Exclusion of one pedigree affected by adult onset primary open angle glaucoma from linkage to the juvenile glaucoma locus on chromosome 1q21-q31

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Abstract
A locus for autosomal dominant juvenile onset primary open angle glaucoma (POAG) was recently assigned to chromosome region 1q21-q31. In the present study, a large Greek family with autosomal dominant adult onset POAG was investigated using microsatellite markers. Exclusion of linkage of the adult onset POAG gene to the region D1S194-D1S191 was obtained in this pedigree. Therefore, the data provide evidence that juvenile and adult onset POAG are genetically distinct disease entities.
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Key words: glaucoma; autosomal dominant; linkage analysis.

Glaucoma is a leading cause of blindness worldwide. It is a heterogeneous group of disorders, the majority of which are associated with an open, normal appearing anterior chamber angle with normal trabecular meshwork and are termed primary open angle glaucoma (POAG). The relatively late age at onset of most forms of POAG has complicated the efforts to identify the mode of inheritance, but autosomal dominant inheritance has been described in families with juvenile2-4 as well as adult onset POAG.2 5-8

A locus for juvenile onset POAG (GLC1A) was recently assigned to the long arm of chromosome 1 in a large family with autosomal dominant inheritance,9 and confirmed in other families of juvenile onset.10 11 The candidate region D1S194-D1S191 covers 23 cM at 1q21-q31. Analysis of recombinant haplotypes in the families reported improved the localisation of the gene responsible to a 10 cM region (D1S196-D1S218).9-11 A huge pedigree has been reported with autosomal dominant POAG of either juvenile or adult onset, and the same haplotype between loci D1S196 and D1S212 was recognised in all affected subjects, suggesting a common locus for the juvenile and adult forms of POAG.12

In the present study, blood samples were collected from 50 members of one large pedigree identified in Epirus, Greece (fig 1). The clinical findings in affected subjects were consistent with adult onset POAG, including characteristic glaucomatous changes of the optic disc and visual field, increased cup to disc ratio, intraocular pressure commonly more than 30 mmHg at the time of diagnosis, and no other signs of congenital or secondary glaucoma. The age at diagnosis was 30 years and older. The POAG in this family appears to be transmitted in an autosomal dominant fashion. Forty six people above 30 years of age were children of affected patients and therefore at 50% risk of

Figure 1 Adult onset primary open angle glaucoma segregating in a family from Epirus, Greece. Filled symbols indicate affected subjects. Only people above 30 years of age are shown. An asterisk indicates that the person was genotyped and used for linkage analysis.
having inherited the disease causing mutation. Eighteen of these were found to be affected, which gives a calculated penetrance of 78% above 30 years of age.

Oligonucleotides flanking microsatellite DNA polymorphisms on human chromosome 1q21-31 were as published elsewhere.15 PCR amplification was performed according to a previously published protocol.16 Linkage between POAG and microsatellites was analysed using the computer program package LINKAGE version 5.1,15 assuming autosomal dominant inheritance with a disease allele frequency of 0.01, and using locus distances from the published genetic map of human chromosome 1.15 Only people above 30 years of age were included in the analysis (37 of 50 subjects) (fig 1). Lod scores were calculated under two models. The first model assumed full penetrance. The second model assumed a fixed penetrance of 0.78 above 30 years of age.

Pairwise lod scores between POAG and chromosome 1 microsatellites are shown in table 1. Locus D1S218, which was completely linked in the three previous reports of juvenile onset POAG,3-11 shows exclusion of linkage in our pedigree both under a model assuming full penetrance and under a model assuming a fixed penetrance of 0.78 above 30 years of age. The exclusion distances for each marker under the full penetrance model was 15 cM (D1S218), 7 cM (D1S196), 3 cM (D1S191), and less than 1 cM (D1S194). Analysis of marker-marker linkage within the family was consistent with the published genetic linkage map17 (data not shown). The results of three point analysis are shown in table 2. The subregions D1S194-D1S196, D1S196-D1S218, and D1S218-D1S191 are excluded in our family under both models. The data indicate that the POAG gene in our pedigree is highly unlikely to lie in the entire critical region on chromosome 1 (D1S196-D1S218) and suggest that genetic heterogeneity exists within the autosomal dominant form of POAG, providing evidence for at least one other autosomal locus.

In light of the distinct clinical features between juvenile onset and adult onset POAG, genetic heterogeneity as the cause of an eye disorder such as POAG is to be expected. Additional locus heterogeneity might be expected from reports consistent with autosomal recessive inheritance.10-12 It is hoped that further linkage analysis in this and other families will eventually result in the identification of the disease causing genes and thereby elucidate the pathogenesis of all types of POAG.

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