Letters to the Editor

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Localization of a Gene (*CORD7*) for a Dominant Cone-Rod Dystrophy to Chromosome 6q

To the Editor:

The cone-rod dystrophies are a heterogeneous group of retinal disorders, often leading to registrable blindness, that are characterized by an initial loss of cone photoreceptors, followed by the degeneration of rod photoreceptors. Recent genetic studies have mapped the disorder to a number of different chromosomal locations (Evans et al. 1994; Kelsell et al. 1997), although, to date, mutations have been identified in only three genes, *peripherin/RDS* (Nakazawa et al. 1994, 1996*a,* 1996*b;* Kohl et al. 1997), *CRX* (Freund et al. 1997), and retinal guanylate cyclase (Kelsell et al., in press). In the present study, a new chromosomal localization for an autosomal dominant cone-rod dystrophy is reported. In accordance with the guidelines of the Nomenclature Review Committee, "*CORD7*" has been assigned as the gene designation for this disorder.

A four-generation British family was recruited for the study. Affected members of the family first became aware of reduced color vision and visual acuity between the ages of 20 and 40 years. As the disorder progressed, they reported difficulty seeing in bright light, and one individual (IV-1; fig. 1*A*) reported visual problems in dim light. At the onset of symptoms, retinal pigmentary changes were already present around the fovea, simulating a bull's eye dystrophy, which developed to macular atrophy. Electrophysiological tests in advanced disease showed that scotopic rod responses were barely detectable and that all cone responses were severely attenuated (fig. 1*B*) but with no change in implicit time. Pattern electroretinography (ERG) was extinguished, in keeping with the severe macular dysfunction. No significant intraocular asymmetry was present.

EDTA blood samples were obtained from eight affected family members, eight unaffected family members, and four spouses, for linkage analysis (fig. 1). DNA was extracted from these samples with a Nucleon II extraction kit (Scotlab Bioscience). Genotyping was performed with microsatellite-marker loci, as described elsewhere (Kelsell et al. 1995). In brief, 100 ng DNA samples were PCR amplified and labeled by $\alpha[^{32}P]$-dCTP incorporation. These amplified products then were separated by denaturing PAGE and were visualized by autoradiography.

Data were collected with LINKSYS 3.1 (Attwood and Bryant 1988), and two-point linkage analysis was performed with the MLINK subprogram of LINKAGE package 5.10 (Lathrop et al. 1984). Allele frequencies were calculated from the four spouses in this family as well as from an additional 10 normal individuals taken from four other British families. The cone-rod dystrophy phenotype in this family was analyzed as an autosomal dominant trait with complete penetrance and a frequency of .001 for the affected allele.

Since a variety of retinal degenerations have been mapped to chromosome 6 (Nichols et al. 1993; Small et al. 1993; Weleber et al. 1993; Wells et al. 1993; Nakazawa et al. 1994; Stone et al. 1994; Kelsell et al. 1995; Reig et al. 1995; Kohl et al. 1997), we chose this region of the genome as the first candidate area for linkage analysis. Two-point linkage data for the family studied (data not shown) excluded the 6p12 region occupied by *peripherin/RDS* and the 6q14-q16.2 region occupied by the genes for North Carolina macular dystrophy (*MCDR1;* Small et al. 1993) and progressive bifocal chorioretinal atrophy (*PBCRA;* Kelsell et al. 1995). Significant linkage was obtained at the Stargardt-like dominant progressive macular dystrophy region on chromosome 6q13-q15 (Stone et al. 1994). Two-point LOD scores obtained after genotyping 16 microsatellite-marker loci are shown in figure 2. Significant linkage was obtained at two of these marker loci, with a maximum LOD score of 3.61 (recombination fraction of 0.00) at *D6S1681*. The haplotypes that define the most likely chromosomal interval for the disease-causing gene are indicated in figure 2. Affected individual III-3 is recombinant at *D6S430* (as well as at the more centromeric marker locus *D6S257*), placing the disease gene telomeric to *D6S430*. Affected individual II-2 is recombinant for *D6S1625* (as well as the more telomeric marker locus *D6S252*), placing the disease gene centromeric to *D6S1625*. Three of the marker loci (*D6S1619, D6S1681,* and *D6S456*) that give maximum LOD scores at zero recombination were completely in-

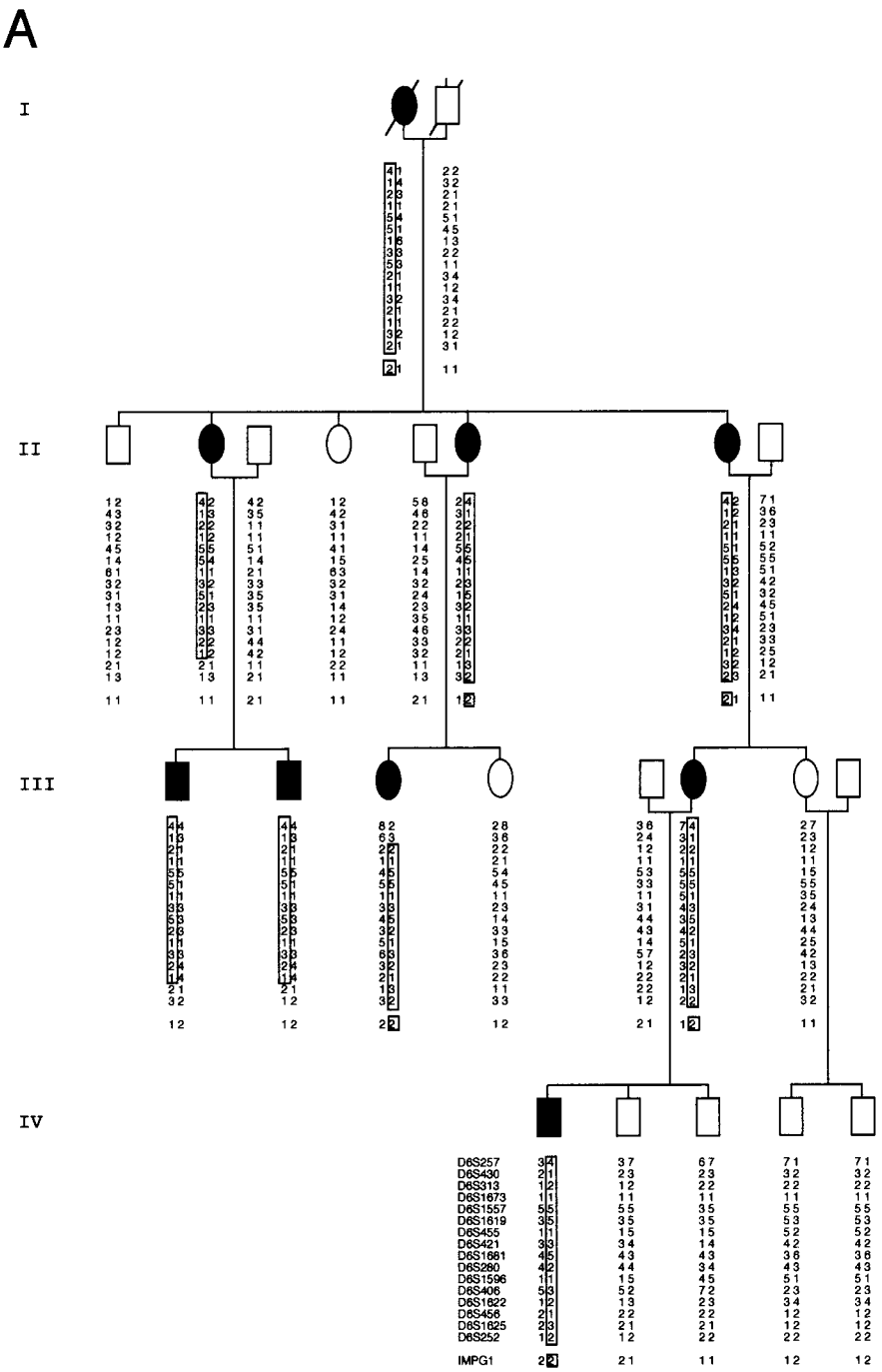
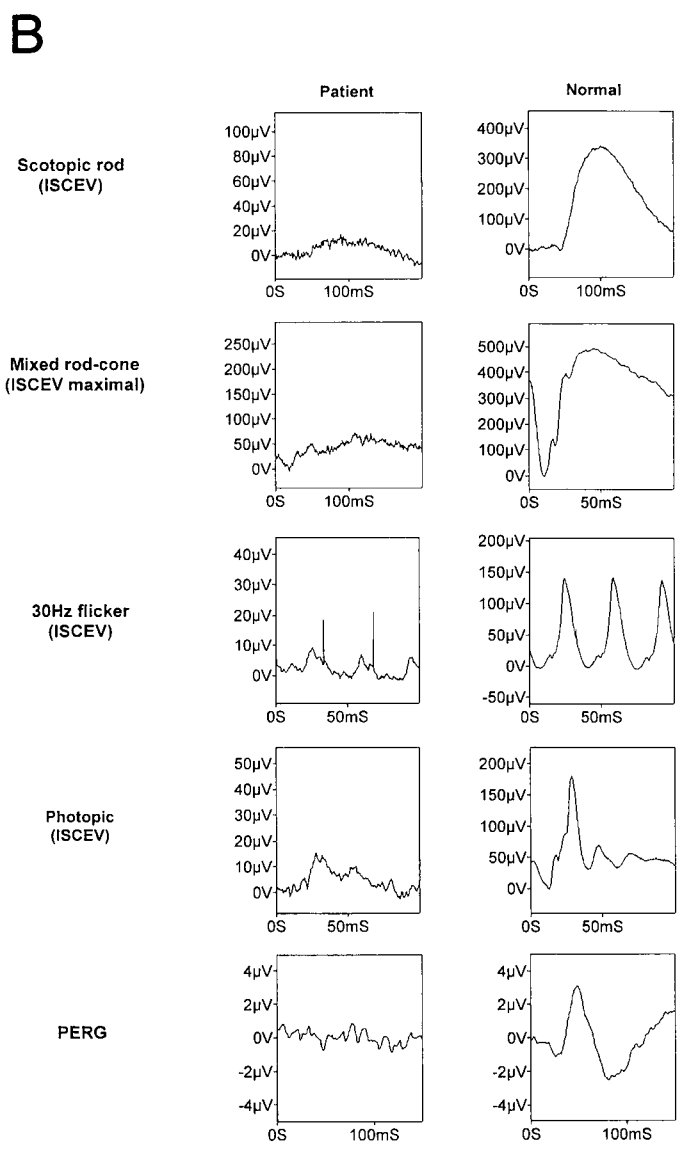


Figure 1 *A, CORD7* pedigree and haplotype results for 16 microsatellite-marker loci situated on chromosome 6q. The identities of microsatellite markers are shown to the left of individual IV-1. The haplotype that appears to be segregating with the disease in this family is boxed. The bottom entry in the list represents the C and G alleles of the *IMPG1* gene. The brackets indicate inferred haplotypes, for individuals I-1 and I-2. *B,* ERG traces from patient II-6 and from a normal control. Except for the pattern ERG ("PERG"), note that different axis scales are used for patient and control traces.

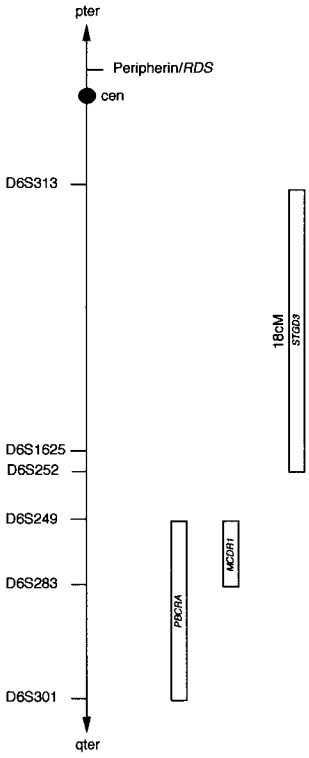
formative in these recombinant individuals. Therefore, the disease-causing gene in this family has been localized between *D6S430* and *D6S1625*, a region estimated to be 7 cM in size (Dib et al. 1996).

IMPG1 is an interphotoreceptor matrix proteoglycan gene that has been localized to chromosome 16q14.2-q15 (Felbor et al., in press). It therefore is a good functional candidate for retinal dystrophies mapping to this



region of the genome (see Gehrig et al., in press). Exon 13 contains a frequent C/G polymorphism (Gehrig et al., in press) that enabled us to follow the segregation of the *IMPG1* gene in our CORD7 family. The exon was amplified by use of primers and reaction conditions, as described elsewhere (Gehrig et al., in press); sequencing was performed with the PCR-amplification primers by use of AmpliTaq FS polymerase cycle sequencing with dye-labeled dideoxyterminators, and the products were visualized on an Applied Biosystems model 373 sequencer. In figure 1, the C and G alleles are indicated as 1 and 2, respectively. The presence of a crossover in affected individual II-2 places the *IMPG1* gene telomeric to *CORD7* and excludes it as the disease gene.

An autosomal dominant Stargardt-like disease (STGD3) (Stone et al. 1994) also maps to this region of chromosome 6. Clinically, this disorder is quite distinct from CORD7; it is described as a childhood-onset maculopathy with white/yellow flecks in the midperipheral retina. In contrast, the CORD7 disease is of middle-age onset, and no flecks are present in the macula or peripheral retina of affected individuals. However, the possibility that different mutations in the same gene are responsible for STGD3 and CORD7 cannot be ruled out, since clinical heterogeneity is not an infrequent finding. For example, different mutations in the *peripherin/RDS* gene result in retinitis pigmentosa, macular dystrophy, cone-rod dystrophy, pattern dystrophy, or cen-



	Recombination fraction							
Marker	0.00	0.05	0.10	0.20	0.30	0.40	Zmax	θ max
D6S257	-∞	2.02	2.02	1.65	1.09	0.44	2.05	0.07
D6S430	-∞	2.02	2.02	1.65	1.09	0.44	2.05	0.07
D6S313	1.51	1.35	1.18	0.83	0.45	0.12	1.51	0.00
D6S1673	0.90	0.81	0.72	0.51	0.29	0.09	0.90	0.00
D6S1557	1.51	1.35	1.18	0.83	0.45	0.12	1.51	0.00
D6S1619	2.11	1.91	1.70	1.24	0.72	0.22	2.11	0.00
D6S455	2.41	2.19	1.95	1.44	0.89	0.35	2.41	0.00
D6S421	2.07	1.89	1.70	1.30	0.85	0.38	2.07	0.00
D6S1681	3.61	3.30	2.97	2.26	1.45	0.59	3.61	0.00
D6S280	3.31	3.02	2.72	2.05	1.31	0.52	3.31	0.00
D6S1596	1.13	1.04	0.93	0.71	0.47	0.24	1.13	0.00
D6S406	2.41	2.19	1.95	1.44	0.89	0.35	2.41	0.00
D6S1622	2.11	1.91	1.70	1.24	0.76	0.32	2.11	0.00
D6S456	2.22	2.03	1.84	1.43	0.96	0.43	2.22	0.00
D6S1625	-∞	2.02	2.02	1.66	1.11	0.47	2.05	0.07
D6S252	-∞	-0.09	0.30	0.45	0.32	0.11	0.45	0.20

Figure 2 Macular dystrophies mapping to human chromosome 6. The table to the right shows the two-point LOD scores for linkage between *CORD7* and marker loci situated on chromosome 6q. The 7-cM region to which *CORD7* maps and the previous 18-cM localization for *STDG3* are depicted schematically to the left of the table. The approximate positions of the other macular dystrophy genes mapping to chromosome 6, with their flanking marker loci, also are shown (not to scale). The peripherin/*RDS* gene maps to the short arm of chromosome 6, and the regions for *MCDR1* and *PBCRA* map below the *STDG3* locus.

tral areolar choroidal dystrophy (Nichols et al. 1993; Weleber et al. 1993; Wells et al. 1993; Nakazawa et al. 1994; Reig et al. 1995; Kohl et al. 1997), and a similar situation is seen for the *ABCR* gene, in which different mutations cause either recessive Stargardt macular degeneration (Allikmets et al. 1997) or recessive retinitis pigmentosa (Martinez-Mir et al. 1998).

Two other retinal dystrophies principally affecting the posterior pole of the eye have been mapped just telomeric to *STGD3* (Small et al. 1993; Kelsell et al. 1995; also see fig. 2), and cytogenetic alterations affecting the chromosome 6q region have been associated with a variety of other retinal diseases (Milosevic and Kalicanin 1975; Hagemeijer et al. 1977; Pierpont et al. 1986; Tranebjaerg et al. 1986). This has led to the suggestion that there may be a family of retinal genes located on chromosome 6q (Small et al. 1992; Kelsell et al. 1995).

The mapping of *CORD7* in this study adds to the expanding list of localizations for cone-rod dystrophies. Clearly, more family studies are required to determine the quantitative importance of each locus. The cloning of the disease genes should aid in our understanding of the etiology of this diverse set of degenerative disorders.

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