JUVENILE GLAUCOMA LINKED TO GLCIA IN A PANAMANIAN FAMILY*

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ABSTRACT

Purpose: To carry out clinical and genetic characterization of juvenile-onset primary open-angle glaucoma (POAG) inherited as an autosomal dominant trait in a Panamanian family.

Methods: Twenty-two members of a six-generation Panamanian family underwent an ophthalmologic evaluation. Blood samples were collected from 20 of these individuals for preparation of DNA for use in screening of microsatellite repeat genetic markers via polymerase chain reaction.

Results: Eleven living family members covering 4 generations were diagnosed as affected with open-angle glaucoma of primarily juvenile onset. Four of 6 other at-risk individuals examined and enrolled were characterized as unaffected and two as indeterminate. Two additional individuals were not included in this study because they were too young to characterize or to provide a blood sample. Three spouses of affected family members were also examined and found not to have glaucoma. Of clinical

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importance was the finding of markedly elevated intraocular pressure (IOP) in 2 affected brothers, both of whom were advised to have urgent filtration surgery; the finding of elevated IOP in the only seeing eye of the mother of these brothers, causing us to advise her to pursue more aggressive treatment; and the finding of early signs of glaucoma in a previously undiagnosed 9-year-old family member. Linkage analysis using selected microsatellite repeat markers in the 1q21-q31 region revealed strong evidence for linkage to the GLC1A gene with a maximum lod score of 3.75 for marker D1S431 at a recombination fraction of 0.00.

Conclusions: The most likely interpretation of our data is that a mutation in the GLC1A gene is responsible for juvenile-onset POAG in this Panamanian family, thus expanding the countries of origin where this gene has been found to exist. The numbers of families with GLC1A glaucoma now reported from only a few centers worldwide raise questions about whether this disease may be more common than once thought. Evaluation of treatment histories and clinical outcomes in members of this and other previously reported families indicates that ophthalmologists need to understand the necessity for urgent filtration surgery in most cases of GLC1A glaucoma if vision is to be preserved.

INTRODUCTION

Since the first report of linkage of a form of juvenile-onset POAG to chromosome 1q21-q31,[1,2] numerous investigators have confirmed in multiple families linkage to the officially named GLC1A locus.[3-10] Reported ancestry of these families has included French, English, German, Irish, and Danish origins. While characterization of the phenotype of this genetic disorder has usually included onset under 20 years of age with very high intraocular pressure, poor or no response to medical therapy, and need for early filtration surgery, there have been reports of variability in the phenotype.[2-10] Some families demonstrate onset of their glaucoma in the "juvenile" age-group most typical of GLC1A glaucoma, but a report[9] of later adult-age onset in some cases raises questions about whether there is a clear-cut line between juvenile-onset and adult-onset disease. In other families, there are occasional cases of individuals who have passed the disease along to their children or who have the disease allele-carrying haplotype but who show minimal or no manifestations of glaucoma as of the time of participation in the studies, although no follow-up studies have been done to determine whether in cases of nonpenetrance, glaucoma develops later.[2,7-10]

The present family, UM:GL57, shows the classic phenotype of this

disorder and no evidence of reduced penetrance. Being of Panamanian origin, UM:GL57 adds to the evidence that GLC1A glaucoma may be more widespread and common than was thought to be the case prior to the recent genetic studies cited above that raised interest and awareness of the disease. We report the clinical findings in this family that serve to emphasize why examination at an early age of all at-risk family members is essential and that ophthalmologists need to be aware of the necessity of performing filtering surgery early in this disease. Finally, we report the results of linkage analysis of GLC1A-region markers tested on family UM:GL57 and discuss the importance of eventually determining whether or not a patient with glaucoma carries this defective gene or another, yet unidentified causative gene defect.

SUBJECTS AND METHODS

Through the proband of family UM:GL57, who lives in the United States, contact was made with the remainder of the family in Panama. A field trip was arranged whereby 21 family members traveled to Panama City for clinical evaluation. A professional interpreter was utilized during the Panama City examinations and informed consent procedures. The proband was examined separately at the W.K. Kellogg Eye Center in Ann Arbor, Michigan. All family members participating in the study received complete information about the study and signed a consent form approved by the University of Michigan Medical Center Institutional Review Board.

Each family member underwent careful history taking to determine previous ocular status, ocular drug therapy, general medical status, other medication usage, and knowledge about the family in general. An ophthalmologic examination was performed by one of us (P. R. L.) that included visual acuity testing, refraction, slit-lamp biomicroscopy, IOP measurement by applanation, gonioscopy, and optic nerve assessment. In addition, 40 mL of venous blood was obtained by venipuncture from all of the 11 known affected individuals, 4 unaffected siblings of affected individuals, 2 spouses with affected children, 1 spouse whose child turned out to be too young to sample, and 2 at-risk individuals whose clinical status could not be assigned with certainty as marked on the pedigree (Fig 1). Diagnostic status assignments for generations 1 and 2 was derived from family history.

The blood was collected into vacutainer tubes containing ethylenediaminetetraacetic acid (EDTA). DNA was prepared with the use of the Blood and Cell Culture Maxi Kit from Qiagen according to the manufacturer's protocols for isolation of DNA from blood. Microsatellite repeat markers tested here were previously published.[11, 12] Markers D1S252,

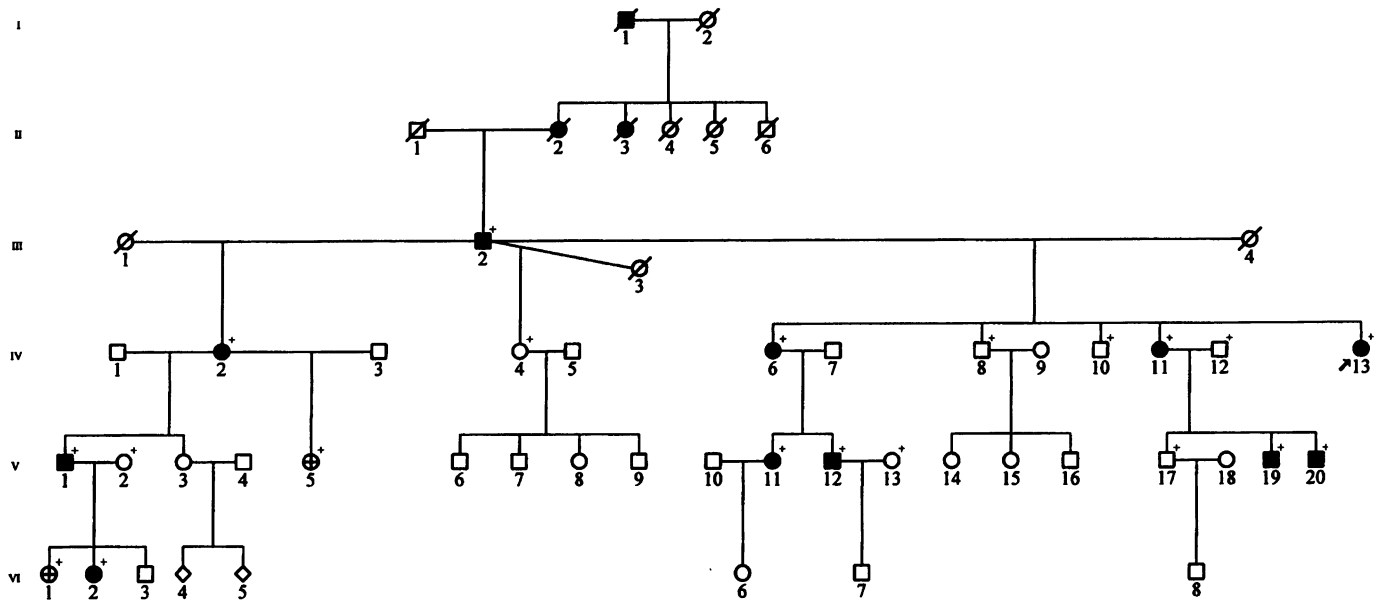

FIGURE 1

Juvenile glaucoma pedigree UM:GL57. Males are indicated by squares and females by circles. Affected individuals are shown as solid symbols, unaffected individuals as open symbols. Uncertain status is indicated with a plus sign within the open symbol for 1 individual with ambiguous clinical signs and for 1 individual who has a normal phenotype at a very young age. Plus signs next to symbols indicate individuals from whom clinical information and blood samples were obtained. Diagonal arrow indicates proband.

D1S196, D1S433, D1S431, D1S452, D1S218, D1S212, D1S191, and D1S306 were amplified by polymerase chain reaction (PCR)[13-15] by using reaction mixture and size fractionation previously described by Richards and associates[3] and thermal cycling conditions as follows: 5 minutes at 94 °C followed by 40 cycles of [20 seconds at 94 °C, 20 seconds at 55 °C, 1 minute at 74 °C], followed by 10 minutes at 74 °C and storage at 4 °C . D1S305 was assayed in the same way, except that thermal cycling was carried out as follows: 5 minutes at 94 °C followed by 5 cycles of [10 seconds at 94 °C, 10 seconds at 62 °C, 20 seconds at 72 °C], followed by 30 cycles of [10 seconds at 94 °C, 10 seconds at 54 °C, 20 seconds at 72 °C], followed by 10 minutes at 72 °C and storage at 4 °C . The reported order and spacing of the markers tested or discussed in this paper are cen-D1S252-10cM-D1S305-22cM-DIS196-1cM-D1S431-1cM-D1S433-4cM-D1S452-3cM-D1S218-3cM-D1S212-7cM-D1S191-15cM-D1S306-ter[9, 12]

Linkage analysis was performed by the method of lod scores[16] using the parameters of the autosomal dominant GLC1A model previously used in our analysis of juvenile glaucoma families UM:JG1 and UM:JG3.[3, 10] This model assumes 90% penetrance, no sporadic cases, and a disease allele frequency of 0.001. The computer program MENDEL[17] was used to carry out these calculations.

RESULTS

CLINICAL DATA

Table I contains a summary of some of the clinical data on members of this pedigree. The hereditary pattern through 6 known generations (4 generations currently living) is autosomal dominant (Fig 1). The mean age at diagnosis is 19 years (range, 9 through 43). The mean for the maximum observed IOP in affected individuals is 42.6 mm Hg (range, 23 through 59). The youngest age at diagnosis is 9 years; we cannot identify the age at onset, because these 3 already had elevated IOP at the time of this first examination. None of the 3 had symptoms, nor had there been prominent glaucomatous damage detected at the examination. The next youngest known age at diagnosis in this family is 16 years. Three were 19, one 20, another 21, and another 25 at diagnosis. The senior living member of the family, III-2 in Table I and in Fig 1, reported diagnosis of his disease at age 43. He was able to drive a truck until age 68, but he recalls that his vision in 1 eye was already very poor at the time of diagnosis and that he had been seeing spectral halos prior to his initial examination.

Interestingly, this family demonstrates variability in the apparent interval between the time symptoms first appear and the time required before permanent visual loss occurs if not treated. For instance, individ-

TABLE I: CLINICAL FEATURES OF 17 AT-RISK SUBJECTS EXAMINED

ID#	AFFECTED ?	AGE AT DIAGNOSIS (AFFECTED)	CURRENT AGE	HIGHEST IOP	LAST RECORD OF VISION	REFRACTIVE ERROR	COMMENTS
III-2	Yes	43	83	Unknown	NLP OU	-------	Drove truck until age 68
IV-2	Yes	20	60	"Very high"	NLP OU	-------	Symptoms at age 18; NLP OS by age 20
IV-4	No		58	17	20/30 20/20	RE+3.00 LE +3.00	
IV-6	Yes	19	58	Unknown	20/20 OU	RE +1.00 LE +2.25	Symptoms at age 16; filtering surgery at age 24
IV-8	No		51	15	20/30 20/20	RE +1.00 LE + 1.00	
IV-10	No		48	19	20/30 20/20	RE + 0.25 LE +0.25	
IV-11	Yes	21	47	53	20/25 NLP	RE +0.25 --------	Filtering surgery OU; IOP OD 24 on our exam
IV-13	Yes	19	44	"Very high"	20/20 20/20	RE +0.87 LE -3.25	Filtering surgery at age 19
V-1	Yes	25	42	"Very high"	20/20 20/20	RE -0.50 LE -0.25	Filtering surgery at age 27
V-5	Uncertain		32	21	20/30 20/25	RE +0.87 LE +0.75	Suspect at age 4; treated with meds ages 4-32; IOP now 15 with no treatment
V-11	Yes	9	28	38	20/25 20/25	RE -0.62 LE -0.12	Filtering surgery at age 9

TABLE I: (CONTINUED)

ID#	AFFECTED ?	AGE AT DIAGNOSIS (AFFECTED)	CURRENT AGE	HIGHEST IOP	LAST RECORD OF VISION	REFRACTIVE ERROR	COMMENTS
V-12	Yes	9	27	34	20/20	RE -1.00	Filtering surgery at age 9
					20/20	LE -0.50	
V-17	No		26	10	20/20	RE -0.25	
					20/20	LE -0.50	
V-19	Yes	16	23	59	20/50	RE -3.00	Highest IOP was found during our exam;
					20/20	LE -3.25	previous highest IOP was 29
V-20	Yes	19	19	49	20/40	RE -3.50	Highest IOP was found during our exam
					20/15	LE -2.25	
VI-1	Uncertain		11	20	20/20	RE -0.87	
					20/20	LE -.50	C/D 0.3; 0.1
VI-2	Yes	9	9	23	20/20	RE -0.62	C/D 0.5; 0.7
					20/20	LE -0.50	

ual IV-6 recalled symptoms of headaches, nausea, and blurred vision in the mornings beginning at age 16. Yet she was not examined until age 19, at which time the diagnosis of glaucoma was made. She was treated medically for 5 years and did not undergo filtration surgery until age 24. While she has glaucomatous optic nerve damage bilaterally, the cup-disc ratio is 0.8 x 0.85 in the right eye and 0.5 x 0.6 in the left. Vision is 20/20 in either eye. On the other hand, this subject's older sister, IV-2, noted "cloudy vision" in her right eye at age 18. When she first saw an ophthalmologist at age 20, she was told that she had lost all vision in her left eye and that the right eye needed immediate surgery. This subject now has no light perception in either eye. The right cornea is totally opaque; the left optic disc reveals complete glaucomatous cupping.

The proband, IV-13, went for an examination at age 19 as a result of the diagnosis of her older sisters. She was found to have "very high" IOP and underwent bilateral filtration surgery. She now has 20/20 vision in either eye with blebs that have functioned well for 25 years. Her cup-disc ratio is 0.1 on the right and 0.2 on the left.

The family members examined included 11 affected individuals: 4 who were unaffected, 2 for whom characterization was uncertain, two who were seen by us but not included in this study because they were too young to allow for an adequate examination, and 3 spouses of affected individuals, all of whom had normal ophthalmic examinations. Not only were we able to thoroughly evaluate the phenotypic characteristics of the glaucoma in this family, but we were able to make an early diagnosis of glaucoma in a 9-year-old girl.

In addition, we found significant problems in 3 family members (2 brothers and their mother) for whom medical attention was urgently required. The brothers, V-19 and V-20, had IOPs of 59 mm Hg and 49 mm Hg, in their right and left eye, respectively. They were advised to have filtration surgery on an urgent basis. Their mother, IV-11, had an IOP of 24 mm Hg in her only seeing eye while receiving medical therapy. She was advised to obtain urgent follow-up and probably needs repeated filtration surgery.

As noted in Table I, there is no pattern to the refractive errors in affected versus unaffected subjects. The range of spherical equivalent is from +2.25 to -3.50 among those affected and from +3.00 to -0.50 in those unaffected. While several affected individuals had abundant iris processes to the trabeculum, some had none. A few of the unaffected family members had significant numbers of iris processes. Interestingly, individual IV-6 had grade 4 iris processes, while her 2 affected children, V-11 and V-12 had rare and no iris processes, respectively. Thus, it appears that

there is no characteristic angle appearance in this family that is tied to the disease. One of the most consistent characteristics in the family is the poor response to medical therapy and/or to laser trabeculoplasty.

GENETIC TESTING

Significant evidence of linkage was found between the disease phenotype in family UM:GL57 and markers D1S433, D1S431, and D1S212. Data shown in Table II indicate a maximum lod score of 3.75 at a recombination fraction of 0.00 for marker D1S431 with nearest flanking recombinants between disease and markers D1S305 ($\hat{Z}$=0.2 at $\hat{\theta}$=0.26) and D1S306 ($\hat{Z}$= 1.42 at $\hat{\theta}$=0.13). Haplotype analysis also identifies D1S305 and D1S306 as the flanking markers (Fig 2).

DISCUSSION

Linkage analysis suggests that the glaucoma in family UM:GL57 is the result of a gene located between markers D1S305 and D1S306 in the vicinity of markers D1S433, D1S431, and D1S212, which have previously been shown to be linked to the GLC1A glaucoma gene.[1-10] Our large

TABLE II: LOD SCORE TABLE FOR FAMILY UM:GL 57

	RECOMBINATION FRACTION							
LOCUS	.01	.05	.10	.20	.30	.40	$\hat{r}$	$\hat{z}$
D1S252	-0.30	0.89	1.22	1.23	0.92	0.43	0.15	1.28
D1S305	-0.85	-0.20	0.03	0.18	0.19	0.13	0.26	0.20
D1S196	1.95	1.81	1.63	1.24	0.80	0.32	0.00	1.98
D1S431	3.69	3.44	3.13	2.43	1.65	0.78	0.00	3.75
D1S433	3.39	3.17	2.87	2.23	1.51	0.71	0.00	3.45
D1S452	1.74	1.63	1.49	1.19	0.85	0.46	0.00	1.76
D1S218	0.59	0.56	0.51	0.41	0.29	0.16	0.00	0.60
D1S212	3.34	3.10	2.80	2.15	1.42	0.65	0.00	3.40
D1S191	1.78	1.67	1.53	1.22	0.87	0.47	0.00	1.81
D1S306	0.54	1.22	1.40	1.33	1.00	0.55	0.13	1.42

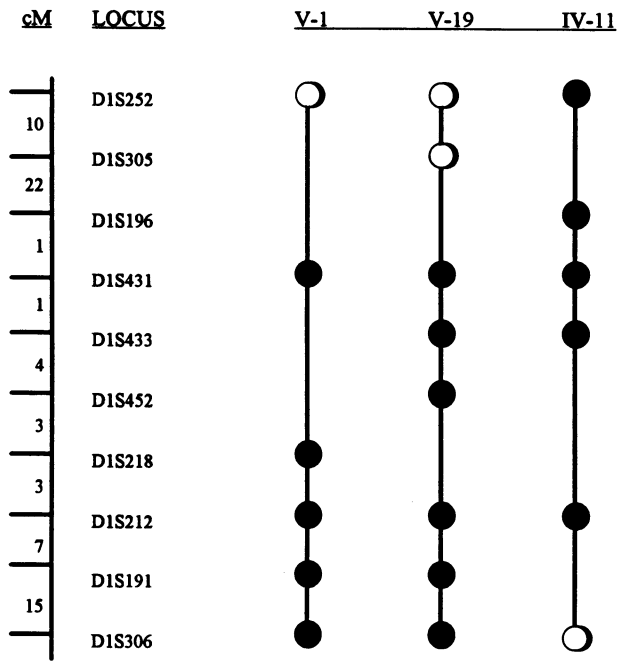

FIGURE 2

Haplotype analysis of 3 recombinant affected individuals shows presence of alleles derived from the disease-gene carrying chromosome of the affected parent (•) or alleles from the chromosome not carrying the disease gene in the affected parent (o). All positions not marked with a circle were uninformative. Column labelled cM indicates spacing between markers. Numbering of individuals is based on their positions in Fig 1.

genetic inclusion interval (56 cM on the Genethon map) contains the GLC1A genetic inclusion interval, reported to be 23 cM for family MOL87G, in which linkage was first observed by Sheffield and colleagues,[1] and 8cM for our family UM:JG3.[10] Haplotype analysis indicates that the actual recombination events in this family could potentially define a much smaller interval than D1S305-D1S306, but uninformative markers in the key recombinant individuals prevent precise localization of the recombination events using the data presented here. Since our data suggest that the recombination events are not located internal to D1S431-D1S212, experiments aimed at further localization of these recombination events were not carried out.

The large size of the genetic inclusion interval leaves open the highly unlikely possibility that the UM:GL57 glaucoma gene could be a different

glaucoma gene located near GLC1A. The need for caution in interpreting our results is exemplified by studies of the RP2 and RP3 genes on the X chromosome, where evaluations of many families were required to demonstrate the presence of 2 separate loci.[18,19] However, localization of the GLC1A gene has been quite consistent among all of the families reported so far for which small inclusion intervals have been identified. Therefore, by far the most likely interpretation of these data is that the glaucoma gene in family UM:GL57 is GLC1A.

To our knowledge, this is the first report of GLC1A glaucoma appearing in a Panamanian family. On the basis of the increasing number of families reported by a few centers, it is evident that this form of POAG is more common than once believed as the number of families reported to have the disorder increases rapidly. Reported families with GLC1A glaucoma include those of English, French, Irish, German, Danish, and now Panamanian ancestry, indicating that this form of glaucoma is likely distributed widely. It remains to be seen what role this gene may play in families of other origins. The GLC1A-region markers from chromosome 1q do not show linkage to POAG in reports of juvenile glaucoma families of African American[8] and Swedish ancestry[6] or in a family with glaucoma of middle-age onset.[20] Thus, it appears that the GLC1A gene may not be the only gene that can cause POAG.

Response to medical therapy and/or to laser trabeculoplasty is poor in our family, as it is in most families with GLC1A glaucoma reported to date. Variability in phenotype within and among families, along with the finding that adult-onset POAG cases can carry the defective GLC1A gene, makes it imperative that ophthalmologists be aware of the existence of GLC1A glaucoma and the need for early filtration surgery in those with the classic phenotype. If the patient presents with early-onset, open angles, unusually high pressures, lack of iris hypoplasia, and a history of autosomal dominant inheritance, the ophthalmologist should consider the possibility of GLC1A glaucoma before initiating treatment. Treatment decisions could be assisted by genetic marker testing on the family and/or information on the history of response to medical and surgical therapies among affected relatives of the patient. As more is learned about the genetic basis of glaucoma, information on phenotype and genotype will play an increasingly important part in the diagnosis and treatment of our patients with glaucoma.

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DISCUSSION

DR DOUGLAS E. GAASTERLAND. There is more than 1 type of juvenile glaucoma. The types are similar in having early age of onset in some affected individuals, with the age range extending to the 40s in others. Those with the disease have elevated intraocular pressure. Some, but not all, have an anomalous anterior chamber angle with a large number of iris processes. Elevated intraocular pressure appears to be a prerequisite for glaucomatous optic neuropathy in affected individuals. The paper of Lichter and coauthors shows that some obligate carrier members of affected families may not have elevated intraocular pressure; when this occurs, the patient does not develop the neuropathy. Therapeutic reduction of intraocular pressure preserves visual function; yet in some forms of juvenile glaucoma, as in the present family, which is shown to have hereditary juvenile glaucoma linked to the GLC1A gene, surgical glaucoma intervention is required because medical treatment and laser trabeculoplasty are not effective.

Three of the 52 Edward Jackson Memorial Lectures have dealt with heredity aspects of glaucoma.[1-3] In familial juvenile glaucoma, the usual inheritance is autosomal dominant.[3] The gene causing many of the familial cases, located on the long (q) arm of the first chromosome, has been linked to a locus on chromosome lq designated GLC1A . Testing the array of members of the Panamanian family in the present report has revealed a genetic pattern linked to this gene. This is the first report of this gene in a Panamanian family. As the authors point out, other families with this genetic defect have been reported, and many of European origin.

There are other genes associated with primary open-angle glaucoma and with juvenile glaucoma. In some families, inheritance appears to be polygenetic, multifactorial,[1] or both.[3]

The biochemical knowledge and vocabulary required for understanding hereditary glaucoma are daunting.[4] This is particularly pertinent to the terms used by those doing genetic molecular biochemical testing. The terms describe the complex of steps that allow localization of genes.

Human cells have 23 pairs of chromosomes.[5] On these chromosomes are somewhere between 50,000 and 100,000 structural genes, responsible for guiding production of structural proteins. On each chromosome there is space between genes (noncoding DNA) filled with a polyglot of the 4 base molecules. Undoubtedly, these molecules have a purpose, though it is not immediately apparent.

There are 2 approaches to localizing a gene. The first is to identify a defective structural protein in an affected individual, work backward

through the sequence of amino acids in the protein to identify the required sequence of bases in the gene, and then search for a match of the sequence with the structural chain of bases in the 23 chromosomes. The other approach, positional cloning,[5] is identifying affected members of families and searching for whether there are matches in the uptake of radioactive markers added to their DNA to labeling of known genes. This linkage is accomplished by breaking the patient's nuclear chromosomal DNA into fragments, amplifying the fragments, incubating the fragments with markers, then searching chromatographically until a match is found between the staining pattern in the patient's DNA labeling and the known gene markers. The markers are specific for chromosome and locations on chromosomes. This process has been used in the present study to show that the family UM:GL57 belongs to the group of families with juvenile glaucoma linked to the GLC1A gene.

To date, only families of European descent have been found to have juvenile glaucoma related to the GLC1A gene. We know this is not the only gene involved in glaucoma, since other families have hereditary glaucoma and no linkage to this gene. The report expands our knowledge by demonstrating this form of glaucoma in a family of Panamanian origin. Patients in this family exhibit no response to medical treatment for glaucoma or to trabeculoplasty. Filtering surgery is the only intervention found to control the elevated IOP. Reducing elevated IOP has preserved visual function in some members of this family. The study of the family is informative in demonstrating no relation of the glaucoma to refractive error or to anterior chamber angle appearance. Some affected individuals have abundant iris processes, while others do not. Among family members not having glaucoma, some have abundant iris processes and others do not. The authors emphasize that when we discover patients in clinical practice with high intraocular pressure (IOP) and young onset of inherited glaucoma, they may not respond to medications or trabeculoplasty; they may have glaucoma related to the GLC1A gene. Such patients require filtering surgery.

Since these patients have an open anterior chamber angle and some functioning outflow capability, it is tempting to consider whether they would benefit from early laser ciliary ablation.

The reported clinical study of affected members of family UM:GL57 indicates a defective outflow pathway, involving at least the conventional (trabecular) pathway and possibly the unconventional (uveoscleral) pathway. Lack of response to medications indicates that the structures involved in aqueous humor formation in affected patients are altered by the genetic defect. Perhaps this pair of observations indicates a genetic defect

impacting anterior segment microvasculature. Optic nervehead damage in affected individuals is caused by IOP elevation, and surgical IOP reduction is therapeutic. Therefore, I speculate that expression of the GLC1A gene does not alter structural proteins in the optic nervehead.

Dr Lichter and coauthors have studied a Panamanian family with hereditary juvenile glaucoma. They have found the genetic defect in this family with juvenile-onset glaucoma to be linked to the GLC1A locus on chromosome lq. A similar linkage exists in other European families with juvenile glaucoma. The authors emphasize the clinical difficulties faced by patients with this type of glaucoma. The study of this family increases our understanding of the heritability of glaucoma. It is a step on our pathway to identifying one of the structural defects that cause glaucoma. This suggests that we may someday find a specific (probably biochemical or genetic) treatment for this glaucoma. Such would resemble the curative treatment of angle-closure glaucoma with iridotomy. In both of these glaucomas the optic neuropathy is caused by elevated IOP; therapeutic reduction of IOP inhibits or stops progression of the nerve damage.

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ROBERT RITCH, M.D. We have a paper coming out in the Archives which will have been published by the time this discussion is published. We looked at unrelated patients with juvenile "primary" open-angle glaucoma and found a significantly reduced trabecular meshwork height compared to controls. Do you think that we could find a way to confirm this with ultrasound biomicroscopy on one of your families and also if we might be able to use this test as a predictive test on the younger children in the pedigree? Also, can you think of a candidate gene in this region which would code for a structural protein or a gene active in development which might affect the size of the trabecular meshwork?

BRIAN YOUNGE, M.D. Dr. Lichter, I just wanted to say I think that is a marvelous set of findings for this disease. One of the questions relates to a patient that Richard Brubaker and I had followed for a number of years.

It was a familial case. Brother and sister both had juvenile onset glaucoma. Probably 18 to 20 years in the onset. When the younger sister was diagnosed her pressures were in the high thirties or low forties and there was the beginning of cupping; we saw reversible visual field defects on the automated perimeter. I think that is a little uncommon and we still have not published this case because we are going to follow her a little bit longer. I wondered whether you had seen that reversible type of field defect in these fairly young onset people with very high pressures.

Thank you.

ROBERT DREWS, M.D. I thought Dr. Ritch was going to ask the question, but since trabeculectomy is needed in these cases, don't we have biopsy material to look at histopathologically or with electron microscopy?

PAUL LICHTER, MD. Thank you all for your nice questions and particularly thanks to Dr. Gaasterland for his discussion. I should also tell you that he is a very cordial discussant having sent me his comments and questions and printouts of his slides in advance and I thank him for that.

Let me start with Dr. Gaasterland's questions. He asked if ciliary ablation would possibly be of help. I suppose it might. Drug treatment in these patients is generally ineffective, but aqueous suppressants lower the pressure somewhat. It is just not nearly enough to solve their problem medically. Ciliary ablation is not a favorite treatment of mine early on. So I would not have experience with that in patients like this, but I suppose there might be a chance that it would help for those of you who might be inclined to do that. Since filtering surgery has been so successful in these patients that seems to me to be the way to go.

A second question was the issue of a patient just turning up in your office. The example was a 33-year-old patient with no family history yet a phenotype that matches this disease. Let's say that you do not know the family history. It is possible, of course, that there was a family history of glaucoma that we did not know about. Dr. Gaasterland also brought up the fact that genes can change. There can be spontaneous mutations in genes such that later on this patient's offspring could be at risk for the disease and until we clone the gene we will not be able to know that. Once we have the gene, of course, then we can look for mutations in individuals. Right now that is not at all possible, but it soon will be. We will be able to look at the DNA of a glaucoma patient to see if they carry the gene. As it is, we can evaluate children from families who we know carry the GLC1A gene defect to see if these children carry the affected haplotype. That is particularly valuable. Remember I showed you a nine-year-old girl who

had just slightly elevated pressures, and asymmetric discs, but I felt that she had early glaucoma. In fact that was confirmed. So we could go to the lab and find out if we are right or wrong about that diagnosis in that family.

Dr. Ritch asked a question about his study on ultrasound biomicroscopy in patients with juvenile onset glaucoma showing a reduced height to the trabeculum. We have not used such a study in these patients. Dr. Ritch is an expert in ultrasound biomicroscopy and hopefully will expand on his studies. Dr. Ritch asked whether a gene could be postulated as a candidate gene, perhaps a gene that codes for a structural protein. I cannot, off hand, think of a particular one, but there have been a number of candidate genes already looked at and nothing has been found as to the gene that is causing this disease.

Dr. Younge talked about a brother and sister followed by Dr. Brubaker for years who had elevated pressures. These young adults had disc damage and field loss, and their field loss reversed. We have seen that as have others. That is a known event. It can occur in glaucoma. It seems that whatever stresses the nerve fibers can result in a field defect and then when the stress has let up the process may not yet be irreversible. So while uncommon, that can happen.

And lastly, Dr. Drews asked if all these patients are getting filtering surgery why don't you have these specimens and I am assuming he is then leading to a question about using the specimens to find the gene. That is not so easy because one needs an enormous amount of trabecular meshwork specimens to be able to actually get CDNA libraries to look for candidate genes from that library. So unfortunately right now that is not the best approach in these families. It would be possible to build up a CDNA library of anterior segment tissue and see what the genes are that are expressed in those tissues. That is something that is on our list of things to do. Hopefully we will get to it. The whole process as you can realize is a complex one, time consuming, money consuming, people consuming. There is much to be done. But over the years with the work that we as well as others are doing in glaucoma genetics I really do think we will find these answers .

So, again, I want to thank the discussants and thank the Society for allowing me to present this paper.