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Familial Glaucoma Iridogoniodysplasia Maps to a 6p25 Region Implicated in Primary Congenital Glaucoma and Iridogoniodysgenesis Anomaly

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Summary

Familial glaucoma iridogoniodysplasia (FGI) is a form of open-angle glaucoma in which developmental anomalies of the iris and irido-corneal angle are associated with a juvenile-onset glaucoma transmitted as an autosomal dominant trait. A single large family with this disorder was examined for genetic linkage to microsatellite markers. A peak LOD score of 11.63 at a recombination fraction of 0 was obtained with marker *D6S967* mapping to chromosome 6p25. Haplotype analysis places the disease gene in a 6.4-cM interval between the markers *D6S1713* and *D6S1600.* Two novel clinical appearances extend the phenotypic range and provide evidence of variable expressivity. The chromosome 6p25 region is now implicated in FGI, primary congenital glaucoma, and iridogoniodysgenesis anomaly. This may indicate the presence of a common causative gene or, alternatively, a cluster of genes involved in eye development/function.

Introduction

Familial glaucoma iridogoniodysplasia (FGI; MIM 137750) is a form of open-angle glaucoma in which developmental anomalies of the iris and irido-corneal angle are associated with a juvenile-onset glaucoma. It is transmitted as an autosomal dominant trait with complete penetrance. A number of families worldwide have been reported with this condition (Courtney and Hill 1931; Berg 1932; Stokes 1940; Hambresin and Schepens 1946; McCulloch and MacRae 1950; Martin and Zorab 1974). Affected individuals have a distinctive appearance of the irides. The iris color is described as either dark slate-grey or chocolate brown and appears flat, featureless, and lacking in crypts. Many affected individuals also have the abnormal gonioscopic finding of pale tissue, believed to be of mesenchymal origin, covering the trabecular meshwork.

Here we present the results of a genetic linkage study of FGI in a single large Caucasian pedigree. The LOD scores and haplotype data presented for six microsatellite markers provide evidence of linkage to a 6.4-cM interval in the chromosome 6p25 region. Clinical data documenting novel phenotypes provide evidence of variable expressivity.

Methods

Pedigree Ascertainment

The family has twice been reported in the clinical literature (Zorab 1932; Martin and Zorab 1974). The pedigree can be traced back nine generations to a Scot living at the time of the battle of Culloden Moor in 1745 and known as "Ian of the Blackberry Eyes" as a result of the striking appearance of his irides (fig. 1). As in other similar FGI pedigrees, the iris appearance has been used as a reliable marker for the development of glaucoma (Hambresin and Schepens 1946; Francois et al. 1950; McCulloch and MacRae 1950; Martin and Zorab 1974). In this family the affected iris usually has a typical slate-grey color against which the sphincter pupillae can be seen as a pale central ring (fig. 2*A*). Gonioscopy usually reveals abnormal pale tissue covering the surface of the trabecular meshwork. Sometimes a prominent circumferential blood vessel can be seen overlying this tissue.

The development of highly informative polymorphic microsatellite markers regularly spaced throughout the human genome presented the opportunity to map this disorder to a specific chromosomal locus. For this purpose, 71 members of the family, belonging to a single large branch originating in the fifth generation, were recruited for study. In all cases, informed consent was obtained. Forty-six subjects, 24 of whom were affected, were entered into the linkage analysis. The majority of subjects were examined by one or more of the authors, and, where this was not possible, information was obtained from records or reports provided by other ophthal-

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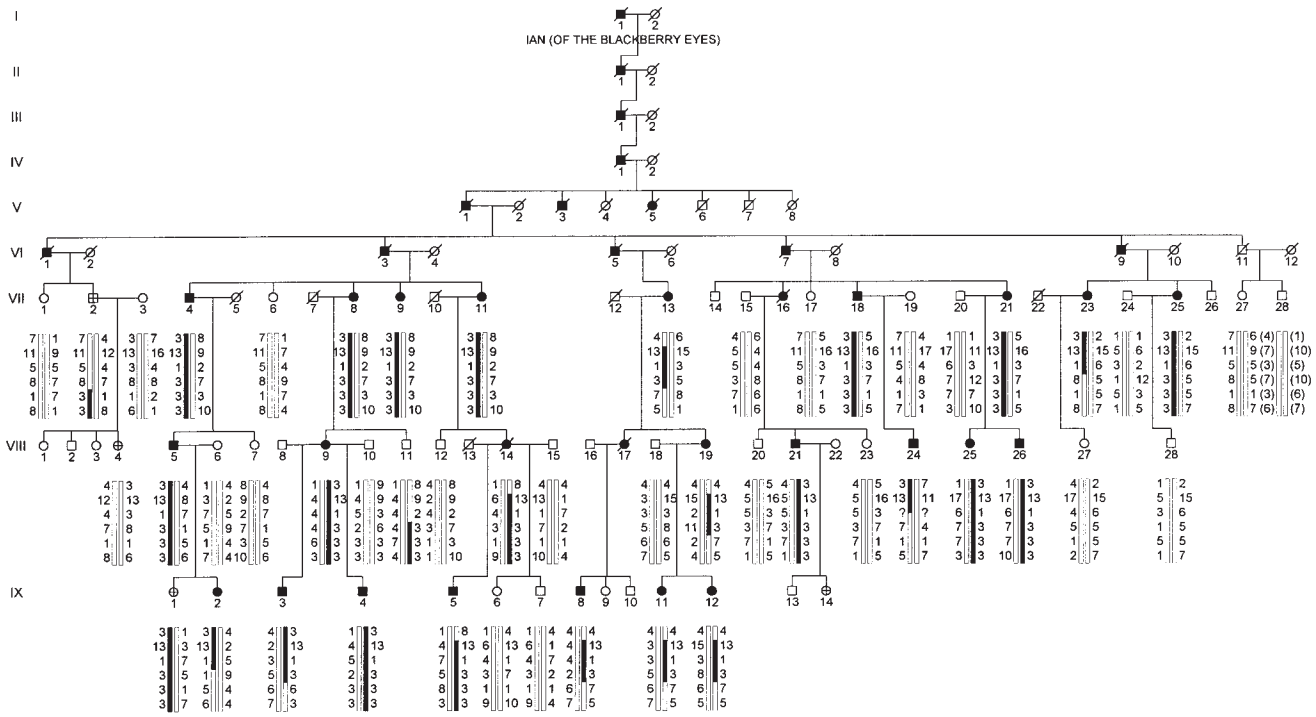

Figure 1 Nine-generation FGI pedigree. Blackened symbols denote affected individuals; diagonal slashes denote subjects with uncertain diagnostic status; blackened bars denote the haplotype segregating with glaucoma; and question marks (?) denote alleles that could not be unequivocally assigned for that marker. The marker order, from telomere to centromere, is *D6S1600-D6S967-D6S344-D6S1713-D6S1668-D6S1574*.

mologists. The examination included measurement of visual acuity, assessment of pupil responses, slit-lamp biomicroscopy, optic-disk examination, applanation tonometry, and visual-field testing. Whenever possible, a gonioscopic examination was also performed. Affected status was assigned to individuals manifesting the characteristic abnormalities of the iris and irido-corneal angle and/or juvenile-onset open-angle glaucoma. Criteria for diagnosing glaucoma were (1) intraocular pressure (IOP) >21 mmHg, in the presence of persistent visual-field defects or optic-disk cupping, or (2) IOP >30 mmHg, with or without visual-field defects or cupping.

Linkage Analysis

DNA was prepared from peripheral blood or mouthbrush samples, by standard procedures. Microsatellite markers from the CEPH Généthon and Utah Center for Human Genome Research collections were used to genotype 50 members of the family, 24 of whom were affected and 26 of whom were unaffected, by application of conventional methods described elsewhere (Toma et al. 1995). Linkage to all known mapped glaucoma loci (Ton et al. 1991; Murray et al. 1992; Sheffield et al. 1993; Safarazi et al. 1995; Akarsu et al. 1996; Mears et al. 1996; Stoilova et al. 1996; Wirtz et al. 1997; reviewed in Raymond 1997) and to chromosomes with reported anomalies linked to glaucoma (reviewed in Nielsen and Tranebjaerg 1984; Nishimura et al. 1995) was sought before a total genome search was undertaken.

Allele scoring was conducted independently by two observers, and the consensus results were entered into appropriate files and were processed by the Linksys program, version 4.1 (Attwood and Bryant 1988). Two-point linkage analysis was performed on an IBM-compatible desktop computer with the MLINK component of the LINKAGE program, version 5.1 (Lathrop and Lalouel 1984). Calculations were performed for an autosomal dominant model assuming a penetrance of 1.0, a gene frequency of .0001, and a mutation rate of 10^{-6}. The allele frequencies for each marker were calculated on the basis of data from nine married-in spouses. Being more representative of the population from which the family derives, these values were used in preference to the published figures. Recombination frequencies were assumed to be equal for males and females. Haplotype analysis was used to determine the flanking markers defining the interval containing the disease gene.

Results

Clinical Findings

All individuals with the characteristic iris appearance have, without exception, gone on to develop glaucoma at

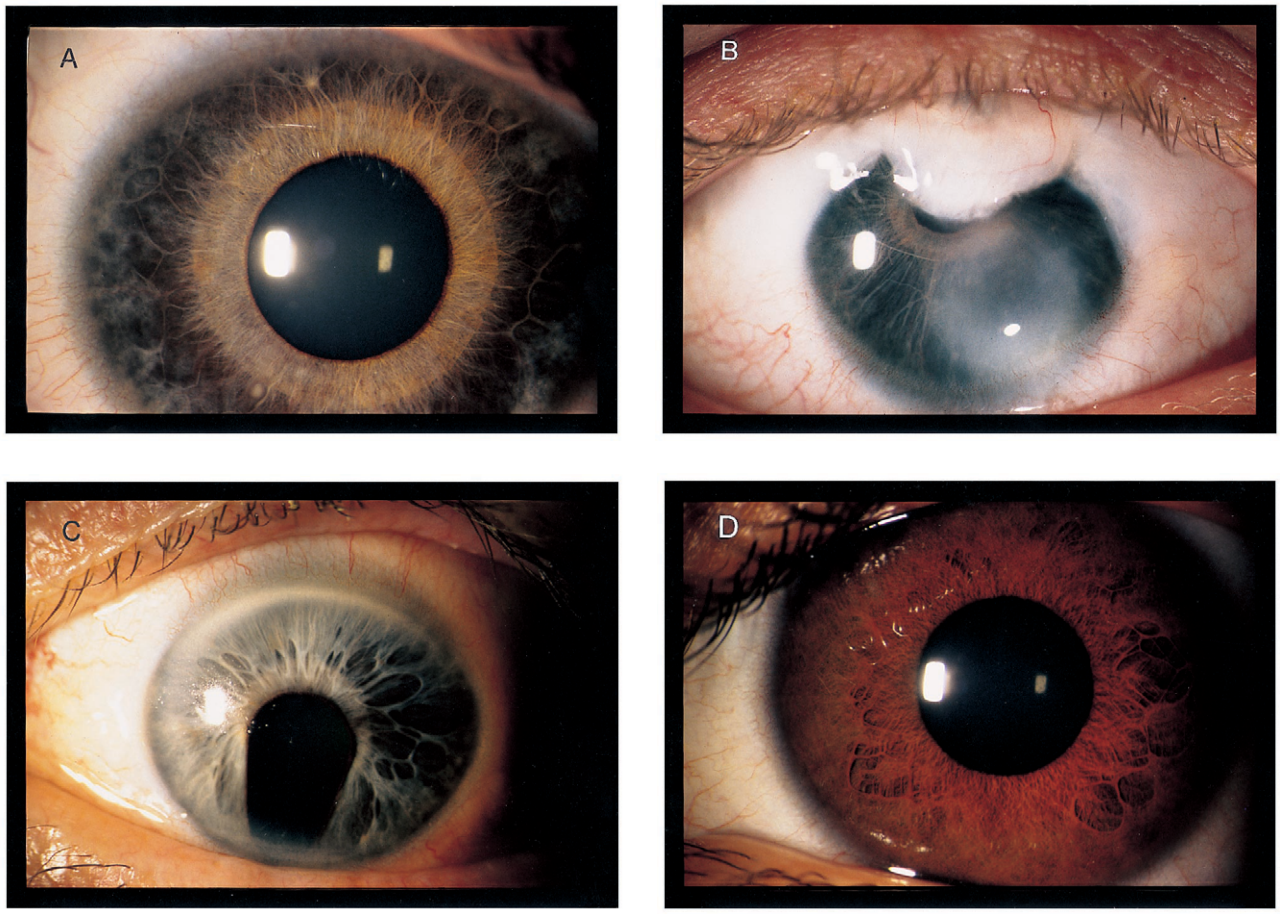

Figure 2 Ocular anterior-segment photographs of members of pedigree. *A,* Right eye of individual IX-5, showing the characteristically featureless slate-grey iris with the sphincter pupillae visible as a pale ring encircling the pupil. *B,* Right eye of individual IX-3, showing the typical iris coloration and, in addition, a disk of paraxial corneal thinning and opacification inferonasally, to the margins of which are attached iris strands. The upwardly displaced pupil is believed to be secondary to an iris-inclusion operation for glaucoma, which has created the cystic conjunctival bleb seen encroaching onto the corneal surface superiorly. *C,* Left eye of individual VII-2, showing a coloboma of the iris inferonasally. *D,* Left eye of individual IX-1, showing small amounts of abnormal pale tissue on the surface of the iris peripherally.

age <40 years. Conversely, no individual with "normal" irides has developed glaucoma at age <40 years. The earliest recorded onset of glaucoma is at 12 years of age. One individual with characteristically abnormal irides is now age 33 years and has yet to develop glaucoma. One branch of the family (VII-2 and offspring) and one individual (IX-1) were excluded from the linkage analysis, as a result of diagnostic uncertainty. Individual VII-2 has light-blue irides, a coloboma of the iris in the left eye (fig. 2*C*), and iris processes extending, in one quadrant of the right eye, to the cornea. His daughter (VIII-3) has hazel irides, which, in a previous study (Martin and Zorab 1974), had been considered to be "partially affected." Individual IX-1 has brown irides that look normal except for the bilateral presence of small amounts of pale surface tissue peripherally (fig. 2*D*). At present she has no signs of glaucoma. In contrast, her sister (IX-2) has the typical slate-grey irides and has been on treatment for glaucoma since age 12 years.

No member of the family has had primary congenital glaucoma. None of them has been found to have Axenfeld anomaly, Rieger anomaly, or aniridia and its associated posterior-segment changes, such as macular hypoplasia and optic-nerve hypoplasia (Nelson et al. 1984). In addition, we found within the family no evidence of any of the common systemic abnormalities associated with Rieger syndrome, such as abnormal dentition, maxillary hypoplasia, and redundant umbilical skin (Jorgenson et al. 1978). However, one individual (IX-3) has, in the left eye, a disk of paraxial corneal thinning and opacification inferonasally, to the margins of which are attached iris strands (fig. 2*B*). These changes, along with bilateral lens opacities, are reported to have been present from birth.

Table 1

Two-Point Linkage Data

	LOD Score at θ =							
Locus	.00	.05	.10	.20	.30	.40	Z_{max}	θ_{max}
D6S1600	−∞	6.79	6.53	5.37	3.81	1.92	6.79	.05
D6S967	11.63	10.67	9.66	7.49	5.06	2.40	11.63	.00
D6S344	11.54	10.61	9.64	7.55	5.20	2.57	11.54	.00
D6S1713	−∞	4.70	5.07	4.47	3.17	1.47	5.07	.10
D6S1668	−∞	1.56	2.49	2.71	2.11	1.07	2.76	.16
D6S1574	−∞	3.75	4.44	4.19	3.12	1.59	4.50	.13

Linkage Analysis

On the basis of accepted linkage criteria (Morton 1955), exclusion was obtained for all the tested candidate regions except the telomeric end of chromosome 6p, to which linkage was found. The highest LOD score (Z_{max}) obtained was 11.63 at a recombination fraction (θ) of 0, with marker *D6S967* (see table 1). Repeating the analysis with published CEPH allele frequencies did not significantly alter the results (maximum decrease of any Z_{max} was 0.45). No published allele frequencies were available for the Utah marker *D6S967*. Recalculation with a reduced penetrance of .9 still gave a significant LOD score, of $Z_{max} = 11.12$ at $\theta = 0$, with *D6S967*.

Haplotype analysis revealed, in individuals VII-2, VII-13, VII-23, VIII-11, VIII-14, VIII-24, IX-2, and IX-3, recombination events that place the gene within a 6.4-cM interval between the flanking markers *D6S1713* and *D6S1600* (fig. 3). If it assumed that the disease-linked haplotype seen in individuals VII-4, VII-8, VII-9, VII-11, VII-18, VII-21, and VII-25 represents the ancestral haplotype, then two recombination events have occurred between individual V-1 and his grand-daughter VII-13. Her resultant haplotype shares with the ancestral haplotype the alleles *D6S1713, D6S344,* and *D6S967*. This interpretation is consistent with these markers being within the interval containing the disease gene and segregating with her affected descendants.

Multipoint analysis with the complete set of markers spanning the disease interval was not possible, because of the high number of alleles per markers. Three-point analysis of *D6S1600* and *D6S1713* against the disease was performed with the LINKMAP component of the LINKAGE program. The result was $Z_{max} = 10.2$ in the 6.4-cM interval between the markers. This is ⩾2 LOD units greater than that for the adjacent intervals. A three-point analysis with markers *D6S967* and *D6S344* from within this 6.4-cM interval gave $Z_{max} = 12.42$.

Haplotype analysis was also performed on results from the three individuals who, because of diagnostic uncertainty, had been excluded from linkage analysis. Individual VII-2 appears to have inherited a recombinant chromosome that has normal alleles for both markers flanking the disease interval. On this basis he is not carrying the disease gene and therefore appears to constitute an example of sporadic unilateral coloboma. His daughter (VIII-4) therefore cannot be affected and in fact can be seen to have inherited her father's maternally derived chromosome. These results are in keeping with the observation that neither VII-2 (age 72 years at time of study) nor VIII-4 (age 39 years at time of study) has developed signs of glaucoma.

Individual IX-1 has inherited the entire glaucoma-linked haplotype and is therefore carrying the disease gene. However, unlike other affected members of the

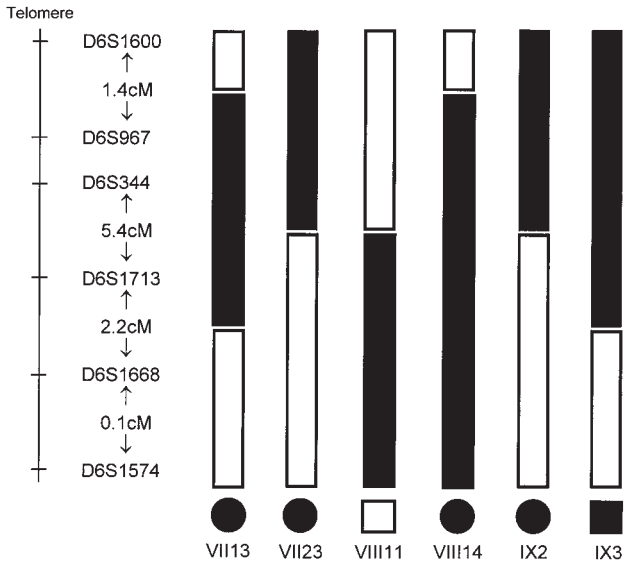

Figure 3 Haplotype analysis, illustrating recombination events between the disease gene and chromosome 6p markers. Affected individuals VII-23 and IX-2 and unaffected individual VIII-11 have a recombination event between *D6S1713* and *D6S344,* placing the disease gene telomeric to *D6S1713*. Affected individuals VII-13 and VIII-14 have a recombination event between markers *D6S1600* and *D6S967,* placing the disease gene centromeric to *D6S1600*. The disease gene therefore lies in the 6.4-cM interval between markers *D6S1600* and *D6S1713*.

family, she has a minimal iris dysplasia (fig. 2*D*). She has yet to develop signs of glaucoma and continues to receive regular eye examinations (age 15 years at time study).

Discussion

We have shown that FGI maps to a 6.4-cM interval in the chromosome 6p25 region between markers *D6S1600* and *D6S1713*. The assignment of this interval is based on recombination events in six individuals, five of whom have been diagnosed as affected after examination by one of the authors of the present report. The haplotype data do not rely on the status of unaffected individuals and therefore are not subject to any error that could arise as a result of incomplete penetrance. The importance of this is illustrated by the finding that individual IX-1, of previously uncertain diagnosis, has inherited from her father the entire disease-linked haplotype.

Other possibly related disorders mapping to the telomeric end of 6p include primary congenital glaucoma (Nishimura et al. 1995), iridogoniodysgenesis anomaly (Mears et al. 1996), and a range of anterior-segment dysgeneses, including corneal opacification, iris hypoplasia, Rieger anomaly, and aniridia (Chitayat et al. 1987; Palmer et al. 1991). Primary congenital glaucoma has been mapped to the region by two translocations with a common breakpoint in 6p25 (Nishimura et al. 1995). Although there are no cases of primary congenital glaucoma recorded in this family, cases have been reported elsewhere, in other pedigrees with autosomal dominant glaucoma (Berg 1932; McCulloch and MacRae 1950; Gillespie 1963). However, the usual mode of inheritance for primary congenital glaucoma is autosomal recessive, and it has traditionally been considered a separate disease entity. The possibility of a developmental abnormality produced by a single gene defect leading to both primary congenital glaucoma and FGI could be explained by differences in severity of malformation of the irido-corneal angle at birth and would support the concept of late congenital glaucoma as proposed by Kluyskens (1950) and developed by Jerndal (1972, 1983). In cases where the malformation is not severe enough to cause primary congenital glaucoma, subsequent dysfunction and cumulative damage could result in delayed onset of the disease. An alternative explanation is that more than one gene has been rendered dysfunctional in the translocation patients, resulting in a more severe phenotype.

Iridogoniodysgenesis anomaly (IGDA) has recently been mapped, by linkage analysis, to the 6p25 region (MIM 601631; Mears et al. 1996). There are similarities between the IGDA phenotype and that seen in the family presented here. Shared features include iris hypoplasia, prominent sphincter pupillae, abnormal angular tissue, and the development of juvenile-onset glaucoma. However, some phenotypes presented here are unique to this family—for example, the subtle iris phenotype seen in individual IX-1 and the lens and cornea abnormalities seen in individual IX-3. The latter case is reminiscent of Peters anomaly, which has been reported in association with deletion of the tip of chromosome 6p (Palmer et al. 1991). FGI also differs from IGDA in the number of cases that proceed to develop glaucoma. Only 74% of affected individuals from the families in which IGDA is linked to 6p25 have proceeded to develop glaucoma. This contrasts with a glaucoma rate of 95%–100% in FGI.

It has been questioned whether FGI is distinct from Rieger syndrome, in which iridogoniodysgenesis is seen with somatic anomalies (Rieger 1935; Chisholm and Chudley 1983). Rieger syndrome has now been mapped to two separate loci, on 4q25 (MIM 180500; Murray et al. 1992) and on 13q14 (MIM 601499; Phillips et al. 1996). One gene from the 4q25 locus has now been cloned (*RIEG1*) and found to be mutated in Rieger syndrome patients (Semina et al. 1996). A form of autosomal dominant iris hypoplasia with juvenile-onset glaucoma (MIM 137600), iridogoniodysgenesis with systemic features (IGDS), has also been mapped to 4q25 (Heon et al. 1995). These patients have ocular findings similar to those seen in FGI and IGDA but also have systemic features of Rieger syndrome. No such systemic features have been found associated with FGI or IGDA. It remains to be seen whether IGDS is allelic with Rieger syndrome. Rieger anomaly in which the ocular anomalies of Rieger syndrome are seen without the systemic disorders has been reported in cases of ring chromosome 6 and terminal deletions of 6p (Chitayat et al. 1987; Palmer et al 1991). All the evidence now suggests that the gene for FGI may also cause Rieger anomaly but not Rieger syndrome.

The various ocular disorders mapping to this region may result from either different mutations within the same gene or the involvement of a cluster of genes with overlapping roles in the development/function of the eye. The range of phenotypes seen within the family described here illustrates variable expressivity of a single disease gene and is in keeping with the wide range of effects produced by other genes causing anterior-segment malformation (Falls 1949; Hittner et al. 1980, 1982; Hanson et al. 1994). Whether IGDA and primary congenital glaucoma are part of the disease spectrum of the same gene remains to be seen.

At present there are no strong positional candidate genes for FGI. Genes mapped to the 6p25 region by FISH include the cluster of serpin genes—*PI6, PI9,* and *ELANH2*—and *FKHL7,* a human homologue of the *Drosophila forkhead* gene (Larsson et al. 1995; Eyre et

al. 1996). Serpin genes are serine proteinase inhibitors known to be involved in the regulation of extracellular proteinases and matrix remodeling. There is evidence to suggest that they are also involved in cell-cycle control, differentiation, and apoptosis and could therefore play a role in development. The forkhead genes are homologues of a *Drosophila* transcription factor that has a DNA-binding motif, the FKH box (Wiegel and Jaekle 1990). *forkhead* is involved in the development of both the anterior and posterior ends of the developing *Drosophila* embryo (Wiegel et al. 1989). Interestingly, the second mapped locus for Rieger syndrome lies in the 13q14 region, to which another *forkhead* homologue, *FKHL3,* has been assigned (Larsson et al. 1995).

None of the murine genes mapping to regions of syntenic homology with 6p25 are good candidates for glaucoma and ocular anterior-segment dysgenesis. At present there are no known mouse mutants with a phenotype resembling FGI. In fact, there is currently no murine model for glaucoma. The development of one should clearly be a high priority, since it would greatly facilitate efforts to unravel the pathogenesis of glaucoma and would permit the testing of novel therapies derived from advances in our understanding.

The cloning of genes for rare heritable forms of glaucoma is one way to increase our understanding of the basic pathogenesis of the disease. In the future it will also allow us to test the hypothesis that the coincidence of subclinical mutations in a number of genes involved in the formation and function of the anterior segment of the eye can be responsible for cases of adult-onset primary open-angle glaucoma, which is by far the most common form of the disease.

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