Original articles

A linkage survey of 20 dominant retinitis pigmentosa families: frequencies of the nine known loci and evidence for further heterogeneity

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Abstract

Autosomal dominant retinitis pigmentosa (ADRP) is caused by mutations in two known genes, rhodopsin and peripherin/Rds, and seven loci identified only by linkage analysis. Rhodopsin and peripherin/Rds have been estimated to account for 20-31% and less than 5% of ADRP, respectively. No estimate of frequency has previously been possible for the remaining loci, since these can only be implicated when families are large enough for linkage analysis. We have carried out such analyses on 20 unrelated pedigrees with 11 or more meioses. Frequency estimates based on such a small sample provide only broad approximations, while the above estimations are based on mutation detection in much larger clinic based patient series. However, when markers are informative, linkage analysis cannot fail to detect disease causation at a locus, whereas mutation detection techniques might miss some mutations. Also diagnosing dominant RP from a family history taken in a genetic clinic may not be reliable. It is therefore interesting that 10 (50%) of the families tested have rhodopsin-RP, suggesting that, in large clearly dominant RP pedigrees, rhodopsin may account for a higher proportion of disease than had previously been suspected. Four (20%) map to chromosome 19q, implying that this is the second most common ADRP locus. One maps to chromosome 7p, one to 17p, and one to 17q, while none maps to 1cen, peripherin/Rds, 8q, or 7q. Three give exclusion of all of these loci, showing that while the majority of dominant RP maps to the known loci, a small proportion derives from loci yet to be identified.

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Retinitis pigmentosa (RP) is an inherited retinal degeneration affecting approximately one in every 4000-5000 people.[1 2] It can be inherited as an X linked, dominant, recessive, or digenic disorder and at least 19 different genetic loci are now implicated in its causation.[3] The dominant form (ADRP) accounted for 19% of all RP in a US survey[2] and 22% in a UK survey.[4] Within this category there is considerable locus heterogeneity. So far there are nine known loci for ADRP, on chromosomes 1cen,[5] 3q21-24 (rhodopsin),[6] 6p12 (Rds/peripherin),[7 8] 7p13-15 (RP9),[9] 7q31 (RP10),[10] 8q11 (RP1),[11] 17p (RP13),[12] 17q (RP16),[13] and 19q (RP11).[14]

Mutations in the rhodopsin gene have been estimated to account for between 20 and 31% of ADRP,[15-21] while peripherin/Rds mutations account for less than 5%.[21 22] The remaining seven ADRP loci were mapped by linkage analysis in large families. Some feeling for the frequencies of these loci can be gained by scanning the available publications. Further ADRP families have been reported as linked to 7q, 17p, and 19q, suggesting that these might be commoner loci.[23-26] However, frequency estimates based on published data would almost certainly be biased. Mutations in known genes can be detected in small pedigrees or even single patients, so these may be over-represented. Conversely as the number of such mutations reported goes up, their scientific priority goes down, so that they may no longer appear in published reports. Also, for linked loci, those discovered several years ago may have been tested more comprehensively in large families than those reported recently. Finally, it would be impossible to determine from such a survey whether any further ADRP loci remained to be found and what proportion of ADRP these loci accounted for.

The aim of this study is to estimate frequencies for the various forms of ADRP by reviewing previously published and new data generated on large ADRP pedigrees in this laboratory. This work has been carried out over the last seven years on ADRP DNA samples derived largely from patients in the Moorfields Eye Hospital Genetic Register and some other sources. Published data from this laboratory have included analyses of both large and small ADRP pedigrees and of single RP patients with a family history indicating dominant inherit-

ance. However, in order to avoid bias owing to the factors described above, this study includes only those pedigrees for which there were sufficient DNA samples available for comprehensive linkage analysis (11 or more meioses). These criteria gave a set of 20 unrelated ADRP pedigrees, 17 of which have been assigned to the known ADRP loci and three of which exclude them.

Materials and methods

Over a period of around 15 years blood samples have been collected from 20 ADRP families with 11 or more meioses. These include 14 English, two Scottish, two Italian, one American, and one South African pedigrees. Where possible, all families were traced back several generations and no evidence of a common ancestor was found for any two of these families. Genomic DNA was prepared from these samples using a Nucleon II DNA extraction kit (Scotlab Bioscience). Microsatellite markers from known ADRP loci were then typed in the families by radioactive PCR amplification and size fractionation on 6% polyacrylamide denaturing gels. For most markers a standard cycling profile of 30-35 cycles at 94°C, 55°C, and 72°C was used, with 30 seconds at each step. Products were labelled with P32 either by end labelling a primer or by incorporation of a small amount of labelled nucleotide. Lod scores were calculated from data files prepared on the LINKSYS (version 3.1) data management package then transferred to the LINKAGE (version 5.1) suite of programs. Linkage analysis was carried out both on a PC and on the Human Genome Mapping Project Resources Centre computing facility. Mutation screening of rhodopsin was carried out first by heteroduplex analysis[27] and then by direct genomic sequencing of PCR amplified exons using a Pharmacia T7 sequencing kit.

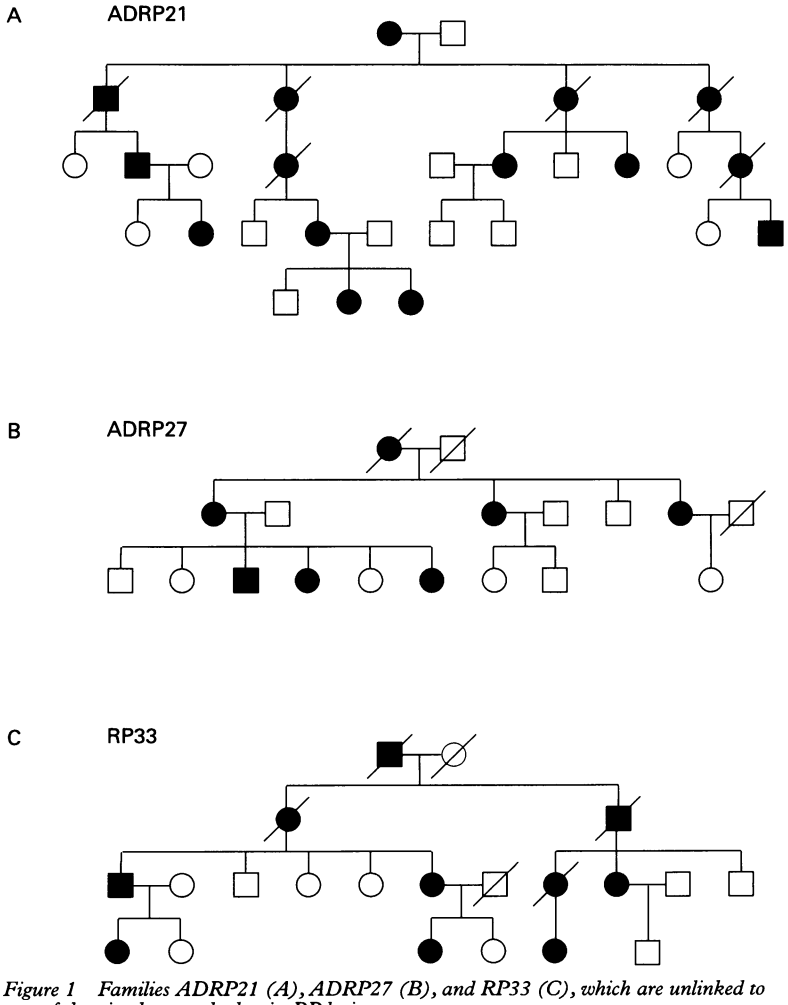

Figure 1 Families ADRP21 (A), ADRP27 (B), and RP33 (C), which are unlinked to any of the nine known rhodopsin-RP loci.

Table 1 Rhodopsin mutations identified in large ADRP families

Codon	*Nucleotide change*	*Amino acid change*	*Lab family name*	*Reference*
23	CCC-CAC	Pro-His	US RP	This study
135	CGG-TGG	Arg-Trp	ADi-1	This study
178	TAC-TGC	Tyr-Cys	ADRP3	18
178	TAC-TGC	Tyr-Cys	ADRP16	This study
190	GAC-AAC	Asp-Asn	ADRP30	31
255	delATC	del Ile	ADRP14	32
345	GTG-ATG	Val-Met	RP2650	This study
345	GTG-ATG	Val-Met	ADRP6	This study
347	CCG-CTG	Pro-Leu	ADRP1	18
Lod score 4.82 at 0 cM with D3S1292			ADRP 26	This study

Results

Of the 20 ADRP families tested, 10 mapped to the rhodopsin locus. In two of these the mutations were identified by direct screening of the rhodopsin gene by heteroduplex analysis, without initial linkage analysis. The remaining eight were first linked to the 3q21-24 region before subsequent rhodopsin mutation screening. Linkage mapping around the rhodopsin locus has in the past been difficult. The markers most commonly used to exclude it were C17 (D3S47), the Southern blot marker first linked to ADRP at 3q,[6] and a microsatellite in intron 1 of the gene itself.[28] However, D3S47 is now estimated to be some 18 cM from rhodopsin[29] while the intragenic microsatellite has a heterozygosity of only 33%. By haplotype analysis in families linked to the 3q region, we have placed rhodopsin in the 5 cM gap between markers D3S1292 and D3S1589 from the Genethon microsatellite map.[30] D3S1292 has a heterozygosity of 85%, and gave a maximum lod score of 21.75 at θ=0.02 with the ADRP phenotype in these families. It has therefore been used in this study as the marker of choice for the rhodopsin-RP locus.

The rhodopsin mutations found in nine of the 10 3q linked families are shown in table 1. The finding of mutations in four of these families has been published previously, while the remaining six rhodopsin-RP families are described here for the first time. Each of the mutations identified had been described by this laboratory or by other researchers before this report. In two cases families shared the same mutation. Families RP2650 and RP1700 both have the codon 345 GTG-ATG (Val-Met) mutation, while families ADRP3 and ADRP16 both carry the codon 178 TAC-TGC (Tyr-Cys) mutation. However, linked haplotypes for both D3S1292 and D3S1589 in each family were different. These data, together with the lack of genealogical evidence for a link between

Table 2 Exclusion data in unlinked families

Locus	Markers ADRP21	Lod scores 0.00	0.01	0.05	Markers RP33	Lod scores 0.00	0.01	0.05	Markers ADRP27	Lod scores 0.00	0.01	0.05
1cen/RP18	D1S498	−∞	−5.18	−2.53	D1S305	−∞	−6.43	−3.08	D1S534	−∞	−5.28	−2.58
RHO	D3S1589	−2.57	−2.41	−1.46	ACPP	−∞	−4.31	−2.20	D3S1292	−∞	−3.45	−1.51
RDS	PolyT	−∞	−4.13	−2.09	PolyT	−∞	−3.01	−1.57	PolyT	−∞	−1.10	−0.48
7p/RP9	MS0006	−∞	−2.56	−0.94	D7S460	−∞	−5.19	−2.51	MS0006	−∞	−4.02	−2.04
7q/RP10	D7S530	−∞	−4.26	−2.09	D7S480	−∞	−2.19	−0.88	D7S530	−∞	−2.01	−0.73
8q/RP1	D8S285	−∞	−2.80	−1.37	D8S166	−∞	−6.45	−3.17	D8S166	−∞	−6.36	−3.64
17p/RP13	D17S831	−∞	−4.54	−2.37	D17S849	−∞	−3.90	−1.89	D17S831	−∞	−3.74	−1.75
17q/RP17	D17S807	−∞	−5.62	−2.89	D17S790	−∞	−3.62	−1.63	D17S807	−∞	−4.40	−2.31
19q/RP11	D19S572	−6.44	−4.03	−2.14	D19S572	−3.75	−2.33	−1.03	D19S572	−3.96	−2.10	−1.18
Xp22/RP15					DXS1214	−∞	−7.31	−3.91				

Exclusion data for the known ADRP loci in the families shown in fig 1. In each case markers used are the closest informative systems, based on current published map refinements. Linkage analysis at the 19q (RP11) locus assumed a penetrance of 0.7, while disease at other loci was assumed to be fully penetrant. For the most recent published locus refinements see the following references: RP9,[37] RP10,[24] RP1,[38] RP13,[39] RP17,[13] RP11,[35] RP18.[5] For the Rds locus, the 3' poly T polymorphism[40] or D6S282 were used. For the rhodopsin locus as well as D3S1292 and D3S1589 (see results) the microsatellite ACPP, mapping 4 cM from rhodopsin[29] was used when necessary. At the RP9 locus we have identified a new poly-CA polymorphism known as MS0006, mapping centrally in the RP9 YAC contig,[37] in a cosmid containing the marker D7S683. This highly informative microsatellite (heterozygosity 0.86) amplifies clearly and is now the polymorphism of choice for testing for RP9 linkage. Primers are ACTCCGCAGTAACATCATGG and CTCTAGTGTTTTCTAAAGCCAG which give a product of approximately 140-160 bp in size.

these families, suggest that these mutations arose independently, though it remains possible that the families are distantly related. One other family, ADRP26, gave a lod score of 4.8 with D3S1292 but has failed to show a mutation in rhodopsin after being screened twice by both heteroduplex analysis and direct sequencing. It has previously been speculated that a second 3q locus existed close to RHO, though subsequent analysis of linked families appeared to exclude this.[33] Such a locus could now be invoked to explain the results obtained in family ADRP26. However, given the apparent absence of any other such families among the many now tested world wide for linkage to rhodopsin, it seems more likely that the mutation is in an adjacent promoter sequence, or that it causes a PCR primer to fail to amplify the altered sequence, so that only the normal allele is seen on screening. A similar case has recently been described in the peripherin/Rds gene.[34] Further analysis of this family is under way in an attempt to identify the mutation involved.

In a further four families, ADRP is linked to the RP11 locus on chromosome 19q. ADRP5, the family first linked to the locus,[14] now gives a peak multipoint lod score of 9.3 with markers D19S572 and AFMc001yb1 at the locus. Families ADRP29, RP1907, and ADRP2 give two point lod scores of 3.19, 3.04, and 2.3 respectively with marker D19S572. These pedigrees show crossovers with all other ADRP loci and share a consistent "bimodal expressivity" phenotype.[35] Haplotype analysis confirms that each of these families is unrelated to the others. One family in the set, known as ADRP7, is the family in which an ADRP locus on chromosome 7p (RP9) was identified.[9] No further families map to this locus. Another pedigree, assigned the number RPD8, is that in which a locus on 17q was discovered.[13] Finally, one pedigree, designated RP1729, maps to the RP13 locus on chromosome 17p, with a multipoint lod score of 5.1 between ADRP and markers AFMc024za5, D17S1529, and D17S831.[36] No families in this set of 20 mapped to the 1cen, peripherin/Rds, 7q, or 8q loci.

In three families, known as ADRP21, ADRP27, and RP33, all of the nine known loci were excluded. These pedigrees are shown in fig 1. In most cases the two point lod scores obtained in these families, shown in table 2, exclude the entire RP interval at each locus at a significance of <-2. Where they did not, other markers were typed and these data were analysed by multipoint linkage using the program Linkmap (data not shown), to extend the region excluded. Also, for family ADRP21, the rhodopsin poly-CA showed an intragenic crossover, but in the other families it proved uninformative. Families RP33 and ADRP21 have instances of male to male transmission, excluding X linked inheritance. However, since ADRP27 has no male to male inheritance, marker DXS1214, mapping to the RP6/RP15 locus, was typed, and a lod score for this marker in ADRP27 is given in table 2. This excludes linkage to the RP15 X linked dominant locus.[41] The severity of the disease in female family members was considered to be inconsistent with X linked inheritance at the RP2 and RP3 loci.[42] The results obtained were thus sufficient to exclude all loci in each family. Table 3 summarises the results described above.

Table 3 Frequency estimates obtained in a genetic survey of 20 large ADRP families

Locus	Families linked/ mutation detected	Total
1cen (RP18)		
RHO	10	50%
RDS		
7p13–15 (RP9)	1	5%
8q11 (RP1)		
7q31 (RP10)		
17p13 (RP13)	1	5%
17q22–24 (RP17)	1	5%
19q13 (RP11)	4	20%
Excluded	3	15%

Discussion

In this report we have described the completed analysis of 20 ADRP families by both linkage analysis and mutation detection. In each family it has been possible either to assign the disease to a known locus or to exclude it from all such loci. This has provided an estimation of

frequencies for the nine known ADRP loci and has also shown evidence for a further locus or loci.

The figure of 50% obtained for the frequency of rhodopsin-RP, assuming that the codon 178 and 345 mutations found in this sample arose independently, is higher than previous estimates. In spite of the small sample size this result is significantly different from published frequencies. Pooling the data from references 15 to 21, a figure of 156 rhodopsin-RP cases out of 653 ADRP patients screened is obtained (24%). With these data as a control, the observation of 10 out of 20 ADRP families with rhodopsin mutations is a significant deviation from the expected ratio ($p<0.01$). This may reflect a bias towards the fully penetrant form of RP associated with most of the rhodopsin mutations described to date, resulting from the selection of large families. There may also be sample bias in that, with the exception of the Italian families, these families are all of northern European origins. Alternatively this may imply that previous surveys have missed a proportion of mutations, since no mutation screening technique guarantees 100% success.[43] This is further illustrated by the apparent absence of a mutation in ADRP26, a family clearly linked to the rhodopsin locus. It is therefore possible that rhodopsin, the gene first implicated in ADRP causation, may ultimately prove to be the most common site for mutations leading to dominant RP. If so, this would be an important result for diagnostic laboratories, which are currently faced with a complex task in attempting to provide a counselling service to RP sufferers.

Of the other ADRP loci only RP11 (19q) appears to account for a substantial proportion of the families studied. Obviously a figure of 20% is only an approximation, but the recent publication of a Japanese family also linked to 19q markers further underlines this locus as a significant cause of dominant RP world wide. For the remaining seven loci one or no families were identified as linked, suggesting that, in this sample of families at least, these were not a major cause of ADRP. Finally, three families or around 15% of the sample are excluded from linkage to any of the known loci. Therefore, while most cases of ADRP result from mutations in the known loci, a further locus or loci remain to be found.

In interpreting the data presented and reviewed in this study, it is necessary to recognise that a sample of 20 families is not large, and therefore these frequency estimates provide only a broad approximation of the true figures. Thus the loci which are represented in this survey by single families cannot be said to be significantly more frequent than those which were not found at all. However, the relative rarity of large ADRP pedigrees means that significantly better estimates are unlikely to become available until all dominant RP genes have been cloned. The families sampled will not reflect the sort of geographical variation in frequencies of the different forms of RP seen in other studies,[44] but such variations are probably the result of a founder effect for single mutation events. The 20 families described here derive from a large outbred population and so should provide a good approximation of dominant RP frequencies world wide. For now, this study is at least a baseline for appreciating the relative clinical significance of each of the nine dominant RP loci described so far.

The results presented therefore imply that at least 10 loci are involved in causing ADRP. A further nine are implicated in recessive and X linked RP, while in addition there are at least four loci for Bardet-Biedl syndrome and seven for Usher syndrome, both of which involve RP and other defects. It is thus abundantly clear that RP is a relatively common phenotype associated with defects in many different genes, with each gene involved representing a component necessary for the maintenance of a normal retina. The identification and functional characterisation of each of these genes will undoubtedly improve our understanding of retinal function, which in turn may open up new routes to widely applicable therapies for the many different forms of RP.

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