al. 1991) genes on chromosomes 3q and 6p, respectively. Linkage analysis has implicated another six loci—on 7p (Inglehearn et al. 1993), 7q (Jordan et al. 1993), 8q (Blanton et al. 1991), 17p (Greenberg et al. 1994), 17q (Bardien et al. 1995), and 19q (Al-Maghtheh et al. 1994)—in its causation. Initially, the chromosome 19q adRP locus was localized, in a single large family, to a 22-cM interval between markers D19S180 and D19S214 (Al-Maghtheh et al. 1994). This linkage has recently been confirmed with the identification of a linked family of Japanese origin (Xu et al 1995). The locus has been given the number RP11 (MIM 600138; McKusick 1992). The original 19q family, known as "ADRP5," was diagnosed as having type II/R adRP as defined by Lyness et al. (1985), with apparent incomplete penetrance (Moore et al. 1993). A more detailed analysis in the light of known carrier status led Evans et al. (1995) to assign the term "bimodal expressivity" to the phenotype in this family.

We now report three new adRP families in which the phenotype maps to the RP11 locus. Like the original RP11 family, each has type II/R adRP with the "bimodal expressivity" phenotype. Typing of new 19q markers in all four linked families refines the locus to a 5-cM interval as described below.

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Subjects and Methods

Ascertainment of Phenotype in adRP Families

The adRP families presented in this study were ascertained through Moorfields Eye Hospital, London. ADRP5 and ADRP29 are from the north of England and the south of Wales, respectively, and have a type II/R form of RP with bimodal expressivity. A detailed clinical description of these families has been reported elsewhere (Moore et al. 1993; Evans et al. 1995). RP1907 and ADRP2 are newly identified British RP families that display a similar phenotype. Affected members of all these pedigrees experience night blindness in their teens and are generally registered as blind in their 30s. Some patients have posterior subcapsular lens opacities, and later in the disease process there is also macular involvement. This macular degeneration is more pronounced in members of the ADRP2 family than in the other three families, which may be the result of allelic variation such as that seen at the rhodopsin or RDS/peripherin loci.

Bimodal expressivity is defined by the presence of asymptomatic individuals who have both affected parents and affected children. Such individuals are shown as shaded symbols in figure 1. In this figure there also are shown a number of individuals who carry the affected chromosome 19 haplotype yet who do not have affected children. Since these individuals cannot be proved to be disease carriers they are shown as normal; but, given the linkage results obtained, it is likely that these individuals are carrying the mutated gene. Nevertheless, in linkage analysis these cases were treated as normal while the known carriers (shaded in fig. 1) were considered affected.

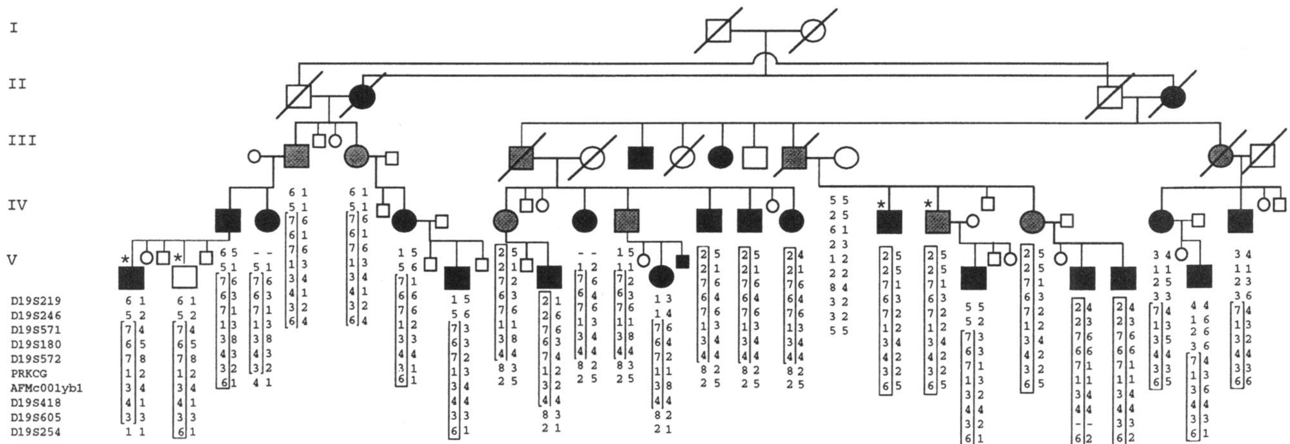
On examining families ADRP5 and ADRP29, Evans et al. (1995) concluded that 65% of gene carriers were affected whereas 35% remained asymptomatic. A similar analysis of families ADRP2 and RP1907 reveals 13 affected individuals among 19 haplotype carriers (including both categories of haplotype carrier described above), or ~68%, which correlates well with the previous estimate. This count does not include deceased family members, for whom clinical status can be inferred only anecdotally from living relatives.

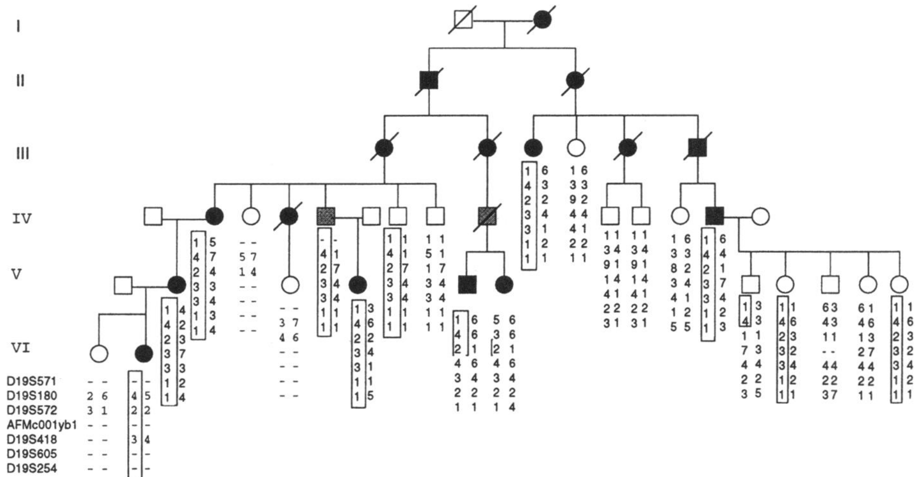
DNA Isolation and Microsatellite Analysis

DNA was isolated from peripheral blood lymphocytes by means of standard protocols. PCR reactions were carried out in 96-well microtiter plates from Omnigene. PCR reactions were performed in a total volume of 12.5 μl, composed of 2 μl diluted genomic DNA (~100 ng), 1 × *Taq* buffer (10 mM Tris-HCl, 50 mM KCl, 1.5 mM $MgCl_2$, and 0.1% nonionic detergent), 0.2 mM each of dNTPs, 2 pmol each of both forward (fluorescently end-labeled) and reverse primers, and 0.5 units *Taq* polymerase. Twenty-five cycles of PCR amplification were performed, at 94°C for 1 min, 55°C for 1 min (unless specified otherwise), and 72°C for 1 min, with an Omnigene thermal cycler. One microliter of each reaction was then diluted in 3 μl of loading buffer (deionized formamide with dextran blue) and 0.5-μl size standard (Rox 2500 standard; Applied Biosystems), denatured at 95°C for 2 min, and kept on ice until being loaded on a 6% denaturing polyacrylamide gel. Electrophoresis was performed in 1 × Tris-borate–EDTA buffer by means of an Applied Biosystems 373 DNA sequencer. Genotype data were collected and analyzed by means of Gene Scan 672 software supplied by Applied Biosystems. Markers D19S180, D19S572, and AFMc001yb1 were genotyped in all families, since they are the closest markers within and flanking the RP11 interval. Other markers were genotyped, where necessary, to confirm linkage or to establish disease haplotype. An *Msp*I polymorphism in the protein kinase C (PRKCG) gene was analyzed by standard Southern blotting techniques. Data for this marker are only shown in ADRP5; in ADRP29 it proved uninformative; in RP1907 the technique was not done, since no recombinant meioses were evident with flanking markers; and for ADRP2 there was sufficient DNA for only partial analysis.

Linkage Analysis

Pedigree information, allele frequencies, and genotype data were processed by means of the Linksys data-management package LS4 (Attwood and Bryant 1988). The adRP disease-allele frequency was assumed to be .0001. Allele frequencies for all markers were estimated on the basis of data for the normal spouses of affected family members. Only affected individuals and normal individuals >30 years old were incorporated in the analysis. However, a penetrance value of .7 (the estimated proportion of symptomatic individuals relative to all disease-gene carriers) was used to account for the incomplete penetrance seen at this locus. A value of .0001 was used to account for possible phenocopies or misdiagnoses. Both this and the penetrance were defined as values of liability classes in the data file generated by LS4. Sex-averaged recombination frequencies were also used. LS4 output files were used as input for the LINKAGE programs (Lathrop and Lalouel 1984). Pairwise and multipoint analyses were performed by means of the MLINK and LINKMAP programs, respectively, from LINKAGE package version 5.1 (Lathrop et al. 1984). Maximum-likelihood recombination fractions (θ's) between pairs of markers were assumed to be as published (Gyapay et al. 1994). For markers derived from different genome maps, these θ's were calculated, in ADRP5 and other families studied in our laboratory, for mapping purposes, by means of the ILINK program from the LINKAGE package. Multipoint analyses were per-





formed on the HGMP Resource Centre computing facility (Rysavy et al. 1992).

Results

ADRP5 is the family that initially showed linkage to markers D19S214 and D19S180 from the 19q13.4 region (Al-Maghtheh et al. 1994). Markers D19S219, D19S246, D19S571, D19S572, PRKCG, AFMc001yb1, D19S418, D19S605, and D19S254 from the 19q13.4 region (fig. 2) were also genotyped in this family. Pairwise linkage analyses between each marker and disease phenotype were performed. LOD scores obtained from these analyses are shown in table 1. Markers D19S572, PRKCG, and AFMc001yb1 gave the highest LOD scores with no recombination. Haplotype analysis with these data in ADRP5 (see fig. 1) localizes the RP11 disease gene to an 8-cM interval between markers D19S180 and D19S605. Critical recombination events with these markers are shown in figure 2. Given the number of alleles for each marker, multipoint analysis with all the markers was not possible. However, a series of multiple three-point analyses for successive combinations of two markers and disease in the region were performed (fig. 3). A maximum LOD score of 9.3 was obtained with markers D19S572 and AFMc001yb1 (fig. 3). This is consistent with the localization obtained by haplotype analysis.

In order to estimate the frequency of adRP caused by mutations at this and other loci and to further refine this localization, other adRP families from the Moorfields Eye Hospital genetic register and other sources were genotyped for various markers between D19S571 and D19S254. In total, 20 large adRP families have been screened for linkage to each of the eight known adRP loci (C. Inglehearn, unpublished data). Three unrelated adRP families, denoted "ADRP29," "ADRP2," and "RP1907," were found to be linked to this locus. Each

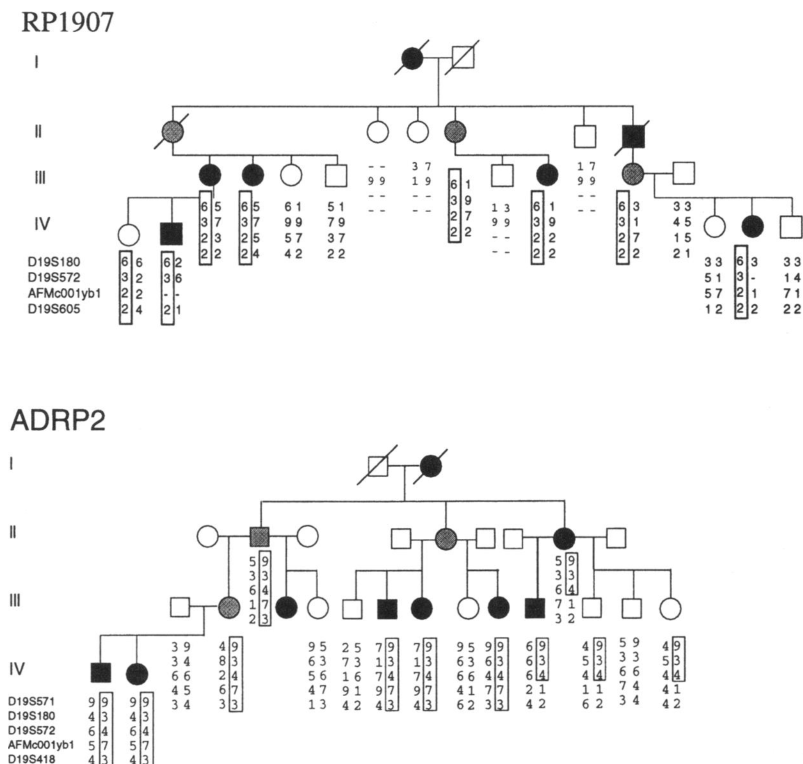


Figure 1 Haplotype analysis of the 19q13.4 markers in ADRP5, ADRP29, RP1907, and ADRP2. The disease haplotypes are boxed. Unblackened-unshaded symbols represent normal individuals; blackened symbols represent individuals with RP; and gray-shaded symbols represent asymptomatic obligate disease-gene carriers who have affected children. In each of the bottom three families there are individuals marked as normal who nevertheless have inherited the disease haplotype. These are almost certainly also asymptomatic gene carriers, but, since they do not have affected children, they were considered as normal individuals in the linkage analysis. The penetrance factor of .7 used in the linkage analysis allows for the ambiguous status of such individuals. Individuals V-7, V-8, V-9, V-10, and V-11 in ADRP29 were not included in linkage analysis, since they were too young to be diagnosed reliably. A dash (–) denotes an unknown genotype, whereas asterisks (*) denote siblings from ADRP5 who inherit the same haplotypes from both parents, although one sibling is affected and the other is an asymptomatic carrier (see the Phenotype of Chromosome 19–Linked [RP11] Families subsection in the Discussion section, above). In the analysis of ADRP5, only affected meioses were used, so only these haplotypes are given. Symbols for other typed individuals are reduced in size but are nevertheless shown, and numbering of the pedigree includes these samples.

of these shows crossovers with markers from all other previously known adRP loci (data not shown), and each has a phenotype similar to that of ADRP5 (type II/R with bimodal expressivity). The RP11 locus is linked, in each family, to a different haplotype of markers in the 19q region, excluding a founder effect.

In family ADRP29 a LOD score of 3.19 was obtained with marker D19S572, with no recombination ($\theta = 0$) (table 1). Multipoint analysis with markers D19S180 and D19S572 by means of the program LINKMAP gave a maximum LOD score of 3.39 at D19S572. Haplotype analysis in individuals V-5 and V-6 (figs. 1 and 2) of this family suggested a recombination event that could have taken place in either II-1 or III-2 and then could have been passed to V-5 and V-6 through IV-9. This recombination occurred between AFMc001yb1 and D19S572, refining the locus to a 5-cM interval between D19S180 and AFMc001yb1 (fig. 2).

In family RP1907 (see fig. 1) maximum LOD scores of 3.04, 2.1, and 2.8 were obtained with markers D19S572, AFMc001yb1, and D19S180, respectively, at $\theta = 0$ (table 1). Multipoint analysis with D19S572 and D19S180 in this family gave a LOD score of 3.12. No critical recombination events with the flanking markers for RP11 were detected.

Pairwise LOD-score analysis in ADRP2 demonstrated linkage to markers D19S571 and D19S572, with LOD scores of 2.2 and 2.3, respectively, at $\theta = 0$ (table 1). Multipoint analysis did not significantly alter these LOD scores. However, a LOD score of 2 is generally accepted as sufficient evidence for linkage of a disease to a previously known locus with similar phenotype, an understanding that often is referred to as "posterior probability." Haplotype analysis in this family, shown in figure 1, demonstrated another recombination event between D19S572 and AFMc001yb1, which confirms the 5-cM refinement obtained in ADRP29.

Previously, another retinal dystrophy locus has been

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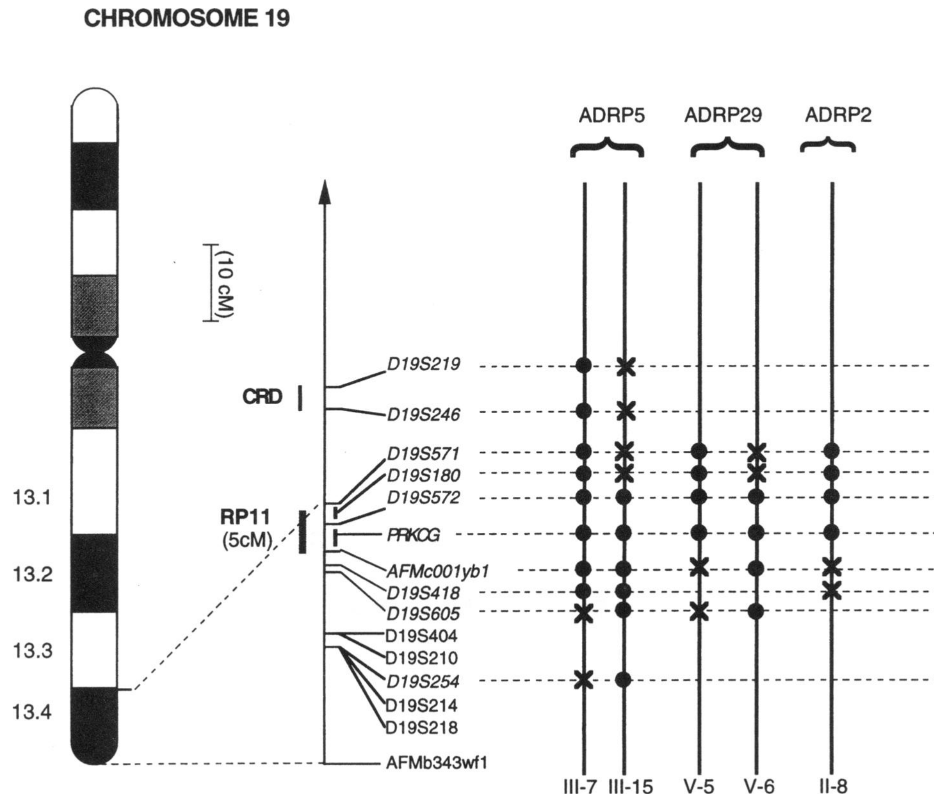

Figure 2 Linkage map of chromosome 19q13.3-q13.4, showing localization of the RP11 gene according to haplotype analysis in ADRP5, ADRP29, and ADRP2. Markers used in this analysis are italicized, and distances are those estimated by Gyapay et al. (1994). The markers D19S180 and PRKCG are placed in an interval by means of haplotype analysis, since they have not been incorporated into the existing Généthon map. Haplotypes of individuals with critical recombination events are denoted by the thicker vertical lines on the right-hand side, with nonrecombinant alleles shown as blackened circles and with recombinant alleles shown as X's. The figure also shows the localization of the CRD locus relative to the RP11 region.

mapped to the interval D19S219-D19S246 on 19q13.3-13.4 (Evans et al. 1994). Multipoint and haplotype analysis in ADRP5 by use of these markers clearly demonstrate the exclusion of the ADRP phenotype from the cone/rod dystrophy interval. Furthermore, haplotype and linkage analysis in ADRP5 and other families made it possible to integrate markers from other genome maps into the current Généthon poly-CA map. These data are shown in figures 2 and 3.

Discussion

RP11: A Major Locus for adRP

So far, four British families from this laboratory—ADRP5, ADRP29, RP1907, and ADRP2—and a Japanese family (Xu et al. 1995) have been linked to the RP11 locus. Haplotype analysis in the four families described here showed no evidence of a founder effect (fig. 1). These families were identified as part of a genetic survey of 20 adRP families with >11 meioses. All of these families now have been linked to or excluded from the known adRP loci (C. Inglehearn, unpublished data). From these data it is possible to estimate that ~20% of adRP results from mutations at the RP11 locus, making it the second most common locus for dominant RP, after rhodopsin.

This observation, together with the bimodal phenotype consistently associated with this locus, raises the interesting possibility that a significant proportion of sporadic or apparently recessive RP also may derive from mutations at this locus. The disease could then appear without any apparent family history, confusing the diagnosis. Sporadic RP accounts for ~50% of all cases and is often assumed to be recessive in origin (Jay 1992).

Linkage Analysis and Further Refinement of the RP11 Locus

Haplotype analysis using newly identified markers in the 19q13.4 region has refined the initial localization in ADRP5 from 22 to 8 cM between markers D19S180 and D19S605. Haplotype analysis in the newly linked ADRP29 and ADRP2 families confirms and further refines this to a 5-cM interval between D19S180 and AF-

Table 1

Two-Point LOD Scores between 19q13.4 Markers and Disease Phenotype in Linked Families

	LOD Score at θ =[a]							Maximum LOD Score (θ̂)
	.00	.01	.05	.10	.20	.30	.40	
ADRP5:								
D19S219	−13.0	−4.4	−.8	.52	1.32	1.27	.79	1.32 (.20)
D19S246	−7.9	−3.5	−1.4	−.4	−.23	.33	.20	.33 (.30)
D19S571	3.06	4.98	5.16	4.81	3.82	2.72	1.43	5.20 (.03)
D19S180	1.99	4.06	4.34	4.08	3.16	1.98	.64	4.35 (.04)
D19S572	7.31	7.19	6.71	6.07	4.67	3.09	1.37	7.31 (.00)
PRKCG	5.71	5.62	5.23	4.72	3.62	2.41	1.12	5.71 (.00)
AFMc001yb1	7.67	7.54	7.00	6.30	4.80	3.15	1.40	7.67 (.00)
D19S418	5.91	5.81	5.40	4.86	3.72	2.46	1.08	5.91 (.00)
D19S605	.98	3.86	4.14	3.90	3.05	2.00	.87	4.15 (.04)
D19S254	−.8	2.88	4.34	4.55	3.98	2.88	1.49	4.55 (.10)
ADRP29:								
D19S571	−6.8	−3.4	−1.7	−1.0	−.4	−.2	−.1	.0 (.50)
D19S180	.6	1.75	2.17	2.13	1.70	1.10	.48	2.17 (.05)
D19S572	3.19	3.13	2.90	2.59	1.94	1.26	.60	3.19 (.00)
AFMc001yb1	−2.7	−.6	.00	.15	.17	.09	.02	.17 (.20)
D19S418	2.26	2.21	2.00	1.73	1.18	.65	.23	2.26 (.00)
D19S605	−2.7	−.5	.13	.29	.29	.18	.07	.29 (.10)
RP1907:								
D19S180	2.80	2.75	2.54	2.27	1.66	.98	.32	2.80 (.00)
D19S572	3.04	2.98	2.76	2.47	1.82	1.10	.37	3.04 (.00)
AFMc001yb1	2.12	2.08	1.92	1.70	1.21	.70	.23	2.12 (.00)
D19S605	.26	.25	.21	.17	.10	.04	.01	.26 (.00)
ADRP2:								
D19S571	2.18	2.14	2.01	1.82	1.40	.91	.38	2.18 (.00)
D19S180	.87	.85	.78	.70	.52	.35	.17	.87 (.00)
D19S572	2.30	2.26	2.12	1.92	1.47	.95	.39	2.30 (.00)
AFMc001yb1	−1.5	.26	.83	.96	.86	.59	.26	.96 (.10)
D19S418	−1.5	.26	.83	.96	.86	.59	.26	.96 (.10)

[a] LOD scores were calculated at a disease penetrance of .7, under the assumption of sex-averaged θ's.

Mc001yb1 (fig. 2). Refinement of the locus should facilitate identification of the disease gene through either a positional cloning or a positional candidate approach. Another retinal degeneration locus for cone/rod dystrophy (CORD2) has been mapped to 19q13.3-13.4 (Evans et al. 1994). This refinement excludes the possibility of these two retinal degeneration phenotypes being allelic variants of the same genetic locus and instead confirms the presence of two distinct retinal degeneration loci, separated by ~15 cM (see fig. 3).

Phenotype of Chromosome 19–Linked (RP11) Families

In 1993 Moore et al. published a study of four adRP families with incomplete penetrance. They suggested, on the basis of analysis of these families, that two different forms of incomplete-penetrance RP could be seen. In one form, typified by family 2, gene carriers exhibited a spectrum of phenotypes, including asymptomatic, mild, and severe disease. In contrast, in families 1, 3, and 4 patients were either severely affected or asymptomatic. Family 2 has since been linked to chromosome 7p (RP9), whereas families 3 and 4, referred to here as "ADRP5" and "ADRP29," respectively, are now linked to 19q (RP11). More detailed clinical analysis of these families, in the light of known genotypes, provided further support for the two different forms of incomplete penetrance (Evans et al. 1995; Kim et al. 1995). We now report two new adRP families, ADRP2 and RP1907, both linked to 19q and both showing the "all or nothing" form of incomplete penetrance referred to here as "bimodal expressivity." Furthermore, family 1, described by Moore et al. (1993) as falling into this category, shows a segregation pattern suggestive of linkage to 19q, although LOD scores are not significant. Two other new small families that also appear to have the bimodal inheritance pattern also showed weak linkage to 19q markers. No family with this phenotype has yet been excluded from linkage to the RP11 region. It can therefore be concluded that, so far, at least five and perhaps as many as eight RP families have mutations at

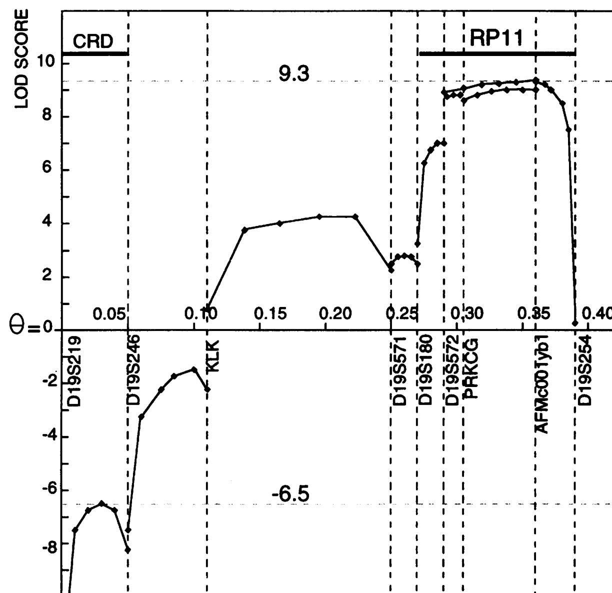

Figure 3 Multiple three-point analyses between marker pairs and disease phenotype in ADRP5, by use of 19q13.4 markers (Gyapay et al. 1994; NIH/CEPH 1992). Distances are based on our own data rather than on the Génèthon map, since two of the markers used were from the NIH/CEPH map. These distances were calculated by means of the ILINK program from LINKAGE package version 5.1. Two-point LOD scores for marker KLK in family ADRP5 have been published previously (Al-Maghtheh et al. 1994).

this locus. On this basis it appears likely that this relatively common locus for dominant RP is uniquely associated with a bimodal RP phenotype.

Environmental factors seem unlikely to play a major role in this characteristic phenotype, since their influence would be expected to be dose dependent and should therefore produce a graded, rather than an "all or nothing," phenotype. The term "digenic inheritance" has been used to describe the situation in which simultaneous mutations of two genetic loci are involved in disease pathogenesis (Kajiwara et al 1994). It is possible that digenic (or multigenic) inheritance could explain bimodal expressivity at the 19q RP locus. One hypothesis put forward by Evans et al. (1995) is that the second component in disease causation could be the apparently normal allele of the RP11 gene in each patient. However, in ADRP5 there are two examples of pairs of siblings who appear to have inherited, from both parents, the same haplotypes at the RP11 locus; yet one is affected whereas the other is an asymptomatic carrier (fig. 1, individuals marked with an asterisk [*]). Since double recombinants in such a small, well-mapped region are unlikely, this appears to exclude an allelic effect as the only factor, although it still could be involved as a component in a "multigenic" effect. The other component(s) would result from polymorphisms or mutations at a different locus or loci and could be inherited from either parent, by recessive, dominant, or X-linked modes. Such an effect therefore could be mapped only by model-independent linkage techniques such as sib-pair analysis and would be practical only with a very large sample of patients.

An alternative hypothesis that could be invoked to explain the bimodal expressivity phenotype is expansion or contraction of a triplet-repeat codon, such as has been associated with other neurodegenerative disorders (Ross 1995). A cursory examination of the pedigrees in figure 1 does appear to support an increase in severity in subsequent generations, a phenomenon known as "anticipation," which has been associated with triplet-repeat–expansion disorders. However, this is unlikely to be significant, since normal younger members of the families are less likely to consent to give blood, reducing the apparent frequency of asymptomatic carriers in the lower generations. Nevertheless, we have tested for and excluded expansion of CAG repeats as a cause of RP in a number of adRP families, including ADRP5, using the repeat-expansion–detection (RED) technique (T. J. Keen and C. Inglehearn, unpublished data).

Prospects

Informed genetic counseling using a haplotype-based diagnosis is now available for most family members. Symptomatic individuals can be given a clearer picture of the expected progression of the disease, while their risk of having affected children can be more accurately estimated, as ~35% (on the basis of penetrance value) rather than 50%. Similarly, asymptomatic gene carriers >30 years of age will probably remain unaffected for the rest of their lives, although, once again, their children will be at a 35% risk of developing symptomatic RP. Identification of the disease gene and mutation spectrum leading to retinal degeneration in RP11 families would further improve counseling, increase our understanding of RP causation and normal eye function, and could lead to an understanding of the biological basis of bimodal expressivity in these families.

Acknowledgments

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