Clinical description and genome wide linkage study of Y-sutural cataract and myopia in a Chinese family

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Purpose: To describe the clinical characteristics of a Y-sutural cataract associated with myopia in a large Chinese family and to identify the causative gene and mutation.

Methods: An autosomal dominant Y-sutural cataract and myopia were identified in members of a large family of Han ethnicity living in southern China. Ophthalmological examinations were performed and a medical history was taken. Blood samples were collected for DNA isolation. A genome wide scan was performed using markers spaced at about 10 cM intervals for genotyping and two point linkage analysis. Candidate genes were sequenced.

Results: Bilateral lens opacities, the only sign of cataract in early childhood and the most prominent sign in all affected individuals, involved the entire anterior Y and posterior inverted Y sutures, showing a feather duster like appearance. The Y-sutural cataract in this family mapped to an 11.4 cM (13.5 Mb) region between D3S3606 and D3S1309 on chromosome 3q22 with a maximum lod score of 5.7 at $\theta=0$ for D3S1292. Sequence analysis of the beaded filament structural protein 2 (*BFSP2*) gene identified a previously described c.697_699delGAA (E233del) mutation which was present in all individuals with Y-sutural cataract but not in unaffected individuals and controls. Myopia, observed in 10 out of 12 cataract patients and significantly higher than that in unaffected offspring and siblings (1 out of 8), was independently mapped to a 61.2 cM (59 Mb) region between D3S3606 and D3S1262 on 3q21.3-q27.2 with maximum lod score of 3.79. **Conclusions:** This Y-sutural cataract is caused by an E233del mutation in *BFSP2* which provides additional evidence supporting mutations in *BFSP2* as a cause for cataract and demonstrates phenotypic variability in cataracts caused by *BFSP2*. The Y-sutural opacity in the lens might be the typical and earliest sign for cataract caused by the *BFSP2* mutation. In addition, these results demonstrate a myopia susceptibility locus in this region, which might also be associated with the

Cataract is the leading cause of blindness in the world [1]. Genetic causes are implicated in half of all congenital and developmental cataracts [2]. To date, at least 35 loci in the human genome have been reported to be associated with various forms of congenital and developmental cataracts [3-38]. Among them, Mutations in 24 genes responsible for such catabeen identified [3,6-8,10,12-14,17racts have 20,24,25,27,28,30-32,34-38]. These genes can be grouped as follows; (1) crystallins, the most abundant proteins in the lens [7,8,18,27,34-36], (2) enzymes necessary for maintaining lens metabolism [12,14,28,38], (3) membrane proteins [6,19,20,32], (4) cytoskeletal proteins [10,11], (5) protein participating in ion transport [31], (6) transcriptional factors [3,17,24,25,30], and (7) genes with as yet undefined functions [13,37].

mutation in BFSP2.

The lens sutures are specific regions where lens fiber cells from opposite directions merge through complex overlapping and interdigitation of the tips of their membranes [39]. During lens development, after formation of the lens vesicle, the posterior lens cells elongate to form the embryonic nucleus. Lens epithelial cells in a germinative zone lying just anterior to the lens equator maintain the ability to undergo mitotic division throughout life. The daughter cells terminally differentiate to form secondary lens fiber cells, which move posteriorly to the lens equator and elongate bidirectionally. The anterior ends of the lens fiber cells progressively insinuate between the lens epithelium and the embryonic nucleus, whereas the posterior ends progressively insinuate between the posterior lens capsule and embryonic nucleus. Elongation continues until the fiber cell ends from opposing directions meet to form the lens sutures. In humans, continuing growth of fetal lens fiber cells form identical but inverted anterior and posterior sutures overlying one another. These are visible as fine anterior Y shaped and posterior inverted Y shaped figures on slit lamp examination [40].

Sutural cataract is defined as an opacity affecting the whole or part of the anterior or posterior suture of one or both eyes. The shape and color may vary from patient to patient. Most sutural cataracts have been reported to be congenital without progression. Sutural cataracts are not uncommon, having been detected in 1% of the population [41]. Y-sutural cataracts have been described as being inherited as both autosomal dominant and X-linked traits [42,43], and an autosomal

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recessive dysmorphic syndrome associated with posterior Y shaped sutural cataracts has been mapped to 14q13-q21 [22]. A linkage and mutational screening study has been carried out looking at candidate loci in a family with autosomal dominant isolated Y-sutural cataracts, but failed to establish linkage to known dominant cataract loci [43]. In addition to isolated sutural cataracts, other types of cataracts in human beings, such as nuclear or cortical cataracts, may have a sutural component [4,10,11,22,23,35,42-50]. Currently, genes with mutations associated with mixed sutural cataracts include β A1- and β B1-crystallins [27,35], cytoskeletal proteins [10,11], transcription factors [24], and Nance-Horan syndrome, a putative nuclear protein with a regulatory function [37]. Mixed cataracts include the cataract-dental syndrome [37,45,47], autosomal

dominant zonular cataracts [27,49], Lamellar and Marner cataract [46], Volkmann cataract [4], pulverulent cataract [35], cerulean cataract [50], and congenital and juvenile onset cataracts [10,11].

Myopia is the most common visual problem in the world. Both environment and genetics have been shown to contribute to myopia [51]. High myopia is usually transmitted as a Mendelian trait but mild and moderate myopia is more likely to be transmitted as a complex multifactorial disease. A number of lines of evidence suggest the importance of genetic factors in the development of myopia, although environmental factors such as near work and a city lifestyle appear to have a great impact on prevalence of myopia. Recent genome wide linkage studies have provided evidence of susceptibility loci



Figure 1. Pedigree and haplotype diagram of the family with Y-sutural cataracts and myopia. Individuals with the upper half of their symbols filled in black have Y-sutural cataracts and those filled in black on the lower half have myopia of -1.0 D or less. Individuals with totally filled symbols have cataract and myopia. Refraction or axial length is unknown for individuals shaded on the lower left quarter only. Black bars show the haplotype of affected individual 25 and parts of that haplotype shared by all affected individuals. Other haplotypes transmitted in the family are encoded with different colors.

for mild, moderate, and high myopia [51-53].

In this study, we report linkage of an autosomal dominant isolated Y-sutural cataract in a large Chinese family to an 11.4 cM region on chromosome 3q22 between D3S3606 and D3S1309 with a maximum lod score of 5.7 at θ =0 for D3S1292. Sequence analysis of the beaded filament structural protein 2 (*BFSP2*) gene, which lies in this interval, identifies a c.697_699delGAA (E233del) mutation in exon 3. Myopia in this family also maps independently to 3q21.3-q27.2, and is associated with cataract in this family. Mutations in *BFSP2* have previously been described in two families, a juvenile onset progressive cataract in a family with an R287W mutation [10] and congenital nuclear, sutural, and stellate or spokelike cortical cataracts in a family with the same E233del mutation [11]. However, isolated Y-sutural cataract such as those seen here have not been identified in the previous reports, and in

neither case was myopia identified in affected individuals.

METHODS

Family and clinical data: An isolated Y-sutural cataract was identified in a Chinese family of Han ethnicity living in southern China. This family contains 15 affected individuals in four generations (Figure 1). Twenty four individuals, including 12 affected and 12 unaffected, participated in this study. Informed consent conforming to the tenets of the Declaration of Helsinki and following the Guidance of Sample Collection of Human Genetic Diseases (National 863-Plan) by the Ministry of Public Health of China was obtained from participating individuals prior to the study. Medical and ophthalmic history, visual acuity, slit lamp, and funduscopic examinations were carried out by ophthalmologists (XG, JY). Myopia was defined as spherical equivalent refraction of -1.00 D or less. Genomic



Figure 2. Photograph of the anterior eye with lens images. A-C: Individual 34 at 4 years of age. Lens opacities were only observed at the anterior Y and posterior inverted Y sutures. C: Photograph taken under retroillumination. D,E: Individual 31 at age 18 with corrected visual acuity of 20/15 in both eyes. Lens opacity was only observed at the anterior Y and posterior inverted Y sutures, which show typical features of the Y-suture cataract. The hazy appearance of the lens in D results from intense scatter lights used to visualize the sutural cataract. F,G: Individual 30 at age 20 demonstrates the Y-suture cataract. The white lens opacity at each branch of the sutures looks like a feather duster. H,I: Individual 23 at 29 years old showing Y-suture opacity combined with punctuate cortical opacities.

DNA was prepared from venous blood as described previously [54].

Genotyping and cataract linkage analyses: Genotyping and a genome wide scan by linkage analyses were carried out as previous described [55]. The cataracts in this family were analyzed as an autosomal dominant trait with full penetrance. The cataract allele frequency was set at 0.0001.

Myopia linkage analysis: Individuals meeting one of the following three criteria were considered to be affected with myopia; (1) Cycloplegic refraction of -1.00 D spherical equivalent or lower in individuals <30 years of age, (2) manifest refraction of -1.00 D spherical equivalent or lower in individuals 30 years or more of age, or (3) axial length >26 mm (this is very stringent as the normal range of axial length in Chinese is 23.5-24.5 mm. An extension of 1 mm would generally result in myopia of -3.00 D). Individual 18, a spouse of individual 19, with visual acuity of 0.8 OD and 0.6 OS at 45 years old, was analyzed as myopic even though her exact re-

fraction data were unknown. This also resulted in power loss rather than type I error in linkage analysis. Individual 34 was set as unknown because of his age, as he may develop myopia later although he had +2.00 D OD and +1.5 D hyperopia at age of 4 years [52]. Linkage analysis of myopia in this family was initially carried out with a penetrance of 0.9 and a phenocopy rate of 0.1 as described [52]. After the initial analysis showed a significant positive lod score, fine mapping was repeated under an additional 80 models in order to identify the range of penetrance and phenocopy values under which a lod score equal to or larger than 3 was preserved. These models used an affected allele frequency of 0.0133 [52] and combinations of 10 penetrances (1, 0.99, 0.95, 0.9, 0.85, 0.8, 0.75, 0.7. 0.65, and 0.584) for the affected allele and eight phenocopy rates (0.0, 0.01, 0.05, 0.10, 0.15, 0.20, and 0.25). Two point linkage analysis was performed using the MLINK program of the LINKAGE program package and maximum lod scores were calculated using ILINK.

	TABLE 1. CLINICAL DATA OF AFFECTED MEMBERS IN THE FAMILY											
Age (age Visual acuity Age at at first Axial length ID Gender surgery) OD OS symptom Cat Refraction OD/OS (mm)												
		y/										
5	F	73 (68)	FC	FC	NA	Y, PC	myopia*	27.5/27.5				
11	М	51	0.07	0.1	7	Y, PC	NA	NA				
		31#	0.5	0.5								
14	Μ	41	0.2	NLP	7	Y, PC	myopia*	30.2/NA				
19	Μ	47 (44)	0.1	0.4	8	Y, PC	-3	27.1/26.6				
20	М	44 (39)	0.6	0.6	13	Y, PC	-3	26.5/26				
23	М	28	0.1	0.2	7	Y, PC	-7	NA				
25	Μ	22	0.2	0.2	7	Y, PC	-10	NA				
27	Μ	14	0.2	0.2	б	Y	-3	NA				
30	F	20 (19)	0.4	0.5	7	Y, PC	-4	26.9/26.7				
31	F	19	1.5	1.5	None	Y	-1.5	NA				
32	F	17	0.3	0.3	8	Y	-5	NA				
34	М	4	0.5	0.5	None	Y	2/1.5	NA				

The visual acuity column(s) indicates the current visual acuity or visual acuity before surgery for those accepted for cataract surgery. Also in this column, FC indicates finger counting and NLP indicates no light perception. In the age at first symptom, "NA" indicates not available and "None" indicates the patient remains asymptomatic. In the Cat (cataract) column, "Y" refers to a Y-sutural cataract and "PC" refers to a punctate cortical cataract. The sharp (hash mark) designates the visual acuity for patient number 11 at age 31 years old. The asterisks identify a classification of myopia based on their obvious extended axial length.

	TABLE 2. TWO POINT LINKAGE RESULTS FOR MARKERS AROUND THE CATARACT LOCUS ON CHROMOSOME 3Q22											
	Pos	ition	Lod score at $\theta=$									
Markers	cM	 Mb	0.00	0.01	0.05	0.10	0.20	0.30	0.40	Zmax	$\theta[est]$	
D3S3606	146.00	128.68	$-\infty$	2.04	2.38	2.22	1.52	0.63	-0.06	2.38	0.05	
D3S1587	148.70	132.28	5.24	5.15	4.77	4.28	3.22	2.06	0.90	5.24	0.00	
D3S1292	148.70	133.11	5.72	5.63	5.25	4.76	3.69	2.48	1.16	5.72	0.00	
D3S3637	152.90	135.79	5.32	5.24	4.89	4.43	3.43	2.30	1.07	5.32	0.00	
D3S3586	156.20	140.48	1.68	1.68	1.66	1.57	1.29	0.94	0.51	1.68	0.01	
D3S1309	157.40	142.21	$-\infty$	1.85 2.30	2.28 1.87	7 1.27	0.56 2.32	0.07				

Three less informative markers (D3S1615, D3S1549, and D3S1576) without recombination between D3S3637 and D3S3586 are omitted from this table, Table 1, and Figure 1. Position data from the Genethon database are listed in cM; position data from the NCBI (build 35.1) database are listed in Mb.

Mutation analysis of BFSP2: Eight pairs of primers (sequence information available on request) were used to amplify the 7 exons and the adjacent intron sequences of the *BFSP2* gene (NCBI human genome build 34.3, NT_005612.14

for gDNA, NM_003571.2 for cDNA). Sequence analysis was carried out as previously described [55].

Restriction endonuclease analysis: Exon 3, in which the 3 bp deletion mutation lies, was amplified using a new pair of

TABLE 3. TWO POINT LOD SCORES FOR MYOPIA												
	Position		Lod score at θ =									
Markers $\theta[est]$	сM	Mb	0.00	0.01	0.05	0.10	0.20	0.30	0.40	Zmax		
D3S3606	146.00	128.68	-0.80	-0.13	0.35	0.41	0.20	-0.05	-0.10	0.42	0.09	
D3S1587	148.70	132.28	2.95	2.91	2.74	2.48	1.86	1.17	0.48	2.95	0.00	
D3S1292	148.70	133.11	3.33	3.30	3.11	2.83	2.17	1.39	0.58	3.33	0.00	
D3S3637	152.90	135.79	3.23	3.19	3.01	2.73	2.08	1.32	0.55	3.23	0.00	
D3S3586	156.20	140.48	1.15	1.14	1.09	1.00	0.80	0.57	0.31	1.15	0.00	
D3S1309	157.40	142.21	2.08	2.06	1.96	1.80	1.37	0.86	0.33	2.08	0.00	
D3S1569	162.00	144.85	0.72	0.75	0.82	0.84	0.73	0.51	0.24	0.84	0.08	
D3S1279	173.00	152.51	1.76	1.76	1.72	1.61	1.27	0.82	0.36	1.76	0.00	
D3S1614	183.10	169.69	1.31	1.29	1.19	1.06	0.80	0.53	0.27	1.31	0.00	
D3S1565	193.00	174.97	0.96	0.94	0.87	0.82	0.72	0.56	0.32	0.96	0.00	
D3S1262	207.20	187.71	-0.20	-0.14	0.08	0.27	0.43	0.41	0.27	0.44	0.24	

Two point linkage results for myopia on chromosome 3q21.3-q27.2 under a model with 90% penetrance and 10% phenocopy rate.



Figure 3. Sequence and RFLP analysis of the c.697_699 mutation. **A**: Forward (left) and reverse (right) sequencing results of normal exon 3 of the BFSP2 gene. **B**: Heterozygous c.697_699delGAA mutation in exon 3. **C**: *Mbo*II digestion of the *BFSP2*-exon 3 PCR products (208 bp/ wt and 205 bp/mutant) from individuals just above each lane. DNA from individuals 1-4, 6, 9, 10, 16, 17, and 36 were not loaded on the gel. The GAA deletion erases one of the three *Mbo*II sites in the amplicon. *Mbo*II cuts the wild type into 87 bp, 65 bp, 30 bp, and 26 bp fragments; it cuts the mutant into 114 bp, 65 bp, and 26 bp fragments; and it cuts the heterozygous wild type and mutant into 114 bp, 87 bp, 65 bp, 30 bp, and 26 bp fragments. The left lane (marked "M") is a 50 bp ladder marker.

primers (E3F: 5'-TCG AAA GGC GGC AGA AGA GGA-3' and E3R: 5'-TTA TGA AGC ACA GGC AGA CAG ATG-3') since the PCR products of affected and unaffected individuals DNA amplified using the sequencing primers were not distinguishable after restriction enzyme digestion. PCR was conducted at 94 °C for 8 min, followed by 5 cycle amplification at 94 °C 30 s, 58 °C 30 s, and 72 °C 30 s; then 35 cycles at 94 °C 30 s, 56 °C 30 s, 72 °C 30 s; finally at 72 °C for 5 min. PCR products (208 bp or 205 bp, 20 μ) were digested with 3 units of *Mbo*II at 37 °C for 2 h and then separated on 2.5% agarose gel electrophoresis.

RESULTS

All 12 affected individuals in this family had bilateral isolated Y shaped sutural cataract present in both the whole anterior Y-suture and the posterior inverted Y-suture (Figure 2). The white lens opacity is linearly superimposed on the branches of the Y- and inverted Y-sutures, giving a feather duster appearance to each branch. In early childhood a mild opacity in the anterior Y and inverted posterior Y-sutures are the only signs of cataract leaving other parts of the lens clear, as shown in a 4 year old boy in Figure 2A-C. At this age, the Y-sutural opacity is obvious under retrotransillumination but was mild under slit lamp examination. Affected children and their parents were unaware of visual problems before 7 years of age. Most patients experience decreased visual acuity around 7 to 8 years of age, although it is unclear whether this results from the Y-sutural cataract or the accompanying myopia (Table 1).

Figure 4. Three dimensional view of lod scores under different penetrance and phenocopy rates. Variation of the lod score with changes in the inheritance model. Phenocopy rates and penetrances yielding significant lod scores (>3) are shown by the projection of the blue shaded region of the surface on the X and Y axes, respectively. Lod scores are shown on the Z axis. The results shown here graphically are taken from data shown in Table 4. The Y-sutural cataract became apparent in most patients during their teenage years (Figure 2F,G). In addition to the typical Y-sutural opacity, a small amount of punctuate cortical opacity was observed in patients around the third decade



TABLE 4. VARIATION OF TWO POINT LOD SCORES FOR MYOPIA AT D3S1292 AND D3S3637 WITH PENETRANCE AND PHENOCOPY RATES

Penet	0	0.01	0.05	0.10	0.15	0.20	0.25	Max with lod>3	
1.00	3.69/3.33	3.71/3.34	3.78/3.38	3.73/3.33	3.53/3.13	3.26/2.86	2.92/2.52	0.23 [3.07/2.67]	
0.99	3.54/3.39	3.60/3.38	3.72/3.39	3.69/3.33	3.49/3.13	3.22/2.85	2.88/2.50	0.23 [3.03/2.66]	
0.95	3.17/3.37	3.30/3.37	3.52/3.38	3.52/3.30	3.34/3.08	3.08/2.80	2.73/2.44	0.21 [3.02/2.03]	
0.90	2.89/3.28	3.04/3.30	3.31/3.33	3.33/3.23	3.17/3.00	2.90/2.71	2.55/2.33	0.18 [3.02/2.84]	
0.85	2.69/3.18	2.85/3.21	3.13/3.25	3.17/3.14	3.00/2.91	2.73/2.60	2.37/2.21	0.15 [3.00/2.91]	
0.80	2.53/3.08	2.68/3.12	2.98/3.17	3.01/3.05	2.84/2.81	2.57/2.49	2.18/2.08	0.11 [2.99/3.10]	
0.75	2.39/2.99	2.54/3.03	2.84/3.09	2.87/2.96	2.69/2.70	2.40/2.34	1.99/1.93	0.08 [2.90/3.03]	
0.70	2.27/2.90	2.42/2.95	2.72/3.01	2.73/2.86	2.54/2.58	2.23/2.22	1.79/1.76	0.05 [2.72/3.01]	
0.65	2.12/2.85	2.30/2.85	2.61/2.93	2.60/2.76	2.39/2.46	2.05/2.07	1.58/1.57	-	
0.584	2.02/2.72	2.17/2.77	2.47/2.82	2.44/2.61	2.19/2.28	1.79/1.83	1.27/1.28	-	
Max	0.76	0.74	0.70	0.78	0.85	0.93			
	[2, 42/3, 01]	[2.52/3.02]	[2, 72/3, 01]	[2,96/3,02]	[3.00/2.91]	[3.01/2.77]	_		

The highest lod score of 3.79 for D3S1292 occurs with 100% penetrance and a 6% phenocopy rate. The "Penet" column indicates the penetrance of the dD and DD genotype (gene carriers). The "Max with lod>3" column indicates the maximum phenocopy rate yielding a lod score (inside brackets) greater than 3 under the different penetrances in each row. The "Max" (bottom of first column) indicates the lowest penetrance yielding a lod score (inside the brackets in the next row down) greater than 3 under the different phenocopy rates in each column. For each combination of penetrance and phenocopy rate, lod scores are given for both markers D3S1292 and D3S3637 as (lod for D3S1292/ lod for D3S3637).

and older (Figure 2H,I). The punctuate cortical opacity progressed very slowly after 30 years of age as patients 50 years old or older had preoperative visual acuity comparable to patients around 30 years old (Table 1). One exception was a 19 year old girl (number 31 in Figure 1) whose cataract phenotype is similar to that of a 4 year old child (compare Figure 2A,B to Figure 2D,E). Her corrected visual acuity is 1.5 in both eyes without any visual symptoms even though she has a mild but typical Y-sutural cataract (Table 1, Figure 2D,E). There was no other opacity in the nucleus or cortex of her lenses under careful slit lamp examination. Her lens appears somewhat cloudy in Figure 2D because stronger scatter lights were used for that lens photograph. The Y-sutural opacity appears to be congenital, but the cortical punctuate opacity is an adult onset event.

A genome wide scan of chromosomes 1 through 22 for cataracts, gave lod scores above 1.5 only for markers D3S1292, D12S326, and D12S1708. Fine mapping defined the cataract locus around D3S1292 and excluded the regions around D12S326 and D12S1708 due to closely linked flanking markers with large negative lod scores. The highest lod scores were obtained with D3S1292 (Zmax=5.72 at θ =0), D3S3637 (Zmax = 5.32 at θ =0), and D3S1587 (Zmax=5.24 at θ =0). D3S3606 and D3S1309 gave obligate recombinations while all markers in between them gave positive lod scores without recombination, suggesting that the disease locus falls into this 11.4 cM (13.5 Mb) region (Figure 1, Table 2).

Visual examination of haplotypes supports the localization provided by linkage analysis (Figure 1). Obligate proximal recombinants occur at D3S3606 in affected individual 5, supported by inheritance in affected individuals 19, 20, 30, 31, and 32, and recombinations with the proximal marker D3S1267 (not shown). An additional proximal recombinant is seen at D3S1267 in unaffected individual 13. Distal recombinants are seen at marker D3S1309 in affected individual 23, also inherited by affected individual 34. These results confirm localization of the disease gene to the 13.5 Mb interval flanked by D3S3606 and D3S1309. This region contains the *BFSP2* gene, mutations in which have previously been shown to be associated with congenital and juvenile onset cataracts [10,11].

Sequencing the 7 exons of the *BFSP2* gene reveals a heterozygous 3 base deletion, c.697_699delGAA (reference sequence: NM_003571.2), in exon 3 resulting in deletion of a glutamic acid residue, p.E233del (Figure 3). This mutation cosegregates with the Y-sutural cataract throughout the family and is present in all 12 affected individuals examined but is absent in all 12 unaffected members in the family. The mutation eliminates one of the 3 *Mbo*II restriction endonuclease sites in exon 3 (Figure 3), allowing efficient population screening. It was not detected in 384 chromosomes from 192 unrelated controls of the same Han Chinese ethnic origin as the family.

Myopia was present in 10 of the 12 affected individuals studied, all but one showing a moderate or high degree of myopia (Table 1). Information regarding refraction and axial length was not available for a 51 year old affected male (individual 11). A 4 year old affected male (individual 34) has mild hyperopia (+2.0 D OD, +1.5 D OS). The myopia is more likely to be of an axial nature rather than being secondary to lens changes since ocular axial length was extended in the 5 affected individuals for whom records are available (Table 1). Among 8 unaffected siblings and offspring of cataract patients in the family (individuals 7, 12, 13, 16, 26, 29, 33, and 35 in Figure 1), only one (individual 33) has a mild degree of myopia (-1.5 D OD, -1.0 D OS).

Linkage analysis of myopia independently of cataract, mapped myopia to a 61.2 cM (59 Mb) region between D3S3606 and D3S1262 on 3q21.3-q27.2 with a maximum lod score of 3.33 at D3S1292 (Table 3, Figure 1) under a penetrance of 0.9 and phenocopy rate of 0.1. As the penetrance and phenocopy rate are varied, a maximum lod score of 3.79 is obtained for D3S1292 with full penetrance and a 6% phenocopy rate (Table 4, Figure 4). For D3S1292, lod scores remain above 3 with phenocopy rates of up to 23% for a penetrance of 1 and with a penetrances as low as 0.7 for a phenocopy rate of 5%. For D3S3637, the lod score remains above 3 with phenocopy rates above 15% for penetrances at or above 90% and with a penetrance at or above 0.7 with a phenocopy rate of 0.05. Examination of the pedigree shows that of 18 offspring of individuals with Y-sutural cataracts and myopia, 10 had cataracts and myopia, 7 had neither, and one had myopia alone. A single offspring of an individual without cataracts or myopia had myopia alone. While the family is relatively small, these results are consistent with nearly full penetrance for the affected allele. A genome wide scan of chromosomes 1 through 22 for myopia alone using a 90% penetrance and a phenocopy rate of 10% gave no lod scores above 2 other than those for markers between D3S3606 and D3S1262.

DISCUSSION

Here we report linkage of autosomal dominant Y-sutural cataracts in a large Chinese family to an 11.4 cM region on chromosome 3q22 between D3S3606 and D3S1309 and identify a 697_699delGAA (E233del) mutation in exon 3 of the BFSP2 gene. Myopia in this family was independently mapped to 3q21.3-q27.2 between D3S3606 and D3S1262. There was a significant association between cataracts and myopia in this family in that, except for one young boy, all individuals with cataracts also had myopia. Based on the genome wide linkage scan, fine mapping on chromosome 3q22, sequencing of PCR products for BFSP2, restriction endonuclease analysis and analysis of control subjects, the Y-sutural cataract observed in the Chinese family appears to be related to the p.E233del mutation of the BFSP2 gene on chromosome 3q22. We have also sequenced the exon and exon-intron boundary regions of the BFSP2 gene in an additional patient from another unrelated Chinese family with a phenotypically similar Y-sutural cataract accompanied with myopia but did not identify any potentially causative mutations in that individual (data not shown). Thus, taking into account the Y-sutural cataract reported previously by Klopp et al. [43], there are two or more genes associated with autosomal dominant isolated Y-sutural

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cataracts. As described previously, the glutamic acid residue deleted as a result of the 3 bp deletion at codon 233 is situated in the filament domain, highly conserved among intermediate filament proteins. Deletion of this residue would drive a phase shift of the succeeding residues, which may affect *BFSP2* structure and its interaction with other filament proteins [11].

An R287W mutation in BFSP2 has previously been described in a family with juvenile onset progressive cataracts [10], and an identical E233del mutation has been identified in a family with congenital nuclear, sutural, and stellate or spokelike cortical cataracts [11]. The morphology of the cataracts in the family reported here is different from those in the two previously reported families, and in neither case was myopia identified in affected individuals. In the juvenile onset progressive cataract family with an R287W mutation [10], cataract morphology was described in 8 cases, including lamellar in 3 cases, cortical in 3 cases, nuclear in 2 cases, and a prominent suture in 1 case. In the autosomal dominant congenital cataract family with an identical E233del mutation [11], cataracts in the affected members were described as congenital nuclear, sutural, and stellate or spokelike cortical cataracts that varied in severity among different individuals. The mildest expression consisted of spokelike anterior and posterior subcapsular cortical opacities with a ground glass appearance throughout the cataract and, most notably, radially oriented fine vacuoles. There were insufficient data to evaluate myopia in this family (Dr. Richard Weleber, personal communication).

In the family described here, Y-sutural opacity is the earliest and the mildest sign, and is the most remarkable sign present in every affected member. In the previously reported family with an R287W mutation, the earliest reported findings were a general haze with a prominent suture [10]. In contrast, the mildest expression of cataract, described as spokelike cortical opacities with radially oriented fine vacuoles in the previously reported family with the E233del mutation [11], looks similar to a sutural opacity if their Figure 1 is compared with the cataract in a patient of this study (Figure 2C). This suggests that Y-sutural opacity in the lens is the common, characteristic earliest and mildest sign of cataracts caused by mutations in the *BFSP2* gene.

The beaded filament structural protein encoded by the *BFSP2* gene is a highly divergent member of the intermediate filament family. The BFSP2 protein is a major component of beaded filaments which are abundant in lens fiber cells, the only cells in which they are known to be expressed. These cytoskeletal structures consist of a 7 to 9 nm backbone filament with 12 to 15 nm globular protein particles spaced along it. The earliest signs of cataract in this family would suggest that the BFSP2 protein plays an important role in distal fine structure organization of lens fiber cells and infrastructure remodeling of cell-cell contact in the distal end of lens fiber cells. This will be clarified as the molecular cell biology of related gene products, including as localization and function of the mutant BFSP2 protein is better studied.

The myopia associated with the cataracts in this family is another interesting point. This myopia is unlikely to be a random event as shown by the statistically significant association between cataracts and myopia, even within this family itself. The association might be even greater than it appears in this analysis. Most of the members of this family live in the countryside where myopia is rare compared to urban populations [51,56-59]. Except for hereditary high myopia, most myopia begins to develop at school age [56]. Therefore, the hyperopia seen in the 4 year old boy (individual 34) with Ysutural cataracts may change to myopia with age [52]. The myopia observed in individual 33 without Y-sutural cataract may just represent a random occurrence of myopia as seen in the general population, especially as it is mild compared to that seen in affected family members. An alternative but less likely possibility is that this individual might represent a divergent assortment of traits determined by two closely linked but separate loci. For example, a myopia susceptibility locus was suggested near this region by a genome wide scan of dizygotic twins [53]. However, this region lies 20 cM distal to the region identified in this family, suggesting these are discrete loci. Finally and most importantly, a genome wide scan independently linked the myopia in the family to 3q21.3-q27.2, and this linkage is maintained under different models with penetrances significantly lower that that suggested by the family structure itself and phenocopy rates ranging from 0 to 0.23, in or above the range of those suggested by previous studies [51,56-59].

BFSP2 does not appear to be expressed in the sclera [60]. However, myopia is not necessarily related only to genes expressed in the sclera, as congenital stationary night blindness accompanied with high myopia has been shown to be caused by a retinally expressed gene (NYX) [61]. Conversely, the myopia seen in patients with Y-sutural cataract may simply be induced by blurred vision. Vision deprivation has been reported to induce myopia in the chicken, mouse, and monkey [62-65]. However, this seems less likely in light of the absence of myopia in other congenital cataracts, even those with a more severe phenotype. Axial elongation has been observed in unilateral cataract as opposed to bilateral cataract but contradicting data also exist [66-69]. Aberrant development of the lens could lead to abnormal development of the eyeball but this has not been observed in lenses of other patients with BFSP2 mutations, which generally are reported to cause isolated cataracts.

In summary, we report an autosomal dominant isolated Y-sutural cataract associated with myopia in a Chinese family. This cataract maps to an 11.4 cM region on chromosome 3q22 between D3S3606 and D3S1309 with a lod score of 5.7 at θ =0 for D3S1292, and is associated with a E233del mutation in the BFSP2 protein. Studies of cataract phenotypes, especially in a larger group of patients with mutations of the *BFSP2* gene, will be very valuable in confirming the common and typical signs of *BFSP2*-related cataract. Myopia in this family also maps independently to 3q21.3-q27.2, although with a larger linked interval. Analysis of *BFSP2* gene variations in populations with and without myopia would be very helpful in elucidating the role of *BFSP2* alterations in multifactorial myopia.

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