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Evidence That the Penetrance of Mutations at the RP11 Locus Causing Dominant Retinitis Pigmentosa Is Influenced by a Gene Linked to the Homologous RP11 Allele

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Summary

A subset of families with autosomal dominant retinitis pigmentosa (RP) display reduced penetrance with some asymptomatic gene carriers showing no retinal abnormalities by ophthalmic examination or by electroretinography. Here we describe a study of three families with reduced-penetrance RP. In all three families the disease gene appears to be linked to chromosome 19q13.4, the region containing the RP11 locus, as defined by previously reported linkage studies based on five other reduced-penetrance families. Meiotic recombinants in one of the newly identified RP11 families and in two of the previously reported families serve to restrict the disease locus to a 6-cM region bounded by markers D19S572 and D19S926. We also compared the disease status of RP11 carriers with the segregation of microsatellite alleles within 19q13.4 from the noncarrier parents in the newly reported and the previously reported families. The results support the hypothesis that wild-type alleles at the RP11 locus or at a closely linked locus inherited from the noncarrier parents are a major factor influencing the penetrance of pathogenic alleles at this locus.

Introduction

Retinitis pigmentosa (RP) is a progressive degeneration of the rod and cone photoreceptor cells in the retina leading to visual loss and often to blindness by middle age. Most cases have no associated extraocular disease (i.e., nonsyndromic RP) whereas a minority of cases have other disease, such as deafness associated with RP in Usher syndrome. Nonsyndromic RP and many forms of syndromic RP exhibit nonallelic heterogeneity. For example, nonsyndromic RP can be inherited as a dominant, a recessive, an X-linked, or a digenic trait (for a review, see Dryja and Li 1995). Within the category of nonsyndromic dominant RP, mutations in genes encoding rhodopsin and peripherin/RDS have been identified as causes (Dryja et al. 1990; Farrar et al. 1991; Kajiwara et al. 1991). Also, unidentified genes causing nonsyndromic dominant RP have been assigned through linkage studies to chromosomes 1cen (Xu et al. 1996*b*), 7p (Inglehearn et al. 1993, 1994; Keen et al. 1995), 7q (Jordan et al. 1993; McGuire et al. 1995; Millán et al. 1995), 8q (Blanton et al. 1991; Xu et al. 1996*a*), 17p (Greenberg et al. 1994; Goliath et al. 1995; Kojis et al. 1996; Tarttelin et al. 1996), 17q (Bardien et al. 1995; McGuire et al. 1996; Mohamed et al. 1996), and 19q (Al-Maghtheh et al. 1994, 1996; Xu et al. 1995). At least one additional dominant RP locus exists (Xu et al. 1996*b*).

In those families with dominant RP showing linkage to chromosome 7p or 19q (specifying the RP9 and RP11 loci, respectively), there is variable expressivity, with some obligate carriers being asymptomatic and showing no evidence of retinal degeneration through ocular examination or by electroretinography (Evans et al. 1995; Kim et al. 1995; Nakazawa et al. 1996). This is in striking contrast to what is found in most families with dominant RP, in which even young patients without subjective visual abnormalities invariably can be shown through ophthalmic evaluation to have signs of retinal degeneration. The basis for the reduced penetrance of mutations at the RP9 and RP11 loci is unknown.

In this article, we present linkage data indicating that dominant RP in all of three reduced-penetrance families ascertained in our laboratory is likely to be due to mutations at the RP11 locus. In addition, we compile and

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analyze data, derived from these families and from those previously reported, that relate to possible causes for the reduced penetrance of RP11 mutations.

Patients, Material, and Methods

Fifty-six family members from the three ascertained families participated in this study, as well as 43 unrelated control individuals (40 without RP or an allied disease and 3 members from a family with Usher syndrome, of whom 1 is an affected individual and 2 are individuals who married into the family). Informed consent was obtained from every participant, and the tenets of the Declaration of Helsinki were followed. This study was approved by the institutional review boards of the Harvard Medical School and the Massachusetts Eye and Ear Infirmary. From each participating patient, 10–50 ml of venous blood were obtained. Leukocyte nuclei were prepared from the blood samples and were stored for as long as 10 years, at −70°C, before DNA was purified by use of standard methods.

Dinucleotide polymorphic markers were analyzed by amplification by PCR of the relevant genomic region. Amplification primers were synthesized (Gibco/Life Technologies) in accordance with either published sequences (for D19S572 and D19S926) (Dib et al. 1996) or sequences from the Genome Database (for D19S180) (http://gdbwww.gdb.org). Prior to amplification, 20 pmol of one of each pair of primers was ^{32}P-end-labeled by use of polynucleotide kinase (New England Biolabs) and 60 μCi γ-labeled ^{32}P (6,000 Ci/mmol; New England Nuclear); equal aliquots of the labeled primer were added to as many as 50 PCRs. The relevant genomic regions were amplified from 50–100 ng of genomic DNA in the wells of microtiter plates. The PCR was performed in 20 μl containing 50 mM KCl, 20 mM tris, pH 8.4 or 8.6, 2 μg BSA/μl, 1.5 mM $MgCl_2$, 0.25 units AmpliTaq (Perkin Elmer), 18–20 pmol of each primer, including 0.4–1.0 pmol of the primer that was ^{32}P-labeled. The solution was placed under 40 μl of mineral oil. PCR entailed 22 rounds of polymerization with annealing temperatures of 50–56°C depending on the specific microsatellite analyzed. Amplified DNA was diluted 1:1 (v:v) with a solution of 95% formamide, 20 mM EDTA, 0.05% bromphenol blue, and 0.05% xylene cyanol. Fragments were separated by electrophoresis through 6% denaturing polyacrylamide gels.

Marker allele frequencies were based on a sample of 57 or 58 unrelated individuals, including 43 unrelated controls (42 for D19S180); 13 individuals who had married into these families; and 1 gene carrier each from two of the families who were the only individuals in the study who possessed an uncommon allele at one of the marker loci. Two-point linkage analysis was performed by use of the MLINK program of the LINKAGE package, version 5.1 (Lathrop et al. 1984). The genetic model used in the linkage analysis for the disease locus was for autosomal dominant inheritance with reduced penetrance estimated at .49 for the susceptible genotype, on the basis of data from the three families. LOD scores were not changed substantially if the penetrance value was within the range of .6–.7 that was used by another group (Evans et al. 1995; Al-Maghtheh et al. 1996). The disease-gene frequency was set at .0001, and all affected individuals were assumed to be heterozygous carriers of the disease allele, whereas all individuals marrying into the families were assumed to be homozygous wild type.

Multipoint analysis was performed with the GENEHUNTER program (Kruglyak et al. 1996). Parameters in the multipoint analysis were the same as those described for the two-point analysis. The marker order and distances used in the multipoint analysis were as follows: D19S180–5.7 cM–D19S572–6.2 cM–D19S926. The distance between D19S572 and D19S926 is as published by Dib et al. (1996) (also see the Généthon database [http://www.genethon.fr]). Since no reliable published distance between D19S180 and D19S572 was available, we used the distance between D19S571 and D19S572 (Dib et al. 1996) as a conservative estimate, since D19S180 has been reported to be located between these two markers (Al-Maghtheh et al. 1996).

The correlation between the inheritance of alleles from the noncarrier parents and the presence of disease in carrier offspring was studied by use of two types of sib-pair analyses based on data derived from the families described in this article and from those reported previously by Xu et al. (1995) and by Al-Maghtheh et al. (1996). First, the sibships with at least one affected and one unaffected carrier were analyzed exclusively. All sib pairs in these sibships were considered independently and were arranged into a 2×2 contingency table according to disease status (discordant vs. concordant) and inheritance of RP11-linked marker haplotypes from the noncarrier parent (same vs. different RP11 haplotypes). A few sib pairs were excluded from the analysis because the inheritance of RP11 alleles from the noncarrier parent could not be deduced with certainty, in some cases because of crossovers in the RP11 region.

A second sib-pair analysis included all carrier sib pairs of all sibships and used the program SIBPAIR (Satsangi et al. 1996). This program allows one to look at affected and unaffected carrier siblings, in contrast with most other nonparametric-linkage-analysis programs that normally perform an affected-sib-pair analysis only. The test statistic is equivalent to a LOD score calculated under a simple recessive model. To correct for within-sibship correlation when there is more than one sib pair in a sibship, the program assigns a weight of $n - 1$ to sibships of size n. When the parents' genotypes are not available, the likelihood is calculated by considering all

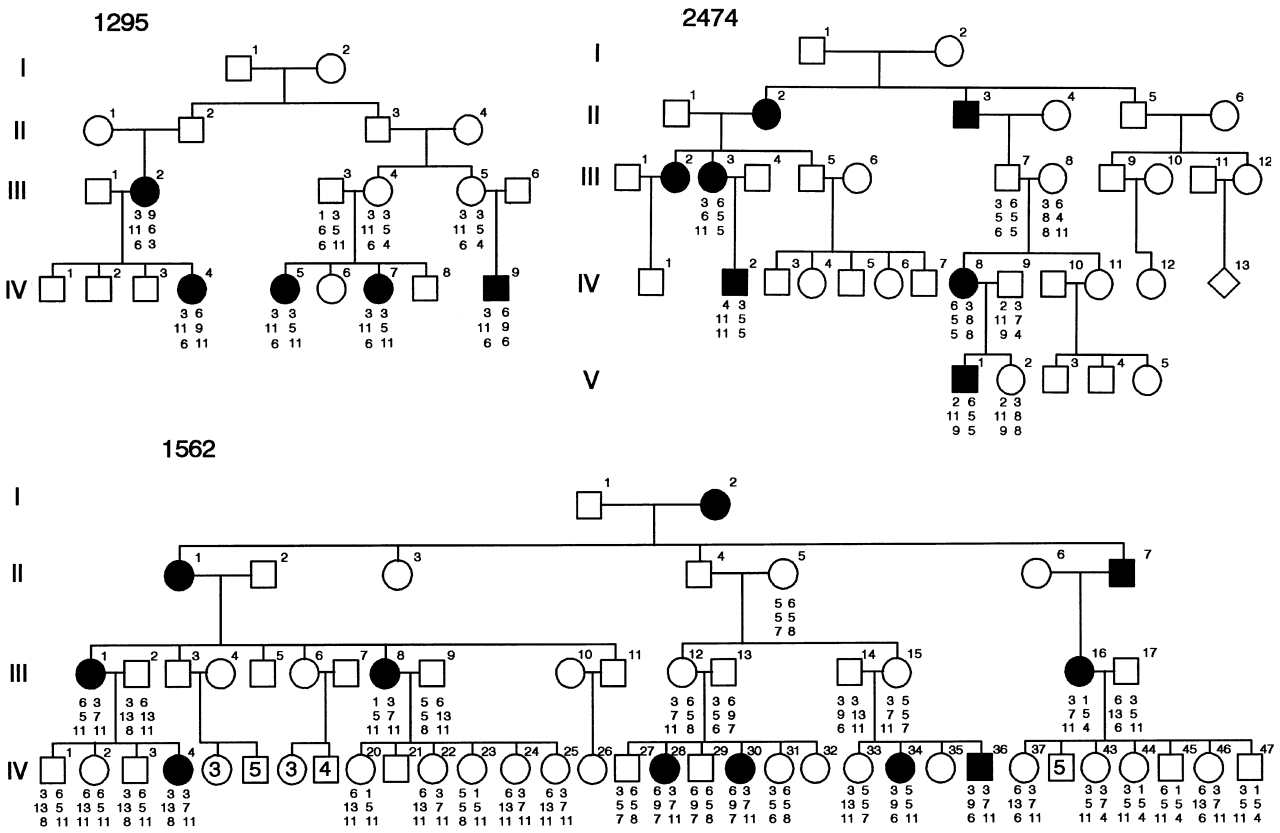

Figure 1 Schematic pedigrees of three families (1295, 2474, and 1562) with dominant reduced-penetrance RP. Blackened symbols indicate affected individuals. The alleles at microsatellite loci D19S180, D19S572, and D19S926 are listed (from top to bottom, respectively) below the symbols for the individuals who donated blood samples for this research. Each family has a different cosegregating haplotype.

possible genotypes for the missing parents, on the basis of allele frequencies provided by the user.

For this second analysis, the three pedigrees described in the present study, the pedigrees described by Al-Maghtheh et al. (1996) (ADRP5, ADRP29, RP1907, and ADRP2), and the pedigree described by Xu et al. (1995) were subdivided into their nuclear components. There were 27 nuclear pedigrees containing at least one carrier sib pair. In the families from this study, marker allele frequencies were calculated as described above. Marker allele frequencies for the families reported by others were estimated from the data in the respective papers by use of the program ILINK of the LINKAGE package (Lathrop et al. 1984). In the analysis of the pedigree described by Xu et al. (1995), marker D19S418 was used in place of marker D19S926. In order to ensure that only the contributions from the noncarrier parents were included in the analysis, we coded all carrier parents as if they were homozygous at all marker loci. The data from the pedigrees presented here, the pedigree from the study by Xu et al. (1995), and the pedigrees described by Al-Maghtheh et al. (1996) were analyzed separately, and the three resulting LOD scores were summed to give the total LOD scores for each marker.

Results

Ascertainment of Families

Three families with dominant RP with reduced penetrance were ascertained from the files of the Berman-Gund Laboratory (for schematic pedigrees see fig. 1). The clinical findings for two of these families (1562 and 2474) have been reported elsewhere, and, in particular, those reports documented the absence of retinal degeneration in some obligate carriers (Berson et al. 1969; Berson and Simonoff 1979). Previously reported linkage data from family 1562 clearly showed that the disease locus in this family was not linked to RP9 on chromosome 7p (Kim et al. 1994). The third family (1295) had not been reported previously in the scientific literature. This family was categorized as having reduced-penetrance RP, since individual III-4 was not found to have RP through clinical examination despite her status as an obligate carrier. Family members II-2, II-3, and

Table 1

Two-Point LOD-Score Analysis for Families 1562, 2474, and 1295

Locus and Family	LOD Score at Recombination Fraction of								
	.0	.01	.05	.1	.2	.3	.4	LOD_{max}	θ_{max}
D19S180:									
1562	−∞	−.96	−.33	−.10	.07	.11	.08		
2474	−3.64	−.89	−.28	−.08	.02	.02	.01		
1295	.58	.56	.49	.40	.25	.13	.05		
Total	−∞	−1.29	−.12	.22	.33	.26	.14	.33	.19
D19S572:									
1562	−∞	1.34	1.82	1.83	1.49	1.00	.47		
2474	.82	.80	.72	.61	.43	.28	.14		
1295	1.70	1.66	1.51	1.32	.93	.55	.23		
Total	−∞	3.81	4.05	3.76	2.86	1.83	.84	4.07	.04
D19S926:									
1562	2.66	2.61	2.40	2.13	1.59	1.05	.52		
2474	1.35	1.32	1.20	1.04	.74	.46	.21		
1295	1.52	1.48	1.34	1.16	.80	.47	.18		
Total	5.53	5.41	4.93	4.33	3.13	1.97	.92	5.53	.00

III-5 are also obligate carriers who are asymptomatic by history, but they have not been examined by us.

Linkage to 19q

In order to test the hypothesis that RP in families 1562, 2474, and 1295 is due to the RP11 locus on chromosome 19q, we examined the segregation of alleles at polymorphic loci from the relevant chromosomal region (fig. 1). The results of two-point and multipoint linkage analyses are shown in table 1 and in figure 2, respectively. The maximum summed multipoint LOD score was 6.47 at $\theta = 0$ from D19S926. Maximum multipoint LOD scores (LOD_{max}) were 3.03, 2.05, and 1.42 for families 1562, 1295, and 2474, respectively. These LOD_{max} scores strongly support the hypothesis that the disease locus in family 1562 is RP11, since the LOD_{max} score is >3.0. The disease in families 2474 and 1295 also is likely to be due to defects at the RP11 locus, although the LOD_{max} scores are <3.0 because of the smaller size of these families.

The detection of a meiotic recombinant between D19S572 and D19S926 in family 1562 (individual IV-34 in fig. 1) places locus D19S572 as a centromeric boundary for the possible location of the RP11 locus. Two other informative recombinants have been identified in families ADRP29 and ADRP2, reported by Al-Maghtheh et al. (1996); these recombinants place locus D19S926 as a telomeric boundary for the chromosomal segment containing the RP11 gene.

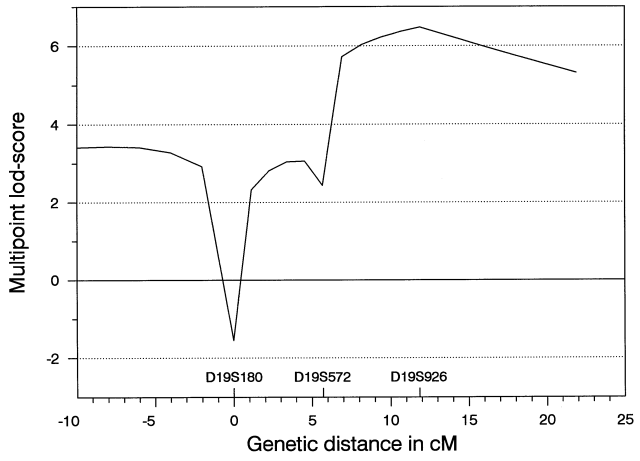

Figure 2 Plot of multipoint LOD scores as a function of genetic distance from locus D19S180. The LOD scores were summed from data from the three families in this study.

Evaluation of Possible Models for Reduced Penetrance

To test models for reduced penetrance in families showing linkage to the RP11 locus, data were obtained from the three pedigrees presented in this article, as well as from the five pedigrees described in previous studies (Xu et al. 1995; Al-Maghtheh et al. 1996). The possibility that penetrance was sex related was assessed by tabulating the number of affected versus unaffected individuals of each gender who were identified as carriers by clinical symptoms or by the RP11-linked haplotype. There were more females than males in the group of affected carriers (47 vs. 35, respectively) and in the group of unaffected carriers (23 vs. 10). Although there was a statistically significant excess of female carriers overall (70 vs. 45; $\chi^2 = 5.4$, df = 1, $P < .025$), the ratio of affected versus unaffected female carriers was not statistically different from that of male carriers ($\chi^2 = 1.04$, df = 1, $P > .25$). The excess of female carriers may have

been due to an ascertainment bias caused perhaps by females being more available or more agreeable than males to participation in these studies. In any event, since the female excess was present among both affected and unaffected carriers, it is unlikely that sex is a major factor influencing penetrance.

A model whereby penetrance is determined by the sex of the parent transmitting the pathogenic RP11 allele appeared to be incorrect, since the ratio of affected versus unaffected carrier offspring from carrier mothers (54 vs. 17, respectively) was not statistically different ($\chi^2 = 1.67$, df = 1, $P > .1$) from the ratio of affected versus unaffected carrier offspring from carrier fathers (23 vs. 14). However, because of incomplete ascertainment, we cannot conclusively rule out the sex of the carrier parent as a factor influencing penetrance.

The third model that we considered was that the wild-type RP11 alleles from the noncarrier parent specify penetrance. Since RP11 remains unidentified, the molecular nature of any possible variation among wild-type alleles remains unknown. However, we were able to test the validity of this model by examining sibships with more than one carrier. This was done in two different ways. The first analysis was confined to those sibships in which there was at least one affected and one unaffected carrier. If the model is correct, the noncarrier parent of such a sibship necessarily would be heterozygous for any wild-type alleles that specify the penetrance of the pathogenic RP11 allele inherited from the carrier parent. Among the offspring who inherit a pathogenic allele from the carrier parent, the affected siblings would all inherit one RP11 allele from the noncarrier parent, and the unaffected siblings would inherit the other.

We found six sibships in which there was at least one affected and one unaffected carrier (determined by linkage to the RP11 region) and in which the origin of the parental alleles in this chromosomal region could be determined. Within these sibships were 26 pairs of carrier siblings. These sib pairs were placed into four categories according to the concordance or the discordance of phenotype (affected vs. unaffected) and of genotype (inheritance of the same vs. different marker haplotypes from the noncarrier parent) (table 2). The distribution of sib pairs was nonrandom ($P = .00005$, by use of Fisher's exact test). In particular, all 10 sib pairs in which both members had the same phenotype inherited the same RP11-linked haplotype from the noncarrier parent; 13 of 16 sib pairs with different phenotypes inherited different haplotypes.

A second sib-pair analysis was performed in which all multicarrier sibships were analyzed, including those in which all carriers had the same disease status. For this latter sib-pair analysis, we calculated the likelihood that a modifier gene transmitted by the noncarrier parents was linked to each marker analyzed separately. The results from the SIBPAIR program again support the existence of a modifier locus in this region, with LOD scores of 3.63 ($P = .00002$), 3.02 ($P = .0001$), and 4.16 ($P = .000006$) for the markers D19S180, D19S572, and D19S926, respectively.

Discussion

The tentative assignment of RP in all three families described in this study to the RP11 locus supports the speculation of Al-Maghtheh et al. (1996) that RP11 is a relatively frequent cause of dominant RP. Including these three families, a total of eight families with dominant RP demonstrate linkage between the disease locus and chromosome 19q13.4 (Xu et al. 1995; Al-Maghtheh et al. 1996). A larger number of families have been reported for only two of the seven loci implicated as causing dominant RP, rhodopsin and RDS. The rhodopsin locus appears to be a recognizably more frequent cause of dominant RP, accounting for ~19%–26% of families (Vaithinathan et al. 1994). The RDS gene, although accounting for disease in several more reported families than RP11, has been under investigation since its identification in 1991 (Farrar et al. 1991; Kajiwara et al. 1991). It is possible that even greater numbers of RP11 cases will be discovered once this gene is identified.

The reduced penetrance of mutations at the RP11 locus is noteworthy. As noted in earlier publications, ophthalmic examinations of asymptomatic carriers in this study's families revealed either no abnormal findings or minimal reductions in electroretinogram (ERG) amplitudes and minimal delays in ERG implicit times that were not diagnostic of RP (Berson et al. 1969; Berson and Simonoff 1979). The analyses presented in this article are relevant to potential genetic mechanisms responsible for the reduced penetrance. The data from the three families reported here, together with those from the families reported elsewhere by other groups, suggest that it is unlikely that the development of RP in a carrier is related to the carrier's sex or to whether a mutant RP11 allele was inherited from the mother or father. However, alleles inherited from the noncarrier parent appeared to have an important role, as discussed below.

On the basis of an analysis of sib pairs, there was a statistically significant correlation between the development of RP in a carrier and the inheritance of the region around RP11 from the noncarrier parent. This correlation might be due to penetrance being highly influenced by otherwise silent alleles at the RP11 locus or by a closely linked locus. Perhaps a biallelic polymorphism at the RP11 locus exists, so that homozygotes or heterozygotes for either allele have no RP. The combination of one of these two alleles in *trans* with a mutant pathogenic RP11 allele would produce RP, and the combination of the other wild-type allele in *trans* with a

Table 2

Phenotype/Genotype Correlation of Sib Pairs from Sibships with at Least One Discordant Pair

	Phenotype/Genotype Correlation			
Source and Sib Pair	Same/ Same	Same/ Different	Different/ Same	Different/ Different
From Xu et al. (1995):				
II-4/II-6	X			
II-4/II-11				X
II-6/II-11				X
From Al-Maghtheh et al. (1996):				
ADRP5:				
IV-6/IV-9				X
IV-6/IV-10	X			
IV-6/IV-11				X
IV-6/IV-12				X
IV-6/IV-14				X
IV-9/IV-10				X
IV-9/IV-11	X			
IV-9/IV-12	X			
IV-9/IV-14	X			
IV-10/IV-11				X
IV-10/IV-12				X
IV-10/IV-14				X
IV-11/IV-12	X			
IV-11/IV-14	X			
IV-12/IV-14	X			
IV-15/IV-16			X	
IV-15/IV-19			X	
IV-16/IV-19	X			
V-1/V-4			X	
ADRP29:				
IV-2/IV-5				X
IV-2/IV-7				X
IV-5/IV-7	X			
RP1907:				
IV-1/IV-2				X
Total no.	10	0	3	13

mutant RP11 allele would not produce RP. If the noncarrier parent is a homozygote for this silent polymorphism, all offspring inheriting a pathogenic RP11 allele from the carrier parent would have the same disease status (either all would be affected or all would be unaffected). In such cases, examination of the segregation of 19q13.4 alleles would be uninformative, since transmission of copies of 19q13.4 from the noncarrier parent would correlate only by chance with the development of RP in carriers. However, in sibships with at least one affected and one unaffected carrier, the noncarrier parent necessarily would be a heterozygote for the presumed modifying polymorphism. In these cases, one version of 19q13.4 should be found in all affected carriers, and the other version should be found in all unaffected carriers. The sib-pair analysis for six suitably selected sibships supports this model, although imperfectly. Pairs of carrier siblings with the same phenotype always inherited the same copy of 19q13.4 from the noncarrier parent. Among pairs of carrier siblings with contrasting phenotypes (i.e., one affected and one unaffected), most inherited different copies of 19q13.4 from the noncarrier parent. A separate analysis of the entire set of sib pairs, including those from sibships without phenotypically discordant pairs, also strongly supported the existence of a modifier gene in the 19q13.4 region.

Possible explanations for the presence of a few pairs of siblings who had contrasting phenotypes but who had inherited the same copies of 19q13.4 from the noncarrier parents include the existence of other factors modifying penetrance (such as other genes or environmental or dietary factors) or the miscategorization of the phenotype of one member of a pair (perhaps owing to inaccuracy in the disease status reported by relatives).

To our knowledge, there are very few precedents for penetrance specified by wild-type alleles in *trans* at a disease locus. The clearest analogue is the hemolytic anemia (hereditary elliptocytosis) caused by dominant mutations in the gene coding for the α subunit of spectrin (Gratzer 1994). Spectrin is a cytoskeletal protein that is

essential for the normal morphology of red blood cells. Mutant versions of α-spectrin produce malformed red blood cells and a severe hemolytic anemia. However, carriers of dominant mutations may be either severely affected and dependent on blood transfusions throughout life or unaffected. The penetrance of mutations is specified by a high-frequency, otherwise-silent polymorphism at this locus that determines the relative level of expression of α-spectrin alleles (Wilmotte et al. 1993). A patient with a high-expressing wild-type allele in *trans* of a pathogenic mutation will be unaffected or very mildly affected. A patient with a low-expressing wild-type allele in *trans* will suffer chronic, severe hemolytic anemia unless the pathogenic mutation is by chance also on a low-expressing allele (Randon et al. 1994).

To a lesser extent, an intragenic polymorphism also influences the severity of fatal familial insomnia or of Creutzfeld-Jakob disease, which are caused by different mutations in the prion-protein gene (Goldfarb et al. 1992), and the effect appears to be mediated by altered conformations of the mutant protein (Monari et al. 1994). However, the modulation of disease severity is slight and in sharp contrast to the presence or the absence of the disease seen in hereditary elliptocytosis or in RP11-linked low-penetrance RP. The biochemical mechanisms by which wild-type alleles at the RP11 locus or at a closely linked locus influence severity remain obscure and probably will remain so until the future identification of the RP11 gene.

Acknowledgments

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