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Mapping a Gene for Adult-Onset Primary Open-Angle Glaucoma to Chromosome 3q

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Summary

Glaucoma is the third-leading cause of blindness in the world, affecting >13.5 million people. Adult-onset primary open-angle glaucoma (POAG) is the most common form of glaucoma in the United States. We present a family in which adult-onset POAG is inherited as an autosomal dominant trait. Twelve affected family members were identified from 44 at-risk individuals. The disease-causing gene was mapped to chromosome 3q21-24, with analysis of recombinant haplotypes suggesting a total inclusion region of 11.1 cM between markers D3S3637 and D3S1744. This is the first report of mapping of an adult-onset POAG gene to chromosome 3q, gene symbol GLC1C.

Introduction

Glaucoma is a leading cause of blindness in the world; the most common form is adult-onset primary open-angle glaucoma (POAG) (MIM 137760; McKusick 1992). The term "open angle" refers to a lack of mechanical closure of the chamber angle by the iris in which the trabecular meshwork appears normal (Shields et al. 1996). In spite of the open angle, POAG patients typically have obstructed aqueous humor outflow and elevated intraocular pressure (IOP). If untreated, this usually leads to damage of the optic nerve and loss of peripheral vision. The increase in IOP is termed "ocular hypertension" when it is consistently >21 mm Hg in both eyes and may precede optic nerve damage by many years. Because the specific defect(s) leading to POAG is unknown, treatment is directed at lowering IOP. This is not always successful, however, in arresting loss of peripheral vision.

Adult-onset POAG is usually recognized as a complex non-Mendelian disorder with a few families segregating the disease as an autosomal dominant or autosomal recessive trait (Johnson et al. 1996*a*). Identifying the pattern of transmission is hampered by the late-onset of the disease; thus, it is difficult to determine whether younger generations are at risk. It is well recognized, however, that a family history of glaucoma increases one's risk for development of glaucoma (Johnson et al. 1996*a*). In a population-based survey, Tielsch et al. (1994) reported 16% of the individuals diagnosed with POAG as having a positive family history. A twin study in Finland estimated the heritability as 10.2% (Teikari 1987). These studies suggest that a multifactorial mode of inheritance is probably the mode of transmission in the majority of cases. However, identifying the glaucoma gene, even in rare families in which POAG is inherited as an autosomal dominant trait, would have a major impact on our understanding of glaucoma (Wiggs 1995).

Juvenile glaucoma, a rare form of open-angle glaucoma, has been localized to chromosome 1, in 10 families (Sheffield et al. 1993; Meyer et al. 1994; Richards et al. 1994; Wiggs et al. 1994; Graff et al. 1995; Morissette et al. 1995; Johnson et al. 1996*b*). In juvenile glaucoma, the age at diagnosis is between 10 and 35 years, in contrast to adult-onset POAG, which is defined by an age at diagnosis of >35 years (Johnson et al. 1996*a*). Nine of the juvenile glaucoma families clearly have a early age at diagnosis in all affected members. The 10th family is a huge multigenerational French Canadian family in which both juvenile and adult-onset glaucoma are being transmitted and both map to chromosome 1 (Morissette et al. 1995) . An adult-onset gene(s) in families in which all affected members have high IOP and are diagnosed after the age of 35 years has not yet been mapped.

In this paper, we present clinical and genetic analysis of a North American Caucasian family with POAG. The gene for POAG in this Oregon family maps to chromo-

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some 3q. This is the first report of the mapping of an adult-onset POAG gene to chromosome 3q.

Subjects, Material, and Methods

Subjects

The patients from the Oregon family described in this report are descendants of a man who settled in Oregon with his wife at the turn of the century. Forty-eight family members and spouses were examined, and blood was obtained from each individual. Records of two additional individuals, one of whom was deceased, were obtained from local ophthalmologists. Blood was obtained from six individuals who were not examined by us either because they lived a long distance away or were in a nursing home. Altogether, blood was collected from 44 family members. Fibroblast cultures were established from skin biopsies from six individuals. This study has been approved by the Institutional Review Board (IRB 3352); informed consent was obtained from each individual before samples were obtained.

All family members were examined by gonioscopy with a Zeiss lens and following the Schaffer grading system, in which grade IV indicates that the iridocorneal angle is $\geq 40°$ (Kolker and Hetherington 1976). Patients were considered affected if they met one of the following criteria: (1) treatment for glaucoma had been instigated prior to our study; (2) two or more of the following findings were present: (*a*) untreated IOP of 24 mm Hg measured by Goldman applanation tonometry (Pohjanpelto and Plava 1974); (*b*) optic nerve head and/or nerve fiber layer analysis was compatible with moderately advanced glaucomatous damage (i.e., a vertical cup/disk ratio >0.7 with or without erosion of the rim) (Hitchings and Wheeler 1980); (*c*) abnormal Humphrey glaucoma hemifield test; (3) definite bilateral nasal steps on Humphrey glaucoma hemifield test.

Individuals were defined as "possibly affected" if they met one of the following criterion: (1) marginal cupping (i.e., vertical cup/disk ratio >0.3 but ≤ 0.5); (2) moderate cupping (i.e., vertical cup/disk ratio ≥ 0.5); (3) untreated IOP >24 mm Hg; (4) moderate cupping and untreated pressure >24 mm Hg; (5) early nasal steps on Humphrey glaucoma hemifield test. Five to 40 ml of blood were obtained, with informed consent, from 9 affected people, 7 possibly affected individuals with optic nerve cupping (2 of whom also had high IOPs), 28 family members, who met none of the three criteria for glaucoma, and 10 unrelated spouses.

Microsatellite Marker Typing

Microsatellite markers reported by Gyapay et al. (1994) and the Utah Marker Development Group (1995) were purchased from Research Genetics. PCR reactions contained 0.25–0.5 U *Taq* polymerase in 6.25-μl volume containing 10 ng of forward and reverse primers, 0.2 mM of each deoxyribonucleotide triphosphates (dATP, dCTP, dGTP, and dTTP), 50 mM KCl, 3 mM $MgCl_2$, and 10 mM Tris-HCl (pH 9.0 at 25°C). Following 5 min at 94°C, 29 cycles of PCR were performed (94°C, 10 s; 55°C, 10 s; and 74°C, 30 s), followed by 5 min at 72°C and stored at 4°C. The resulting PCR products were mixed 1:1 with formamide loading buffer (Sambrook et al. 1989) and 2 μl was applied to an 8% denaturing acrylamide gel containing 5.6 M urea and 32% formamide (Litt et al. 1993). The bands were transferred by capillary blotting to a positively charged nylon membrane (Litt et al. 1993) (Boehringer-Mannheim), probed with a $(CA)_{15}$ 3′ oligomer labeled with digoxigenin-11-dUTP, and detected colorimetrically with the Genius Kit from Boehringer-Mannheim. Amplification reactions were repeated, if they were not readable. If still ambiguous, the sample was omitted from the analysis. Two individuals scored the gels independently.

Linkage Analysis

We conducted two-point and multipoint linkage analyses with the FASTLINK (Cottingham et al. 1993; Schäffer et al. 1994) and VITESSE (O'Connell and Weeks 1995) computer packages. Estimates of the prevalence of POAG in the general population vary from 0.5% to 1.6% (Hollows and Graham 1966; Kahn and Milton 1980; Bengtsson 1981). Wiggs (1995) reports that 2% of Caucasian North Americans >40 years of age are affected with glaucoma. Although as much as 50% of these cases may be genetic in origin (Shin et al. 1977), most are consistent with multifactorial inheritance (Teikari 1987), and only a subset appears to be inherited as an autosomal dominant trait (Lawford 1907–1908; Posner and Schlossman 1949; Kellerman and Posner 1955). Therefore, we assumed autosomal dominant inheritance of a rare gene (frequency = .0001) with age-dependent penetrance. A step-wise age correction was incorporated into the analysis, based on age-at-onset data from the 10 affected individuals in this family for whom data were available (table 1). Four of these 10 had onset between 35 and 50 years of age; the remaining 6 had onset after 50 years of age. We specified this distribution in terms of five liability classes, in which penetrance increased from 0 at age 35 years to .75 at age 70 years, after which it remained constant at .75. We based this penetrance estimate on the disease pattern in this kindred, as well as a published estimate of .74–.80 (Posner and Schlossman 1949). Only those individuals who satisfied one of the three diagnostic criteria described above were considered affected in the linkage analysis; possibly affected individuals were considered unknown with respect to disease status.

Table 1

Clinical Findings in Affected Members

Pedigree No.[a]	Age at Diagnosis (years)	Cup/Disk[b]		Tension[c]		Gonioscopy	Visual Fields	Treatment	Criteria for Inclusion[d]
		OD	OS	OD	OS				
2004	55[e]	.95	.9	26	26	IV	Severe loss OU	Trabeculectomy OU	1
3001	48[e]	.9	.9	26	22	IV[h]	Severe loss OU	Trabeculectomy OU	1
3005	38[f]	.7	.7	21	22	IV	Nasal step OS[i]	None	3
3010	68[e]	.8	.8	24	23	IV	Superior loss OD	β-blockers OU	2
3012	57[f]	.6	.6	22	22	IV	Nasal step OU	None	2
3016	50[g]	.9	.9	18	12	IV	NA	Laser Trabeculoplasty	1
4004	60[f]	.7	.6	26	24	IV	NA	None	2
4010	47[f]	.7	.8	24	24	IV	Nasal step OS	None	2
4024	55[f]	.5	.7	21	25	IV	Nasal step OS[i]	None	3
4025	~80[g]	.5	.9	25	32	IV	NA	Pilocarpine, β-blockers OU	1

NOTE.—NA = not available.

[a] As in figure 1.

[b] Vertical cup/disk ratio: OD = left eye; OS = right eye.

[c] Tension at visit with us or last visit with ophthalmologist.

[d] 1 = treatment (prior to our study); 2 = two or more of the following: (*a*) untreated pressure of ≥24 mm Hg; (*b*) cup/disk ratio of ≥0.7; (*c*) abnormal Humphrey glaucoma hemifield test; 3 = definite bilateral nasal steps on Humphrey glaucoma hemifield test.

[e] Determined by ophthalmologist.

[f] Determined by Dr. Samples.

[g] Self reported or family reported.

[h] With peripheral anterior synechia in angle.

[i] Interpreted as borderline by Humphrey Glaucoma Hemifield test.

We also conducted an affecteds-only analysis, in which only those individuals with definite POAG were coded for affected status. All others (currently unaffected and possible cases) were considered unknown with respect to affected status. Although this results in a loss of statistical power, it accommodates ambiguity with reference to penetrance.

POAG is common in the general population, but the autosomal dominant form(s) is rare. This raises the possibility of phenocopies in families with autosomal dominant POAG. Therefore, we specified a generous phenocopy rate of 2% and assumed the same age-at-onset distribution for phenocopies as for the other affected members.

We analyzed four linked marker loci that span ~11.1 cM on chromosome 3q. The map order and distances between D3S3637, D3S1535, and D3S1569 reflect the results of the most-recent Chromosome 3 Workshop (Smith et al. 1995) and Généthon (Dib et al. 1996). D3S1744 has been mapped to approximately the same location as D3S1593 by the Cooperative Human Linkage Center (CHLC) Sheffield et al. (1995); Murray et al. (1994); Sheffield et al. (1995); Gastier et al. (1995). Therefore, the distance between D3S1593 and D3S1569 from the Chromosome 3 Workshop was used as the distance between D3S1744 and D3S1569. D3S1535 and D3S1569 have been mapped to 3q22 and 3q23 (Smith et al. 1995). Published allele frequencies were available for three markers, D3S3637, D3S1569 (Gyapay et al. 1994; Dib et al. 1996), and D3S1744 (CHLC); Murray et al. (1994); Sheffield et al. (1995); Gastier et al. (1995). These frequencies were comparable to those calculated from 44 control chromosomes from our glaucoma population. Allele frequencies for D3S1535 (The Utah Marker Development Group 1995) were estimated by counting alleles in 72 control chromosomes in our laboratory, since published frequencies were not available.

Results

Inheritance of POAG

POAG was transmitted through three generations in the Oregon family (fig. 1). The founder, who is deceased, was never seen by an ophthalmologist; his diagnosis is based on family reports that he had difficulty seeing in later years and was almost blind near his death in his 90s. All affected individuals have an affected parent, and affected males and females are present in equal proportions (6:6). Seven of the 12 individuals had been identified as having open-angle glaucoma prior to our examining them. Three of the affected members are dead, but we have clinical data on one of them. Thus,

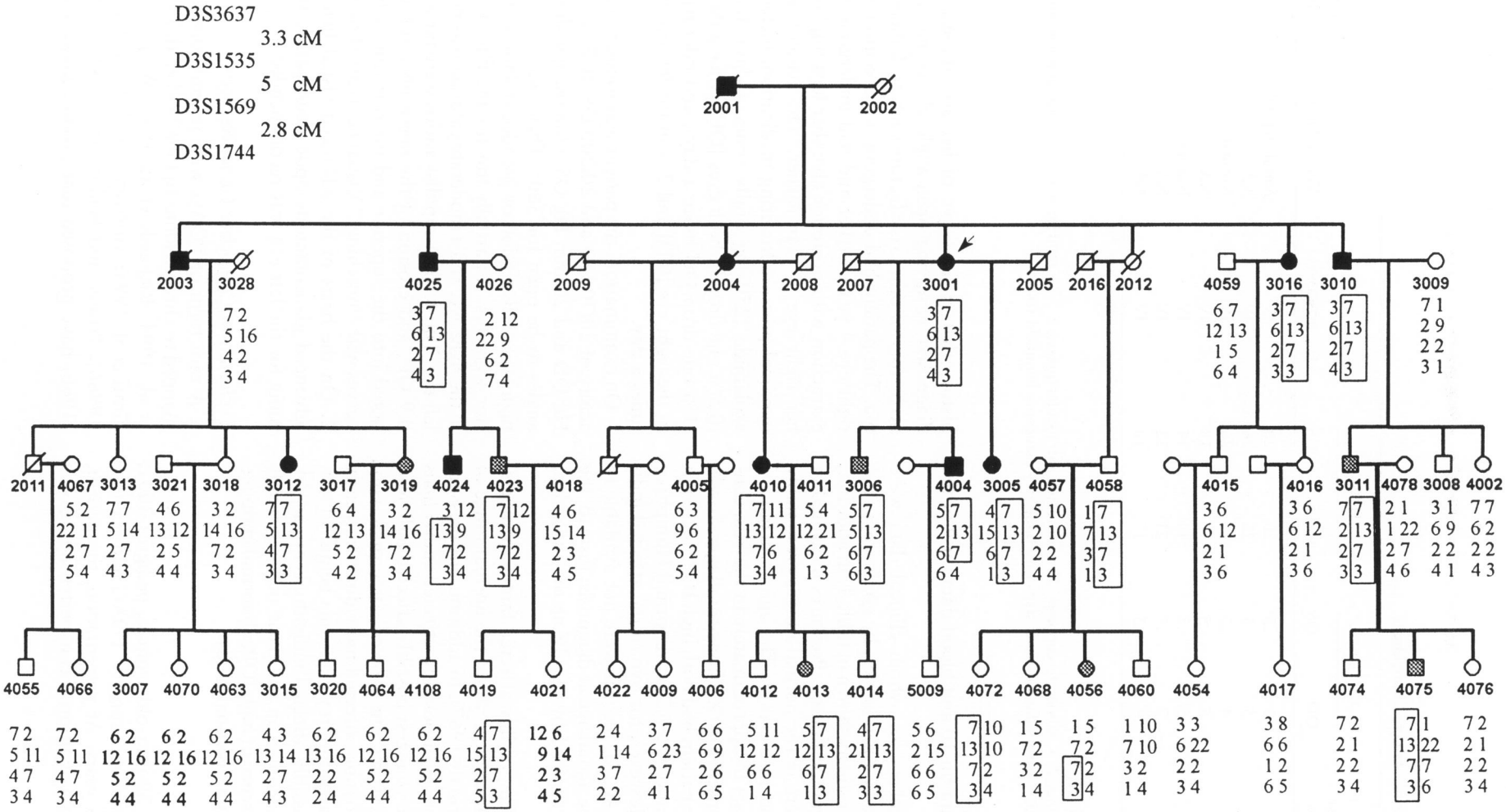

Figure 1 Pedigree of POAG family and haplotypes of chromosome 3q markers. Blackened symbols denote affected individuals; clear symbols denote unaffected individuals. Genotypes are listed in the order given by the map in the box at the *upper right*. Samples were available for all individuals for whom a haplotype is shown. The haplotype of the disease-bearing chromosome is boxed. Possibly affected are indicated by hatching inside the symbol.

Table 2

Clinical Findings in Possibly Affected Individuals

Pedigree No.[a]	Age at Exam (years)	Cup/Disk		Tension[b]		Gonioscopy	Visual Fields	Criteria for Inclusion[c]
		OD	OS	OD	OS			
3006	52	.3	.3	20	20	IV	Nasal step OU	5
3011	49	.5	.5	25	26	IV	NA	4
3019	49	.4	.3	25	26	IV	Normal	3
4013	27	.5	.5	18	18	IV	NA	2
4023	54	.5	.5	14	14	IV	Normal	2
4056	38	.7	.7	21	22	IV	NA	2
4075	19	.4	.5	17	18	IV	NA	1

[a] As in figure 1.

[b] Tension at visit with us.

[c] 1 = marginal cupping; 2 = moderate cupping; 3 = untreated intraocular pressure >24 mmHg; 4 = moderate cupping and untreated pressure >24 mm Hg; 5 = early bilateral nasal steps on Humphrey glaucoma hemifield test.

we have clinical data on 10 and blood data on 9 of the affected members.

All affected members for whom clinical data were available had grade IV open angles, by gonioscopy and abnormal cup/disk ratio as shown in table 1. In addition, high IOP was a common finding. Pressures measured in individual 3016 were in the normal range, presumably because she was on medication. The age at diagnosis ranged from 38 years to approximately in the 80s, consistent with adult-onset POAG. The age at diagnosis was defined as when the patient had both high IOP ($\geq$24 mm Hg) and cup/disk ratio of $\geq$0.7 or abnormal Humphrey visual field tests. However, for two of the affected individuals (3016 and 4025), records were not available to assess accurately the actual age at diagnosis; instead, the approximate age reported by family or the individual was used.

In six of the seven possibly affected family members, vertical cup/disk ratios were above the normal range of 0.3 (see table 2) (Armaly 1967). In addition, the pressure was high in two of seven possibly affected individuals (>24 mm Hg). The youngest possibly affected individuals had normal pressures but showed some optic cupping. One of the possibly affected individuals had early bilateral steps, on a Humphrey glaucoma hemifield test. Thus, all of the possibly affected individuals are at risk for developing glaucoma, on the basis of their family history and the presence of high IOP, abnormal cupping, or abnormal Humphrey visual fields.

Case Report

The proband, a 79-year-old woman, pedigree 3001, was referred for glaucoma surgery. POAG had been diagnosed at age 48 years. At presentation, the patient, whose only medical condition was hypertension, gave a history that at least five of her six siblings had been diagnosed as having open-angle glaucoma. There was no history of other risk factors such as diabetes or myopia. The patient had undergone a trabeculectomy in her right eye 4 years earlier and had undergone a cataract extraction with posterior chamber lens implantation in her right eye 1 year earlier. The patient was using maximal pressure-lowering medication, including acetazolamide (250 mg orally times a day), levobunolol (0.5% one drop in both eyes [OU] twice a day), epifrin (1% one drop OU twice a day), and pilocarpine, (4% in the right eye [OD] and 2% in the left eye [OS]) four times a day.

On examination, the patient was found to have visual acuity of 20/70 OD and 20/200 OS. IOPs were 16 mm Hg OD and 20 mm Hg OS. Gonioscopy showed both angles to be open for 360°. There was no evidence of pigmentary dispersion or pseudoexfolation in the anterior segments. A partially functioning filter was present in the right eye, and a moderate cataract was noted in the left eye. The vertical cup/disk ratios were far in excess of 0.9 OU, and erosion of the nerve fiber substance was noted into the superior and inferior rim of both optic nerves with "notching." Visual fields are shown in figure 2. On the basis of the advanced visual field loss and advanced glaucomatous optic neuropathy, trabeculectomy for the left eye was recommended.

Exclusion of Candidate Genes/Regions

A rare form of POAG with juvenile onset has been mapped to chromosome 1q (Sheffield et al. 1993; Meyer et al. 1994; Richards et al. 1994; Wiggs et al. 1994; Graff et al. 1995; Morissette et al. 1995; Johnson et al. 1996*b*). Posner and Schlossman (1949) and Francois (1966) have proposed that juvenile glaucoma is not a

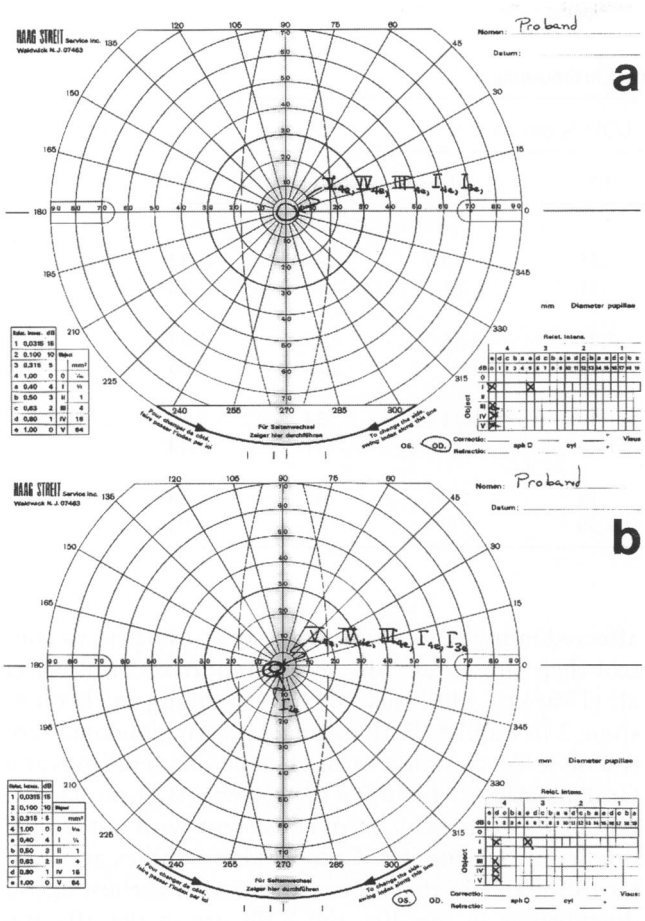

Figure 2 Goldman visual fields of proband at initial presentation. *a,* OD. *b,* OS. This field shows end-stage glaucoma, which has left the proband with only small central vision. End-stage glaucoma often leaves individuals with either small central islands or central and temporal islands. Early glaucomatous field loss starts in the periphery and works its way into the center.

separate entity but instead represents either late-onset congenital glaucoma or early-onset adult POAG. To determine whether our adult-onset glaucoma family mapped to chromosome 1q21-31, we performed a multipoint analysis based on four markers that span the region: D1S194, D1S196, D1S210, and D1S218. The entire 12-cM region spanned by these markers was excluded for linkage with POAG; that is, LOD scores were <-2.0 (data not shown). In conclusion, POAG in the Oregon family does not map to chromosome 1q21-31.

We analyzed four proteoglycans expressed in the trabecular meshwork that are likely candidate genes. These included perlecan, syndecan, versican, and decorin, localized on chromosomes 1p36.1-p35, 2p24-p23, 5q12-q14, and 12q21-22, respectively (Ala-Kapee et al. 1990; Kallunki et al. 1991; Iozzo et al. 1992; Pulkkinen et al. 1992). No evidence for linkage was found with any of the four chromosomal regions.

Genomewide Search

We initiated a genomewide search with microsatellite markers averaging 15 cM apart. In the process, we found encouraging LOD scores on chromosome 3q21-24. Two-point LOD scores are reported in table 3 for both the full-family and the affecteds-only analyses. The maximum pairwise LOD score was obtained with D3S1535 (LOD score = 3.02 at $\theta = 0$ for the full-family data). Simulation of a two-point analysis with a fully informative marker in the full-family analysis resulted in a maximum LOD score of 3.42 ($\theta = 0$). Crossovers occurred at D3S3637 and D3S1744. We conducted a multipoint analysis with all four markers and POAG, which resulted in increased evidence for linkage. The maximum multipoint LOD score was 3.20 at D3S1569 in the full-family analysis and 2.72 at D3S1535 in the affecteds-only analysis (fig. 3). Haplotype data are given in figure 1. Critical crossovers occurred in two affected individuals: 4024 shows a D3S3637-D3S1535 crossover; 4004 shows a D3S1569-D3S1744 crossover. These data indicate that a gene for adult-onset POAG is located within the 11.1-cM region bounded by D3S3637 and D3S1744.

Six of the seven possible POAG cases carry at least part of the disease-bearing chromosome in the Oregon family. They range in age from 19 to 54 years; half are younger than the earliest age at onset (see table 2). Four currently unaffected individuals carry the disease haplotype; three of these four are <37 years of age.

Discussion

This is the first report of the mapping of adult-onset POAG phenotypically characterized by the triad of high IOP, compromised disk/cup ratio, and field-vision loss. A gene for normal tensive glaucoma, which is less common than POAG, has recently been mapped to chromosome 2 (Stoilova et al. 1996). Our mapping of adult-onset POAG to chromosome 3 is an important finding because glaucoma is a leading cause of blindness, affecting >2% of the population in the United States (Hollows and Graham 1966). We believe that correct identification of the adult-onset glaucomatous phenotype represents a significant challenge. Clinically, we chose a fairly rigorous definition and have defined possibly affected as adult family members with marginal elevations of IOP or marginal cupping but without field or nerve changes attributable to glaucoma. It is critical to incorporate the possibility of phenocopies in linkage analysis of common, adult-onset disorders, to avoid false-negative linkage results (i.e., affected family member who may actually be a phenocopy is considered a crossover, resulting in negative LOD scores at least at small values of θ). In this family, however, all affected

Table 3

Results of Pairwise Linkage Analyses in POAG Family on Chromosome 3

	LOD SCORE AT θ =					
MARKER	.00	.01	.05	.10	.20	.30
D3S3637:						
Full family	−2.53	−.07	.55	.73	.70	.47
Affecteds only	−1.38	0	.52	.61	.50	.28
D3S1535:						
Full family	3.02	2.98	2.82	2.56	1.95	1.25
Affecteds only	2.12	2.08	1.89	1.65	1.16	.65
D3S1569:						
Full family	1.66	1.62	1.49	1.31	.94	.56
Affecteds only	1.57	1.53	1.38	1.19	.81	.44
D3S1744:						
Full family	−2.82	−.37	.18	.30	.25	.14
Affecteds only	−1.97	−.83	−.26	−.09	−.02	−.01

individuals carried the same disease haplotype at D3S1535-D3S1569. Thus, reduction of the phenocopy from 0.02 to 0.01 (or even to 0) had very little effect on LOD scores.

Most of the currently unaffected individuals >50 years of age do not carry the disease haplotype. In the full-family analysis, these are considered nonrecombinant individuals and, as such, make a substantial contribution to the LOD score. In the affecteds-only analysis, the reduction in the LOD scores is primarily because of the removal of these older, unaffected individuals.

The POAG reported in the Oregon family represents a fairly typical picture of POAG in the general population, with onset after the age of 35 years, high (≥24 mm Hg) IOPs in affected members, and 3 of the 10 affected individuals having to resort to surgery to control their pressures. The recent report by Stoilova et al. (1996) of adult-onset POAG mapping to chromosome 2 in families with normal tension glaucoma represents a less common form of glaucoma (Hollows and Graham 1966). Lichter (1994) reports three POAG families, two of which are consistent with autosomal dominant inheritance. Two of these families are similar to the one in this report, in that the earliest age at diagnosis is in the 30s, the IOPs are in the 20s and 30s, and the response to medical therapy is fair. The third family is a Black family with an earlier age at diagnosis of 29 years. Other families with autosomal dominant inheritance of adult-onset POAG have been reported in the literature; however, data on IOPs, cup/disk ratio, and visual fields were not presented, so it is difficult to compare these families with the one in this report (Francois 1966).

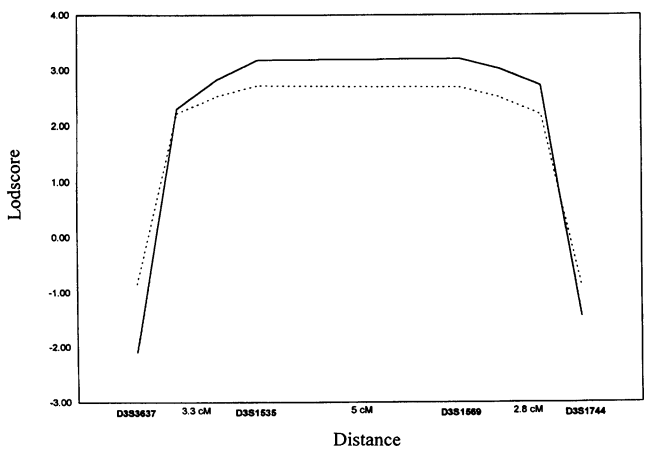

Figure 3 Multipoint linkage results for the analysis with full-family analysis (solid line) and affecteds-only analysis (dotted line).

There are ≥11 genes mapped, to date, to chromosome 3q, between D3S3637 and D3S1744, that are potential candidate genes. These include a membrane endopeptidase (MME), also known as neutral endopeptidase 24.11 and CD10, interleukin 12A, transferrin, ribophorin I, ceruloplasmin, angiotensin receptor I, carboxypeptidase A3, pentaxin-related gene, sucrase isomaltase, and butyrl cholinesterase (Yang et al. 1984; Barker et al. 1989; Gaughan et al. 1991; Brevario et al. 1992; Sieburth et al. 1992; Pollak et al. 1993; Naylor et al. 1994; Rolfs et al. 1994; Suzukawa et al. 1994; Smith et al. 1995;). Of these, MME is the most likely candidate gene for POAG. MME is a 100-kD type II integral membrane glycoprotein expressed on many cell types (Shipp and Look 1993), including the trabecular meshwork (data not shown). This glycoprotein is a neutral endopeptidase that has

been implicated in control of IOP (Wolfensberger et al. 1994). Mutational analysis of this gene is now underway in our POAG family.

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