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Genetic homogeneity for inherited congenital microcoria loci in an Asian Indian pedigree

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Purpose: Congenital microcoria is a rare autosomal dominant developmental disorder of the iris associated with myopia and juvenile open angle glaucoma. Linkage to the chromosomal locus 13q31-q32 has previously been reported in a large French family. In the current study, a three generation Asian Indian family with 15 congenital microcoria (pupils with a diameter <2 mm) affected members was studied for linkage to candidate microsatellite markers at the 13q31-q32 locus.
Methods: Twenty-four members of the family were clinically examined and genomic DNA was extracted. Microsatellite markers at 13q31-q32 were PCR amplified and run on an ABI Prism 310 genetic analyzer and genotyped with the GeneScan analysis. Two point and multipoint linkage analyses were performed using the MLINK and SUPERLINK programs.
Results: Peak two point LOD scores of 3.5, 4.7, and 5.3 were found co-incident with consecutive markers D13S154, DCT, and D13S1280. Multipoint analysis revealed a 4 cM region encompassing D13S1300 to D13S1280 where the LOD remains just over 6.0 Thus we confirm localization of the congenital microcoria locus to chromosomal locus 13q31-q32. In addition, eight individuals who had both microcoria and glaucoma were screened for glaucoma genes: myocilin (*MYOC*), optineurin (*OPTN*) and *CYP1B1*. Using direct sequencing a point mutation (144 G>A) resulting in a Q48H substitution in exon 1 of the *MYOC* gene was observed in five of the eight glaucoma patients, but not in unaffected family members and 100 unrelated controls.
Conclusions: We have confirmed the localization of the congenital microcoria locus (MCOR) to 13q31-q32 in a large Asian Indian family and conclude that current information suggests this is a single locus disorder and genetically homogeneous. When combined with the initial linkage paper our haplotype and linkage data map the MCOR locus to a 6-7 cM region between D13S265 and D13S1280. The DCT locus, a member of the tyrosinase family involved in pigmentation, maps within this region. Data presented here supports the hypothesis that congenital microcoria is a potential risk factor for glaucoma, although this observation is complicated by the partial segregation of MYOC Q48H (1q24.3-q25.2), a mutation known to be associated with glaucoma in India. Fine mapping and candidate gene analysis continues with the hope that characterizing the micocoria gene will lead to a better understanding of microcoria and glaucoma causation. The relationship between microcoria, glaucoma, and the MYOC Q48H mutation in this family is discussed.

Inherited congenital microcoria (ICM) is a rare anomaly, due to the underdevelopment of the dilator pupillae muscle of the iris. The condition is otherwise called congenital miosis (MCOR; OMIM 156600) and has been phenotypically defined as observing pupils of less than 2 mm diameter when the subject is looking at a distant object. MCOR is associated with juvenile open angle glaucoma and myopia but rarely megalocornea, suggesting a common mechanism in the development of the eye [1,2]. MCOR is a defect of intermediate filaments in the terminal fetal stages of differentiation of the anterior pigmented epithelial cell of the iris. This results in the absence of myofilaments and consequent failure of development of a functional dilator pupil muscle [3]. In MCOR, the iris stroma is hypoplastic and the dilator myoepithelium is deranged, hence lack the contractile processes. There is also a report to suggest that in MCOR there is lack of myofilaments and desmin in the stromal cytoplasmic processes of the anterior pigmented cells of the iris [4]. Even though many ocular conditions coexist with microcoria, a strong correlation with glaucoma and much stronger with myopia has been suggested [1]. A study on a 3 generation autosomal dominant family showed the coexistence of goniodysgenesis and late onset congenital glaucoma in all members affected with micorocoria [5]. MCOR has autosomal dominant inheritance but sporadic cases are also reported. Roulliac et al. [6] showed the linkage for MCOR to chromosome loci 13q31-q32 in a large French family with a fully penetrant autosomal dominant form of the disease. We have studied an Asian Indian family with autosomal dominant congenital microcoria [7] for evidence of genetic linkage to the reported locus (13q31-q32). In addition we have screened the family for mutations in glaucoma related genes, namely *MYOC*, *OPTN*, and *CYP1B1*.

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METHODS

Clinical methods: The index case (S58) was a 17-year-old male with juvenile open angle glaucoma who presented with family history of microcoria and glaucoma. On examination his visual acuity was 6/9 N6 in both eyes with a refractive correction of -18.0 D in the right eye and -17.0 D in the left eye. External examination revealed an alternate exotropia with miotic pupils in both eyes. Slit lamp examination was within normal limits. Intraocular pressure (Goldman Applanation Tonometry) was 33 mm Hg in the right eye and 26 mm Hg in the left eye on Brimonidine eye drops twice daily and Timolol 0.5% eye drops twice daily in both eyes. Gonioscopy showed open angles in both eyes with prominent iris processes. On attempted pupillary dilatation with Tropicamide and Phenyepherine, the pupils did not dilate beyond 3 mm in either eye. Examination of the optic disc with 90 D lens showed a 0.6 cup to disc ratio in the right eye with rim thinning and 0.4 cup to disc ratio in the left eye. Visual fields on the Humphrey Field Analyzer (HFA)-24-2 showed a generalized reduction of sensitivity. Intraocular pressure could not be controlled on maximum tolerated medical therapy and he subsequently underwent glaucoma filtering surgery in both eyes (trabeculectomy) following which the intraocular pressure was under control. This family was described by Saxena et al. [7] in 1993. After taking a detailed pedigree (Figure 1), family members who were willing to undergo ocular examination and genetic analysis were invited for evaluation. Twenty three members of the family participated in the study and underwent a complete ocular examination including visual acuity, external examination, pupillary evaluation, slit lamp examination, intraocular pressure measurement, and dilated papillary examination. Optic disc and fundus examination was performed using the 90 D lens. Visual field examination (HFA-24-2) was performed on persons with glaucoma when possible. Axial length measurements were possible in a subset of individuals with microcoria. The index case (S58) had an axial length of 28.37 and 28.43 in the right and left eyes, respectively. Information about the patients is provided in Table 1. The definitions of myopia (spherical equivalent less than or equal to -1.0 D) and microcoria (miotic pupil 2 mm in size or less not dilating significantly pharmacologically) were taken from the work of Rouillac et al. [6].

Laboratory methods: Blood samples were collected from 24 individuals (13 males, 11 females) and DNA was extracted using the phenol chloroform method [8].

Mutation screening for MYOC, OPTN, *and* CYP1B1*:*

The coding regions and exon-intron boundaries of *MYOC*, *OPTN*, and *CYPB1* were screened for mutations in the glaucoma patients by direct sequencing using an ABI Prism 310 genetic analyzer (Applied biosystems, Foster city,CA) using the primers published elsewhere [9-11].

Genotyping for congenital microcoria markers: PCR based microsatellite marker genotyping was performed using dinucleotide fluorescent markers on chromosome 13 at 10 cM intervals (ABI PRISM linkage mapping set, version 2.5). Additional fluorescently labeled dinucleotide markers within the 13q31-q32 region were used for fine mapping. Each PCR was a total of 5.0 µl containing 0.5 µl of 40 nmol dNTPs, 15 mM $MgCl_2$, and 0.125 M of end labeled primers. The amplified products were subjected to capillary gel electrophoresis in an ABI Prism 310 genetic analyzer (Applied Biosystems, Foster City, CA) with ROX -500 internal size standard. The alleles were genotyped using GeneScan software. Binning of the alleles was then done for the linkage analysis.

Linkage analysis: Two point lod scores were calculated using MLINK/LCP software and multipoint LOD scores were calculated using SUPERLINK (V1.3) [12,13] which offers improved speed and memory usage over other linkage software packages. All two point and some multipoint calculations were successfully compared to FASTLINK outputs (V4.1P; data not shown). Linkage analysis was done assuming an autosomal dominant transmission with complete penetrance and a gene frequency of 0.0001 [6]. That model was used to obtain the original microcoria linkage to 13q31-q32 and the pattern of inheritance in the pedigree presented here is very similar to their large French family (autosomal dominant inheritance, with complete penetrance). Increasing the gene frequency to 0.001 or using 99% penetrance did not significantly change the two point LOD scores. Equal marker allele frequencies were used, although two point calculations revealed that the family was very robust to allele frequency variations (data not shown). Multipoint analysis was performed using sex-averaged, intermarker map distances of 4.83, 2.33, 1.9, 2.0, 0.0, 1.0, 3.0, and 5.3 cM between the markers D13S170, D13S265, D13S1300, D13S281, D13S154, D13S1280, D13S1241, D13S159, and D13S158, respectively. The intermarker genetic map distances and the chromosomal order of all markers were obtained using the Marshfield marker data. Physical distances were obtained from Ensemble genome browser. A complete Multipoint map was obtained by overlaying a series of overlapping six point linkage analyses performed with SUPERLINK. The individual six point analyses provided very similar LOD profiles across the map, for example, the peak LOD score at D13S154 varied from 6.0132 and 6.0192 for the four runs that contained this interval.

RESULTS

When compared to the original pedigree as reported by Saxena et al. [7] we could only recruit 24 members for our study, of whom 15 had microcoria. Some family members, particularly the siblings in generation I (4 female and 1 male) of the proband refused to participate in the study. There was a strong correlation of microcoria with myopia and glaucoma in this family. Seven individuals were diagnosed with all 3 conditions; 3 had microcoria alone (Z19, Z37, and Z38) and 5 had microcoria with either myopia (Z22, Z28, Z31, and Z36) or glaucoma (Z30, Figure 1). All glaucoma affected members were screened for mutation in glaucoma genes (*MYOC*, *OPTN*, and *CYP1B1*). Screening of *MYOC* showed a G to A mutation in exon 1 resulting in the substitution of histidine for glutamine (Q48H) at codon 48 in five individuals (Z21, Z30, Z33, Z35, and S58; Figure 1) in the family affected with glaucoma. The other two members (individuals Z19 and Z31) who were positive for the Q48H mutation showed normal visual fields and optic disc

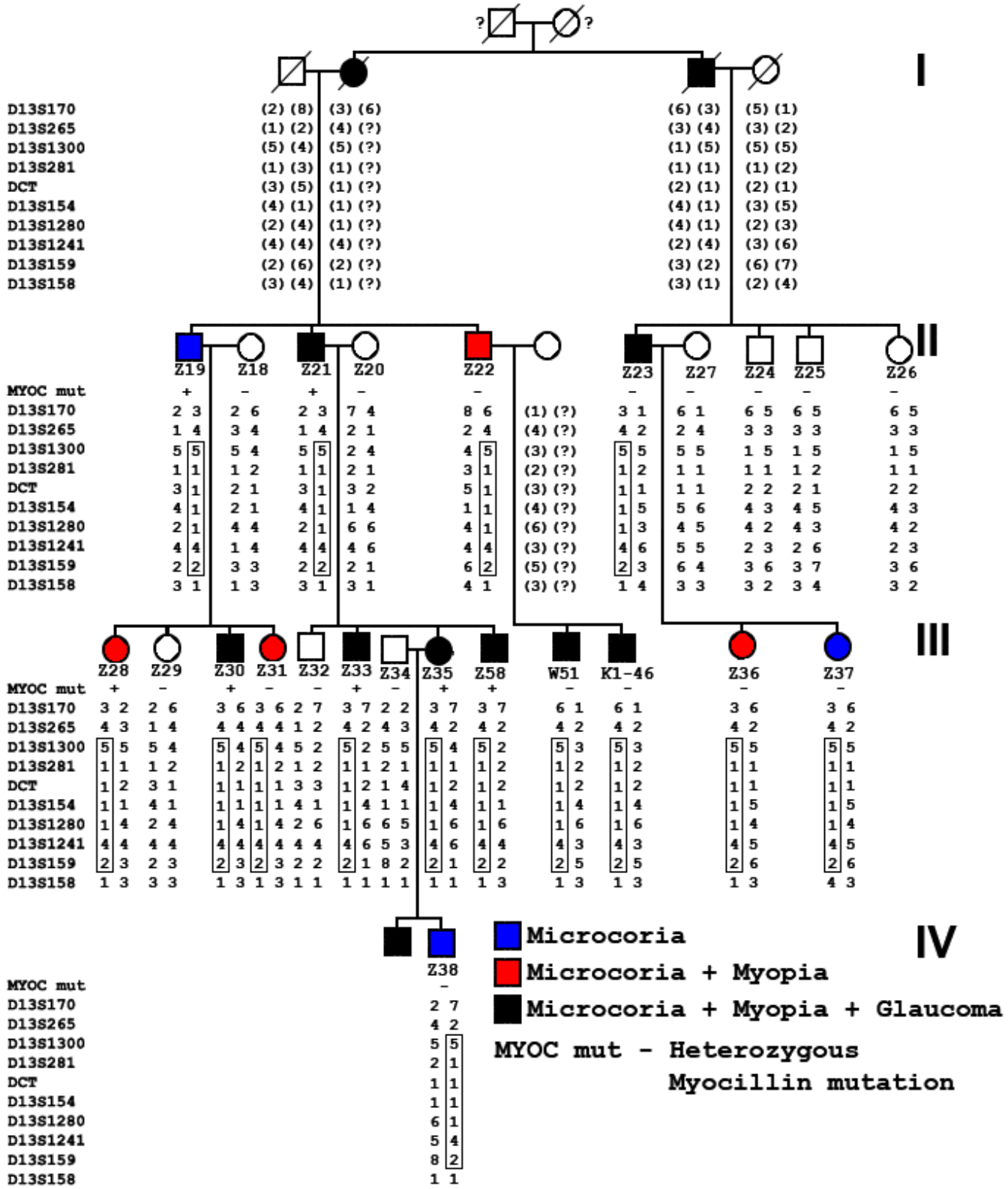

Figure 1. MCOR pedigree with haplotypes. A four generation congenital microcoria pedigree that shows the haplotype analyses for the markers D13S170-D13s159 in the 13q31-32 region and the distribution of microcoria, glaucoma, and myopia phenotypes in the family members. The question marks in the pedigree indicate an unknown phenotype. Numbers within parentheses indicate reconstructed haplotypes. The haplotype segregating with microcoria is shown as a vertical box in the pedigree.

Table 1. Clincial features of all the affected individuals of the MCOR pedigree

ID number	Age, sex	Refractive error	IOP (mm Hg; OD, OS)	Cup/disc ratio (OD, OS)	Humphrey visual fields	Comments
Z19	45, M	Emmetrope	19,21	0.3, 0.3	Normal	Axial length: 22.46 mm (OD), 22.76 mm (OS)
Z21	55, M	Myopia	12	GOA	NA	Bilaterally blind (light perception vision), corneal decompensation (OS), historically had myopic corrections
Z22	65, M	Myopia (-2.0 D)	18,16	NP	NA	
Z23	40, M	Myopia	NP	NP	NA	Bilaterally blind (perception of light vision), after trabeculectomy both eyes. Historically had myopic corrections
Z28	23, F	Myopia (-1.0 D)	18,16	0.2, 0.3	NA	
Z30	12, M	Myopia (-3.0 D, -3.5 D)	29,43	0.3, GOA	NA	Axial length: 23.57 mm (OD), 25.62 mm (OS)
Z31	16, F	Myopia (-2.0 D)	14,14	0.4 (OU)	NA	
Z33	24, M	Myopia (-22.0 D)	13,14	GOA, 0.4	Biarcuate defect (OS)	Post trabeculectomy (OU)
Z35	25, F	Myopia (-8.0 D)	18,18*	0.2 (OU)	Normal	Baseline IOP: 35 mm Hg
Z36	15, F	Myopia (-1.0 D)	13,15	0.2, 0.3	NA	
Z37	16, F	Emmetropia	18,18	0.3 (OU)	NA	
Z38	5, F	Emmetropia	NA	NA	NA	
S58	17, M	Myopia (-17.0 D, -18.0 D)	33,26*	0.6, 0.4	Generalized reduction of sensitivity	Index Case
W51	33, M	Myopia (-12.5 D)	32,19*	0.8, 0.6	Nasal step (OD), generalized reduction of sensitivity (OS)	
K1-46	35, M	Myopia (-3.28 D)	25,17*	0.6, 0.2	Superior arcuate (OD), nasal defects (OS)	Axial length: 22.95 mm (OD), 22.96 mm (OS)

All individuals listed displayed microcoria. The table details clinical data for the pedigree individuals relevant to the diagnosis of myopia (refractive error and axial length, where available) and glaucoma (intraocular pressure [IOP], cup/disc ratio, and visual field status). It was not possible (NP) to assess the IOP and/or the cup to disc ratio in some eyes. Some data were not available (NA) in all patients. A cup to disc ratio was not estimated in eyes with glaucomatous optic atrophy (GOA). Patients using ocular hypotensive agents are indicated with an asterisk.

except for an increase in IOP in individual Z19 (Figure 1) which was observed at the age of 50 years. Individuals Z23, W51, and K1-46 affected with glaucoma did not show the Q48H mutation. Screening of the *OPTN* gene did not show any potential disease causing mutations, only a silent (G>A) heterozygous variant (T34T) in exon 4. Screening of the *CYP1B1* gene in these individuals did not show a mutation but demonstrated Leu432 and Ser453 polymorphic variants in exon 3.

Linkage to chromosomal locus 13q31-q32 (multipoint analysis): An initial chromosome 13 screen was conducted using a 10 cM ABI map for mapping the congenital microcoria locus. This resulted in a peak LOD score of 2.62 (at q=0.05) co-incident with marker D13S265. As expected this peak was within the region previous believed to contain the microcoria locus [6]. Fine mapping was then performed using ten markers spanning the same region of interest mapped to 13q31-q32. The peak two point LOD score of 5.32 was obtained co-incident with D13S1280, while markers D13S154 and D13S159 also gave LOD scores over 3. Interestingly a maximum LOD score of 4.68 (Table 2) was obtained for a compound dinucleotide repeat at the dopachrome tautomerase (DCT) locus [14] (GenBank L33829). The disease associated haplotype block "centromeric 5-1-1-1-1-4-2 telomeric" (D13S1300 to D13S159) was seen in all the individuals with MCOR (Figure 1). Affected individual Z38 has received the disease haplotype via a recombination event between markers D13S265 and D13S1300. There is a recombination event in individual Z37 for the marker D13S158 (Figure 1). Inferred haplotypes suggest that individual Z25 has received a normal haplotype via a recombination event between markers D13S265 and D13S1300. Individual Z28 has received a normal haplotype (from unaffected mother) via a recombination between markers DCT and D13S154. The multipoint map (Figure 2) is consistent with all these findings. Using the absolute penetrance model, infinity scores co-incident with D13S170, D13S265, and D13S158 represent the recombination events mentioned above. The peak multipoint LOD score is co-incident with D13S154 (6.02), although the whole region from D13S1300 to D13S1280 is over LOD 6. We also

Table 2. Two point lod scores for the markers D13S170-D13S159 in 13q31-q32

	LOD scores (by θ)										Peak	
Marker	0	0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.45	θ	LOD
D13S170	-∞	2.68	2.82	2.70	2.44	2.11	1.72	1.28	0.82	0.36	0.093	2.83
D13S265	-∞	2.62	2.53	2.30	2.01	1.67	1.30	0.91	0.52	0.18	0.056	2.62
D13S1300	1.96	1.73	1.49	1.25	1.02	0.79	0.57	0.38	0.22	0.09	0	1.96
D13S281	1.12	0.99	0.85	0.72	0.59	0.47	0.35	0.24	0.15	0.07	0	1.12
DCT	4.68	4.28	3.85	3.41	2.95	2.46	1.96	1.44	0.92	0.42	0	4.68
D13S154	3.52	3.13	2.73	2.32	1.90	1.46	1.03	0.61	0.26	0.05	0	3.52
D13S1280	5.32	4.84	4.34	3.82	3.28	2.71	2.12	1.50	0.89	0.33	0	5.32
D13S1241	2.64	2.38	2.12	1.85	1.57	1.28	0.98	0.68	0.39	0.15	0	2.64
D13S159	3.05	2.74	2.43	2.11	1.77	1.42	1.07	0.71	0.39	0.14	0	3.05
D13S158	-∞	0.76	1.03	1.05	0.96	0.80	0.60	0.38	0.18	0.05	0.129	1.06

Two point data analyzed with SUPERLINK (also done using MLINK; data not shown) for the markers spanning the chromosome region of 13q31-q32 with their lod scores at different θ values using a gene frequency of 0.0001.

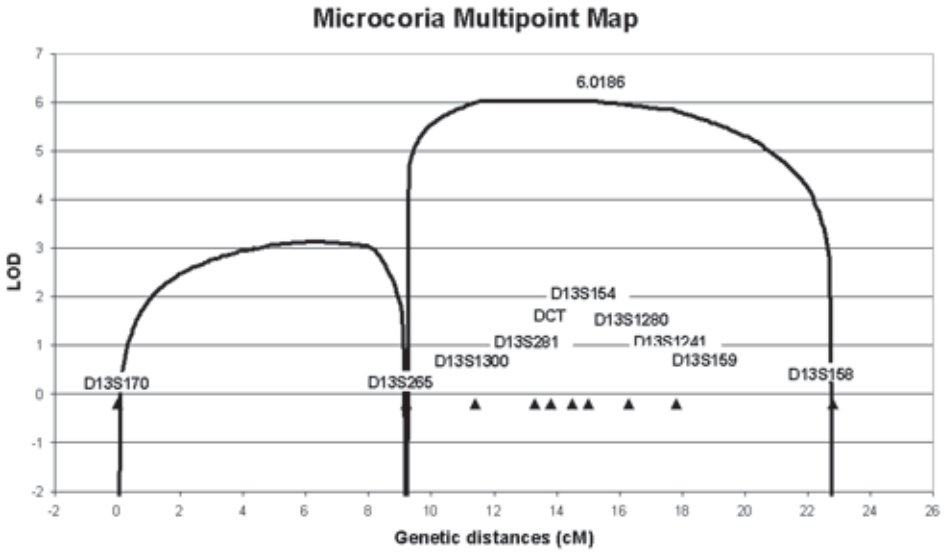

Figure 2. Multipoint map for the markers on chromosomal locus 13q1-q32. Multipoint LOD scores for markers D13S170-D13S158 showing highest lod score of 6.02 for the marker D13s154. The x-axis indicates genetic distance and the y-axis indicates lod score generated by SUPERLINK software.

performed six point model free/nonparametric analysis using the program SIMPLE [15], its parametric algorithm was also run which provided very similar LOD profiles across the map, for example, the peak LOD score at D13S154 varied from 6.0132 and 6.0192 for the four runs that contained this interval. Including an allowance for phenocopies and after performing the linkage analysis using the same model did not significantly alter the peak multipoint scores; with the peak score moving from 6.02 to 5.98 when a pheoncopy rate of 0.83 was applied.

DISCUSSION

A large French family with 31 affected individuals was originally used to map the MCOR gene to locus 13q31-q32, with a peak multipoint LOD score of 13.3 between markers D13S265 and D13S1300 [6]. Here, we have confirmed linkage of the MCOR locus to 13q31-q32. We studied a 21 cM interval in the 13q31-q32 region flanked by markers D13S170 (centromeric) and D13S158 (telomeric). Recombination events with markers and our multipoint data place the MCOR gene 6.4 Mb region between D13S265 and D13S158, with a peak multipoint LOD of 6.02 at D13S154. This is very consistent and confirms linkage with the 8 cM interval flanked by D13S1239 (centromeric) and D13S1280 (telomeric) reported by Rouillac et al. [6] as a region in which recombination event could not be determined.

Bremner et al. [16] studied two British families (one family with 2 available affected members and the other with 3) and suggested genetic heterogeneity in one family, even though they have not typed the key markers between D13S265 and D13S159, within the critical 7 cM region. It is difficult to use details from this paper to add to the MCOR story for a number of reasons. Compared to other known pedigrees, although their families are very small, they report no evidence of associated myopia (70-80% in large 13q linked pedigrees) or glaucoma (30-50%) in large 13q linked pedigrees. Since Bremner et al. [16] have not studied the key markers, those within the D13S265 and D13S154 region, linkage cannot be ruled out. So, while the paper of Bremner et al. [16] suggests that phenotypic heterogeneity may exist within familial microcoria, it does not contribute significantly to the question of whether congenital microcoria is genetically heterogeneous. Combining the results of Roulliac et al. [6] with the data presented here would place the most likely location for the MCOR gene between D13S265 and D13S1280 (4.0 cM). While our peak two point LOD score of 5.32 was obtained for D13S1280, a polymorphic $(AC)_{19}$ repeat [14], at the DCT locus gave a maximum LOD score of 4.68. This is interesting since this gene maps within the most likely interval defined above and has a potential role in disease pathology. TYRP2, the protein product of the dopochrome tautomerase (DCT) gene, is a member of the tyrosinase family expressed in the melanocytes and is involved in pigment formation. The tyrosinase family comprises three members, tyrosinase (Tyr), tyrosinase-related protein 1 (Tyrp1), and dopachrome tautomerase (DCT) [17]. Studies on DCT knock-out mice have shown that the slaty mutation (Dctslt/Dctslt) results in less melanin and severely affects growth of primary melanocytes. However, pathological changes to eye or eye pigmentation were not observed [18].

Mutation screening of the *MYOC* gene was initially performed in glaucoma affected individuals. The *MYOC* gene screening revealed a novel 144G>A nucleotide change resulting in a Q48H substitution in 7 individuals in the pedigree (Figure 1; Z19, Z21, Z28, Z30, Z33, Z35, and S58). The Q48H mutation observed in this family is a rare disease causing variant specific to the Indian population [10,19,20]. The Q48H is also a disease-causing variant in juvenile open angle glaucoma [10] and congenital glaucoma in India [19]. In the pedigree presented here, however, the possibility of this change causing glaucoma could not be confirmed, as 2 of the 7 Q48H carriers did not have glaucoma and one of these two individuals (Z19) showed elevated intraocular pressure.

Other glaucoma candidate genes *OPTN* and *CYP1B1* were screened in Q48H positive and negative glaucoma individuals. These two genes did not reveal any mutations, although a silent mutation (c.412G>A: T34T) in *OPTN* and a polymorphic Leu432 variant in *CYP1B1* were observed. The presence of the Leu432 allele in these individuals is quite interesting as this variant is associated with reduced activity of CYP1B1 enzyme to 4 hydroxylate 17β-estradiol [20]. The T34T mutation in *OPTN* was seen in 23% and the Leu432 allele in *CYP1B1* was found in the heterozygous state in 19% of the unrelated healthy control group (19/100) which shows that these two SNPs are seen in the general population suggesting that the 2 SNPs found in these glaucoma patients are not associated with glaucoma. Even though the pathological role of the Q48H mutation to *MYOC* is established in many reports of Indian glaucoma cases [10,21,22], the role of the mutation in causing glaucoma in the present family is debatable.

The presence of microcoria in all the individuals with glaucoma supports the probability of microcoria being a risk factor for glaucoma in this family as was the case for Toulemont et al. [1]. In addition, segregation of the Q48H mutation is likely to be coincidental to the formation of microcoria, perhaps increasing the number of glaucoma cases seen. Yet, there are other microcoria individuals in this family without glaucoma. The mutation would have easily come from Z19 and Z21's paternal side. It is also important to note that, unlike microcoria, glaucoma is a complex trait, with demonstrated incomplete penetrance, multiple genetic linkages and potential environmental influences. We suggest that further work is required to investigate the potential for microcoria to influence the penetrance of glaucoma. On the other hand there is unresolved debate in the literature about the association of other ocular abnormalities like myopia and glaucoma with congenital microcoria. Toulemont et al. [1] have studied a 83 member family, of which 39 had congenital microcoria and 23 were available for study. Toulemont et al. [1] showed a significant association between microcoria and glaucoma. The authors conclude that the link is not a fortuitous one. Aqueous humor is secreted across the ciliary epithelium by transferring sodium chloride from the stroma to the posterior chamber of

the eye, with water passively following. In microcoria these stromal cells are reported to lack the cytoplasm contractile processes.

Data from Roulliac et al. [6] and the current work indicate that the DCT gene encoding the TYRP2 protein could be the candidate gene for MCOR. Based on substantially more information available today from genomic resources, there are many other potential candidate genes within the interval like Glypican 6 (*GPCC6*) and Muscle-blind like protein (*MBNL*) [23] which could be involved in the pathogenesis of microcoria. In addition, interactions elicited by the congenital microcoria environment in the presence of the mutant protein might contribute to/cause the glaucomatous changes observed in these pedigrees. Identifying the microcoria gene and its functional role will be necessary to substantiate this correlation. Further fine mapping and candidate gene analysis is in progress. Further studies will be important to explore the probable interactions between congenital microcoria and glaucoma.

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