and Nijmegen breakage syndrome: a survey of 50 patients. Cytogenet Cell Genet 49:259–263
Komatsu K (1994) Abstract of the Sixth International Workshop on Ataxia-Telangiectasia. Cancer Res 54:6007–6010
Lange E, Borresen A-L, Chen X, Chessa L, Chiplunkar S, Concannon P, Dandekar S, et al (1995) Localization of an ataxia-telangiectasia gene to an 500-kb interval on chromosome 11q23.1: linkage analysis of 176 families by an international consortium. Am J Hum Genet 57:112–119
Rotman G, Savitsky K, Ziv Y, Cole CG, Higgins MJ, Bar-Am I, Dunham I, et al (1994*a*) A YAC contig spanning the ataxia-telangiectasia locus (groups A and C) at 11q22-23. Genomics 24:234–242
Rotman G, Vanagaite L, Collins FS, Shiloh Y (1994*b*) Three dinucleotide repeat polymorphisms at the ataxia-telangiectasia locus. Hum Mol Genet 3:2079
Savitsky K, Bar-Shira A, Gilad S, Rotman G, Ziv Y, Vanagaite L, Tagle DA, et al (1995) A single ataxia-telangiectasia gene with a product similar to PI-3 kinase. Science 268:1749–1753
Uhrhammer N, Concannon P, Huo Y, Nakamura Y, Gatti RA (1994) A pulsed-field gel electrophoresis map in the ataxia-telangiectasia region of chromosome 11q22.3. Genomics 20:278–280
Uhrhammer N, Lange E, Porras O, Naeim A, Chen X, Sheikhavandi S, Chiplunkar S, et al (1995) Sublocalization of an ataxia-telangiectasia gene distal to D11S384 by ancestral haplotyping in Costa Rican families. Am J Hum Genet 57:103–111
Vanagaite L, James MR, Rotman G, Savitsky K, Bar-Shira A, Gilad S, Ziv Y, et al (1995) A high-density microsatellite map of the ataxia-telangiectasia locus. Hum Genet 95:451–454
Vanagaite L, Savitsky K, Rotman G, Ziv Y, Gerken SC, White R, Weissenbach J, et al (1994) Physical localization of microsatellite markers at the ataxia-telangiectasia locus at 11q22-q23. Genomics 22:231–233
Wegner RD, Metzger M, Hanefeld F, Jaspers NGJ, Baan C, Magdorf K, Kunze J, et al (1988) A new chromosomal instability disorder confirmed by complementation studies. Clin Genet 33:20–32

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Fine Localization of the Locus for Autosomal Dominant Retinitis Pigmentosa on Chromosome 17p

To the Editor:

The term "retinitis pigmentosa" (RP) refers to a group of inherited retinal degenerative disorders. Clinical manifestations include night-blindness, with variable age of onset, followed by constriction of the visual field that may progress to total loss of sight in later life. Previous studies have shown that RP is caused by mutations within different genes and may be inherited as an X-linked recessive (XLRRP), autosomal recessive (ARRP), or autosomal dominant (ADRP) trait. The AD form of this group of conditions has been found to be caused by mutations within the rhodopsin gene in some families (Dryja et al. 1990, 1991; Sung et al. 1991; Ingelhearn et al. 1992) and the peripherin/RDS gene in others (Farrar et al. 1991; Kajiwara et al. 1991; Wells et al. 1992). In addition, some ADRP families have been found to be linked to anonymous markers on 8cen (Blanton et al. 1991), 7p (Ingelhearn et al. 1993), 7q (Jordan et al. 1993), 19q (Al-Maghtheh et al. 1994), and, more recently, 17p (Greenberg et al. 1994). The ADRP gene locus on the short arm of chromosome 17 was identified in a large South African family (ADRP-SA) of British origin. The phenotypic expression of the disorder, which has been described elsewhere (Greenberg et al. 1992), is consistent in the pedigree with an early onset of disease symptoms. In all affected subjects in the family, onset of symptoms commenced before the age of 10 years;

Table 1

Pairwise Linkage between Microsatellite Markers and the ADRP (SA) Locus on 17p

	Recombination Fraction at θ =					
ADRP(SA) vs.	0	.05	.1	.2	.3	.4
D17S849	−∞	3.35	**3.60**	3.14	2.17	.97
D17S1529	2.12	**5.64**	5.21	3.95	2.43	.88
D17S1528	**7.19**	6.70	6.10	4.71	3.12	1.43
D17S831	2.97	**6.66**	6.22	4.93	3.35	1.57
D17S829	−9.15	**.92**	**.92**	.64	.27	.00
D17S1353	−5.13	2.40	**2.72**	2.39	1.63	.73
D17S938	−∞	5.07	**5.43**	4.82	3.49	1.78

Figure 1 Ideogram of human chromosome 17, with an expanded genetic map of the region to which ADRP-SA localizes.

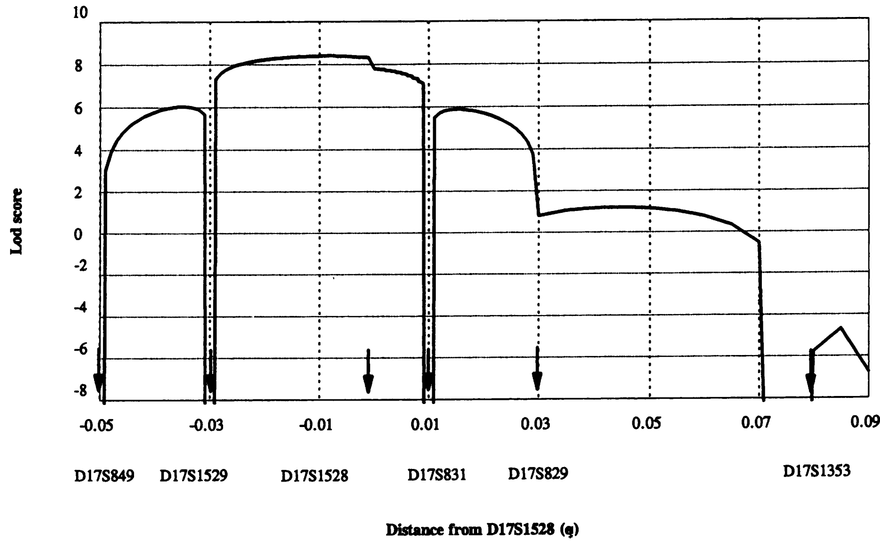

Figure 2 Results of three-point analyses of ADRP against two markers in the family. The map is contiguous.

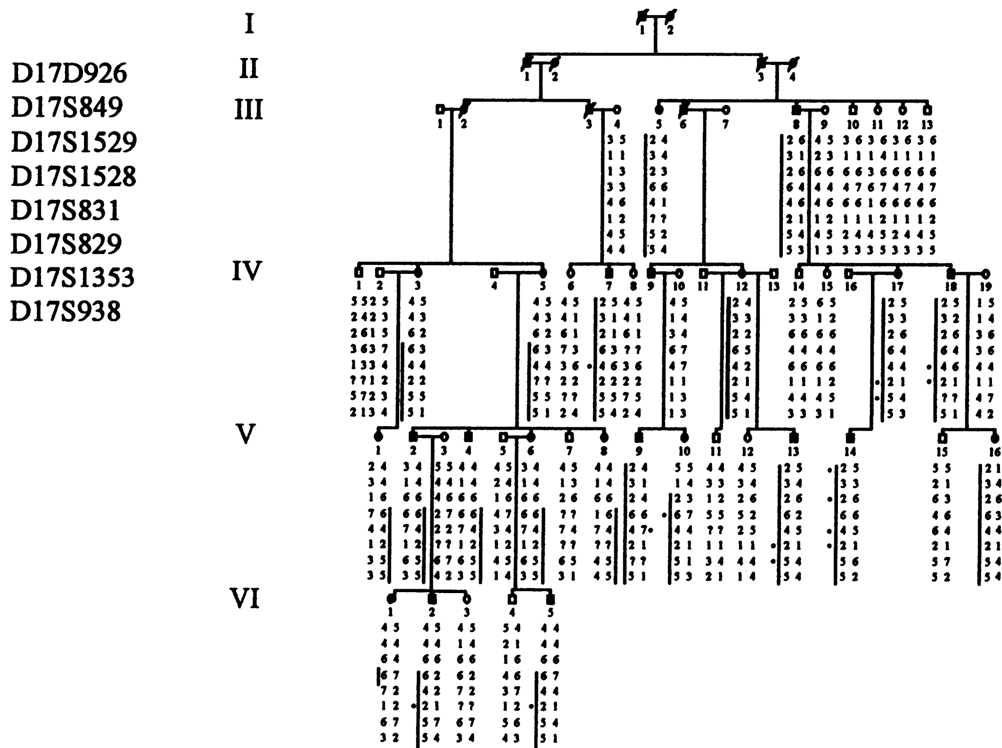

Figure 3 ADRP pedigree, showing the segregation of chromosome 17 marker loci. Haplotypes were constructed, and the haplotype most likely associated with the disease is marked by a solid bar. Genotypes where phase is unknown is indicated by a dot. It can be inferred that individual III-2 has a recombinant chromosome that is passed down to both of her affected offspring (IV-3 and IV-5). This recombination event excludes a location for the ADRP-SA locus at or proximal to D17S1529, whereas the recombination in individual VI-1 places the ADRP-SA locus proximal to D17S831. The meiosis for VI-1 at D17S829 was uninformative; it was, however, assumed recombinant because of the low rate of recombination between D17S831-D17S829 of 0.02 (unpublished Généthon map).

therefore, children under 10 years of age were classified as "clinical status unknown" for the purpose of linkage analysis. A gene frequency of .001 was assumed for the disease, and a penetrance value of 1 was used for the lod-score calculations. In the initial linkage analysis, nine microsatellite markers were used to localize the gene, which was found to be most tightly linked to D17S938 ($Z = 5.43$; $\theta = .1$) and D17S796 ($Z = 4.82$; $\theta = .1$), at 17p13.1 (Greenberg et al. 1994). The human recoverin gene, which had been localized to 17p13.1 (Murakami et al. 1992), was thus a prime candidate for ADRP in this family. The recoverin gene was, however, subsequently excluded from being associated with the phenotype in this family on the basis of two observed recombination events between the phenotype and an intragenic marker (Wiechmann et al. 1994) (data not shown).

A series of three-point analyses were then undertaken with two markers (from the initial set of nine markers) and the disease gene. A peak lod score was obtained between D17S849 and D17S938, indicating the most likely interval containing the ADRP-SA gene.

Thereafter, five additional (previously unpublished Généthon) markers between D17S849 and D17S938 were genotyped in order to further refine the region containing the ADRP-causing gene. Another series of multipoint analyses were performed using these markers. The lod scores calculated between the disease locus and each of these markers are shown in table 1. Marker D17S1528 shows tight linkage to the disease locus with no recombinations ($Z = 7.19$). Two markers, D17S1529 and D17S831, located on either side of D17S1528, showed significant postive lod scores of 5.64 and 6.66, respectively, at $\theta = .05$. Multipoint analyses were performed with 10 markers, starting at D17S849 and ending at D17S804 (fig 1). Allele frequencies for each of the markers were calculated from a number of unaffected unrelated subjects from the population of origin. Two-point and multipoint analysis was performed using the Linkage package, version 5.2, run under OS/2 (Lathrop and Lalouel 1984).

The results are illustrated in figure 2, where a peak lod score of 8.4 was obtained between D17S1529 and D17S1528. The 1-lod-unit support interval only encompasses the regions between D17S1529 and D17S831, with both D17S1529 and D17S831 excluded. This support interval was confirmed by observed meoitic recombinants (fig. 3) in two affected individuals with markers on either side of the support interval.

In conclusion, although the ADRP gene in this family was initially mapped to the 17p13.1 chromosomal region, linkage to the recoverin gene was excluded because of recombinations observed with an intragenic marker (Weichmann et al. 1994). Multipoint analysis has confirmed that the recoverin gene and the ADRP-SA gene loci are different (data not shown). The multipoint data suggest that the disease locus is more likely to be located in the interval D17S1529-D17S831, while D17S1529 and D17S831 themselves were excluded. The recombination fraction for this interval has been estimated to be .04, indicating a genetic distance of ~4.17 cM.

The ADRP-SA gene has been localized relative to very new markers on the Généthon map, thereby refining the physical location of the disease gene. This study has identified markers that could assist in the mapping of the same locus in other as yet unlinked RP families. The interval in which ADRP-SA lies is now sufficiently small to form the basis for the next phase of the study. This would involve physical mapping and positional cloning in an attempt to identify the ADRP-SA gene.

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References

Al-Maghtheh M, Inglehearn C, Keen J, Evans K, Moore A, Jay M, Bird A, et al (1994) Identification of a sixth locus for autosomal dominant retinitis pigmentosa on chromosome 19. Hum Mol Genet 3:351–354

Blanton SH, Heckenlively JR, Cottingham AW, Friedman J, Sadler LA, Wagner M, Friedman LH, et al (1991) Linkage mapping of autosomal dominant retinitis pigmentosa (RP1) to the pericentric region of human chromosome 8. Genomics 11:857–869

Dryja TP, McGee TL, Reichel E, Hahn LB, Cowley GS, Yandell DW, Sandberg MA, et al (1990) A point mutation of the rhodopsin gene in one form of retinitis pigmentosa. Nature 343:364–366

Dryja TP, Hahn LB, Cowley GS, McGee TL, Berson EL (1991) Mutation spectrum of the rhodopsin gene among patients with autosomal dominant retinitis pigmentosa. Proc Natl Acad Sci USA 88:9370–9374

Farrar GJ, Kenna P, Jordan SA, Kumar-Singh R, Humphries MM, Sharp EM, Sheils DM, et al (1991) A three-base-pair deletion in the peripherin-RDS gene in one form of retinitis pigmentosa. Nature 354:478–480

Greenberg J, Babaya M, Ramesar R, Beighton P (1992) Retinitis pigmentosa, AD type I: exclusion of linkage to D3S47 (C17) in a large South African family of British origin. Clin Genet 41:322–325

Greenberg J, Goliath RG, Beighton P, Ramesar R (1994) A new locus for autosomal dominant retinitis pigmentosa on the short arm of chromosome 17. Hum Mol Genet 3:915–918

Ingelhearn CF, Keen J, Bashir R, Jay M, Fitzke F, Bird AC, Crombe A, et al (1992) A completed screen for mutations of the rhodopsin gene in a panel of patients with autosomal dominant retinitis pigmentosa. Hum Mol Genet 1:41–45

Ingelhearn CF, Carter SA, Keen J, Lindsey J, Stephenson AM, Bashir R, Al-Maghtheh M, et al (1993) A new locus for autosomal dominant retinitis pigmentosa on chromosome 7p. Nat Genet 4:51–58

Jordan SA, Farrar GJ, Kenna P, Humphries MM, Sheils DM, Kumar-Singh R, Sharp EM, et al (1993) Localiization of an autosomal dominant retinitis pigmentosa gene to chromosome 7q. Nat Genet 4:54–58

Kajiwara K, Hahn LB, Mukai S, Travis GH, Berson EL, Dryja TP (1991) Mutations in the human retinal degeneration slow gene in autosomal dominant retinitis pigmentosa. Nature 354:480–483

Lathrop GM, Lalouel JM (1984) Easy calculations of lod scores and genetic risks on small computers. Am J Hum Genet 36:460–465

Murakami A, Yajima T, Inana G (1992) Isolation of human retinal genes: recoverin cDNA and gene. Biochem Biophys Res Commun 187:234–244

Sung C, Schneider BG, Agarwal N, Papermaster DS, Nathans J (1991) Functional heterogeneity of mutant rhodopsins responsible for autosomal dominant retinitis pigmentosa. Proc Natl Acad Sci USA 88:8840–8844

Wiechmann A, Haro K, Bowden D (1994) Three microsatellite polymorphisms at the recoverin locus on chromosome 17. Hum Mol Genet 3:1028

Wells J, Wroblewski J, Keen J, Inglehearn C, Jubb C, Eckstein A, Jay M, et al (1992) Mutations in the human retinal degeneration slow (RDS) gene can cause either retinitis pigmentosa or macular dystrophy. Nat Genet 3:213–218

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Nonsyndromic Autosomal Recessive Deafness Is Linked to the DFNB1 Locus in a Large Inbred Bedouin Family from Israel

To the Editor:

Nonsyndromic deafness accounts for ~70% of all genetically determined deafness (Moatti et al. 1990; Gorlin et al. 1995). Several types of nonsyndromic deafness, with a variety of inheritance patterns, have been genetically linked, including dominant, recessive and X-linked forms (Leon et al. 1992; Reardon et al. 1992; Robinson et al. 1992; Chaib et al. 1994; Coucke et al. 1994; Guilford et al. 1994*a,* 1994*b;* Cohen et al. 1995; Friedman et al. 1995). Two of these forms—DFNA3, a dominant form causing moderate to severe hearing loss, predominantly in the high frequencies, and DFNB1, a recessive form causing profound, prelingual, neurosensory deafness affecting all frequencies—have been linked to the same pericentromeric region of chromosome 13 (Chaib et al. 1994; Guilford et al. 1994*b*). This finding is equally compatible with (1) the existence two closely linked deafness genes, (2) different mutations within a single deafness gene, and (3) a single mutation in a single gene that behaves differently in different genetic backgrounds.

We present the linkage analysis of a very large, highly inbred Bedouin family affected with nonsyndromic autosomal recessive deafness. Our analysis indicates that deafness in this family is linked to the DFNB1 locus. In addition to describing the presence of this deafness disorder in a new population, we also present data that narrow the genetic interval of DFNB1. The new DFNB1 interval overlaps that defined for DFNA3. This finding is consistent with the single-gene hypothesis presented by Chaib et al. (1994).

The Bedouin family described in the present study belongs to a tribe founded ~200 years ago by an Arab-Bedouin male who emigrated from Egypt to the southern region of what was then Palestine. He married a local woman and had seven children, five of whom survived to adulthood. Consanguineous marriage has been the rule in the tribe since its third generation. The tribe is presently in its seventh generation and consists of some 3,000 people, all of whom reside in a single geographic area in Israel that is separated from other Bedouin communities. Birth rates within the tribe are high, and polygamy is common.

Within the past three generations, there have been ~80 individuals with congenital deafness. All of these individuals are descendants of two of the five adult sons of the founder. Hearing evaluation of these individuals revealed profound prelingual neurosensory hearing loss with drastically elevated audiometry thresholds at all frequencies (250–8,000 cps). All deaf individuals have an otherwise normal phenotype with the absence of external ear abnormalities, retinopathy, and renal defects. All are of normal intelligence. Some nuclear families in the tribe exhibit pseudodominant segregation of the disease that is due to marriage of deaf persons to hearing carriers of the autosomal recessive gene.

Genotyping was performed with short tandem-repeat polymorphic markers linked to previously reported