A new family of Greek origin maps to the CRD locus for autosomal dominant cone-rod dystrophy on 19q

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Abstract

Retinal photoreceptor dystrophies (RD) are a highly heterogeneous group of genetic disorders of the retina, representing the most frequently inherited form of visual handicap, affecting ~1.5 million people world wide. To date, more than 40 genetic loci have been implicated in RD. One of them, the CORD2 locus, for an autosomal dominant form of cone-rod dystrophy (CRD), maps to chromosome 19q and has previously been reported in a single large family of British origin. We now report a new family with severe early onset CRD, phenotypically very similar to the British family, which also maps to 19q, but is of Greek origin. Haplotype data of the Greek family showed no recombination between and including markers D19S219 and D19S246 and linkage analysis gave a lod score of 2.7 (at $\theta=0$) with marker D19S412, confirming the data obtained in the British family.

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Retinal photoreceptor dystrophies (RD) are a genetically and clinically heterogeneous group of human retinopathies representing the most frequently inherited form of visual handicap, with an estimated prevalence ranging from 1 in 3000 to 1 in 7000.¹ Cone-rod dystrophies (CRDs) constitute a subgroup of the severe inherited forms of RD, characterised by the simultaneous involvement of both the cone and rod photoreceptors.²⁻⁴ Affected patients suffer early and progressive loss of visual acuity and colour vision followed by night blindness and loss of peripheral vision. In later life, vision is frequently reduced to bare perception of light.^{5,6} Considerable clinical heterogeneity has been reported including cases of CRD associ-

ated with a variety of systemic diseases,⁷⁻⁹ and genetic heterogeneity has been well documented with autosomal dominant, recessive, and X linked forms.³

The gene for peripherin/RDS on chromosome 6p has been shown to cause dominant CRD,^{10,11} and two, as yet uncharacterised, genes on chromosomes 17p and 19q have also been implicated.^{12,13} In addition, there are two inferred associations with uncharacterised CRD reported in single cases and localised on chromosomes 17q (associated with neurofibromatosis type I, NF1) and 18q, respectively.^{9,14}

The CRD locus on chromosome 19q (CORD2, MIM 120970) is based on linkage of 19q microsatellite markers to the disease in a large British family from north Wales.¹³ We now report a family based in the region of Attika in southern Greece that constitutes the only known lineage of autosomal dominant CRD in Greece to date and the second family world wide to map to chromosome 19q.

We studied 16 members of a four generation Greek family in which the inheritance pattern of the CRD phenotype was consistent with an autosomal dominant trait, with no evidence of incomplete penetrance (fig 1). Seven people were affected, four unaffected, and five were spouses. Subjects were designated unaffected only if they had no symptoms or clinical evidence of CRD by the age of 15 years. Affected subjects experienced loss of visual acuity and colour vision between the ages of 5 and 10 years, and nyctalopia (night blindness) before the age of 30 years. Examination of their fundi showed marked pigmentation in the macular area, and they all had a central visual field defect detectable by automated perimetry. This defect frequently appeared to be paracentral owing to eccentric fixation. A series of electrophysiological tests on patient IV.3 showed that a reduction in the amplitude of the

Table 1 Two point lod scores (Z) between CRD and markers on chromosome 19q

DNA marker	Recombination fraction (θ)							Zmax	θ_{max}
	0.00	0.05	0.10	0.20	0.30	0.40	0.50		
cen									
D19S225	—	-0.79	-0.53	-0.29	-0.17	-0.10	0.00	0.00	0.50
D19S412	2.71	2.49	2.26	1.77	1.23	0.65	0.00	2.71	0.00
D19S606	1.20	1.09	0.98	0.74	0.50	0.25	0.00	1.20	0.00
D19S604	2.41	2.23	2.04	1.63	1.17	0.63	0.00	2.41	0.00
D19S180	—	-1.10	-0.60	-0.20	-0.06	-0.01	0.00	0.00	0.50
tel									

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Figure 1 Haplotype analysis in the Greek autosomal dominant cone-rod dystrophy pedigree. The black bars represent alleles associated with the disease chromosome. Critical recombination events are observed in II.1, III.1, and IV.2.

photopic ERG preceded a reduction in the amplitude of the scotopic ERG.

Linkage analysis on the Greek family was carried out as previously described.¹³ Linked loci involving cone-rod dysfunction were screened using 13 microsatellite markers.¹⁵ Markers D6S271, D6S286, D13S158, D17S1791, D17S250, and D18S72 excluded linkage to the loci on chromosomes 6p,^{10,11} 6q,¹⁶ 13q,¹⁷ 17p,¹² 17q,⁹ and 18q,¹⁴ respectively (data not shown). Two point lod scores were calculated using data prepared by the LINKSYS data management package as input for the LINKAGE programs.^{18,19}

The Greek CRD family showed linkage to the 19q CRD locus with a lod score of 2.7 at a recombination fraction of zero with marker D19S412. Additional markers (D19S604 and D19S606) in this region were used to confirm linkage to 19q13.3 (table 1). The flanking markers D19S219 and D19S246 for the British family²⁰ were uninformative in the Greek CRD family and therefore the linkage data obtained do not refine the disease region. Recombination events were observed with markers D19S225 (proximally) and D19S180 (distally), thus excluding linkage to the RP11

Figure 2 Schematic diagram indicating the relative position of polymorphic markers on the long arm of chromosome 19.

locus on chromosome 19q13.4,²¹ and corresponding to a genetic interval of 34 cM (fig 2).

Haplotype analysis showed no common disease alleles with the British CRD family across the previously described region, therefore suggesting two independent mutations and exclusion of a founder effect.

Although a number of retinal dystrophies have been well recognised and thoroughly characterised, CRDs seem to comprise a poorly understood subgroup that has undergone relatively little genetic and molecular investigation. To date, there are no published figures on the incidence or prevalence of the disease in any population. However, our present data on a second family mapping to the 19q locus could imply that this is one of the more common loci for dominant CRD, since the other three loci on 6q, 13q, and 17p were reported in single families only, and both the 17q and 18q localisations were based on individual case reports.

The clinical phenotype of this Greek family is very similar to that of the large CRD family reported by Evans *et al.*¹³ Early age of onset of central visual loss and striking macular pigmentation are characteristic of both pedigrees. The visual prognosis in the Greek family appears slightly better, since patients aged between 45 and 50 years are still able to read 20/400. In the British family, patients aged over 45 years had bare perception of light.

In the British family, there is also significant evidence for segregation distortion, a phenomenon that is rarely observed in humans. According to their data, the proportion of affected/unaffected children born to affected mothers was considerably higher than the expected 1:1 ratio. In contrast, in the Greek CRD family three out of five children were born to two affected fathers and inherited the disease. The same proportion is seen for the affected children born to the three affected mothers. However, owing to the small size of the Greek family these findings must be viewed with caution.

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