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ORIGINAL INVESTIGATION

Autosomal recessive juvenile onset cataract associated with mutation in *BFSP1*

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Abstract A genome wide scan in a consanguineous family of Indian origin with autosomal recessive developmental cataracts was performed by two-point linkage analysis with 382 microsatellite markers. It showed linkage to markers on chromosome 20q, between D20S852 and D20S912, with a maximum lod score of 5.4 obtained with D20S860. This region encompasses the beaded filament structural protein 1 (*BFSP1)* gene. Direct sequencing revealed a 3343 bp deletion including exon 6 (c.736-1384_c.957-66 del) predicted to result in a shift of the open reading frame. This mutation was absent in 50 control individuals from south India. This is the first report of a mutation in the *BFSP1* gene associated with human inherited cataracts. This further increases the genetic heterogeneity of inherited cataracts and provides clues as to the importance of *BFSP1* in the cell biology of intermediate filaments and their role in the eye lens.

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Introduction

Cataract is the most frequent cause of visual impairment and blindness worldwide (Congdon et al. 2003). While congenital cataracts are less frequent than age related cataracts, if not treated promptly they can result in irreversible neural blindness. The frequency of non-syndromic congenital cataract is estimated to be 1–6 cases per 10,000 children with one additional case being diagnosed during childhood (Francis et al. 2000). Developmental or juvenile onset cataract is distinguished from congenital cataract by initial clarity of the lens at birth and development of opacities progressively with maturation during childhood or adolescence. Approximately 25% of non-syndromic cataracts are inherited, and they are phenotypically and genetically heterogeneous (Francois 1982; Haargaard et al. 2004; Merin 1991), with autosomal dominant generally considered to be more common than autosomal recessive and X-linked inheritance.

To date, 26 loci causing non-syndromic inherited cataract have been mapped, including those with autosomal dominant, recessive, and X-linked modes of inheritance. Mutations have been identified in 18 genes including those encoding crystallins [*CRYAA* (Litt et al. 1998), *CRYAB* (Berry et al. 2001), *CRYBA1* (Kannabiran et al. 1998), *CRYBA4* (Billingsley et al. 2006), *CRYBB1* (Mackay et al. 2002), *CRYBB2* (Litt et al. 1997), *CRYBB3* (Riazuddin et al. 2005), *CRYGC*, *CRYGD* (Santhiya et al. 2002) and *CRYGS* (Sun et al. 2005)], a cytoskeletal protein [*BFSP2* (Conley et al. 2000)], membrane proteins [*GJA3* (Rees et al. 2000) *GJA8* (Shiels et al. 1998), and *MIP* (Berry et al. 2000), *LIM2* (Pras et al. 2002)] transcription factors [*HSF4* (Bu et al. 2002), *PITX3* (Semina et al. 1998)] and

glucosaminyl (*N*-acetyl) transferase 2 [*GCNT2* (Pras et al. 2004)].

Seven autosomal recessive congenital cataract loci have been mapped to specific chromosomal locations and the mutant genes in five have been identified. These include *CRYAA* on 21q22.3 (Pras et al. 2000), *CRYBB3* on 22q11.23 (Riazuddin et al. 2005), *HSF4* on 16q21 (Smaoui et al. 2004), *LIM2* on 19q13.4 (Pras et al. 2002), *GCNT2* on 6p24.1 (Pras et al. 2004), and loci on chromosomes 9q13-q22 (Heon et al. 2001) and 3p21.3-p23 (Pras et al. 2001).

Beaded fiber specific proteins (BFSPs) belong to the family of intermediate filament proteins (IF). They form beaded filaments, cytoskeletal structures that are unique to the lens (Perng and Quinlan 2005). These comprise a globular protein particle (12–15 nm) attached to a filament (7–9 nm). The central filamentous strand is composed of the 115 kDa protein *BFSP1* (Filensin or CP-115), while the globular head is composed of both BFSP1 and a 49 kDa protein called *BFSP2* (Phakinin or CP-49) (FitzGerald and Gottlieb 1989; Goulielmos et al. 1996). During differentiation of the lens epithelial cells to fiber cells both these protein show maximal accumulation towards the end of the elongation process. Although their role in lens biology has still not been clearly defined, they play an important role in the maintenance of optical clarity of the lens (Blankenship et al. 2001). The critical role of these proteins is emphasized by the presence of cataracts in *BFSP1* and *BFSP2* knockout mice (Alizadeh et al. 2002, 2003) and previously described association of mutations in BFSP2 with autosomal dominant cataracts in humans. (Conley et al. 2000; Jakobs et al. 2000; Zhang et al. 2004).

Here we map autosomal recessive cataracts in an Indian family to a 5.43 Mb interval on chromosome 20q flanked by markers D20S852 and D20S912 and including the BFSP1 gene. Sequencing of *BFSP1* shows deletion of exon 6 in all affected members of the family, demonstrating for the first time, association of human cataracts with a mutation in beaded filament structural protein 1.

Methods

Clinical ascertainment

This study was performed in accordance with the tenets of the Declaration of Helsinki and with the approval of the Institutional Review board and Ethics committee of Aravind Eye Hospital, Madurai, Tamilnadu and the Institutional Review Board of the National Eye Institute, Bethesda, Maryland.

A consanguineous family, 30023, of Indian origin with autosomal recessive developmental cataracts was recruited from the pediatric ophthalmology clinic of the Aravind Eye Hospital, Madurai to participate in this study (Fig. 1). A total of 19 individuals (11 affected and 8 unaffected) were available for this study. All available family members underwent detailed ocular examination, including slit lamp examination, Snellen visual acuity testing, intra-ocular pressure measurement by applanation tonometry and fundus examination. For children under 5 years of age, refractive error was measured using retinoscopy after the application of 1% atropine ointment. For individuals from 5 to 35 years of age, cycloplegia was used and for those above 35 years old tropicamide was applied. Individuals 15, 19 and 23 were the only affected phakic members available for the study while the other members had previously undergone surgery. Small incision cataract surgery (SICS) with IOL implantation was performed on individuals 15 and 19 with the lens power determined using A-scan. In addition, family members were also interviewed to obtain a detailed medical, ophthalmological and family history.

Linkage analysis

Blood samples were collected from consenting family members and genomic DNA was extracted from leukocytes using protocols described by Miller et al. (1988). A genome wide scan of this family was carried out at the National Eye Institute, NIH, MD using 382 fluorescent labeled microsatellite markers (Prism Linkage Mapping set MD-10; Applied Biosystems [ABI] Foster City, CA). Multiplexed PCR was carried out as previously described (Jiao et al. 2000). Genotyping data were collected using GeneScan Analysis 3.0 and analyzed using the Genotyper 3.5 software package from ABI (Foster City, CA). Two-point linkage analysis was carried out with MLINK from the FASTLINK version of the Linkage Program Package, (Cottingham et al. 1993; Lathrop and Lalouel 1984) analyzing the cataracts as a fully penetrant autosomal recessive disease with a disease allele frequency of 0.00001. For the genome wide scan, marker alleles were arbitrarily assigned equal frequencies, while for fine mapping marker allele frequencies were estimated from 25 unrelated individuals of Indian descent. The marker order and distances between the markers were obtained from the Généthon database (http://www.genethon.fr/). While simulation studies could not be carried out in this family because of the multiple consanguinity loops, a perfectly linked marker with ten alleles of equal frequency yields a LOD score of 4.5.

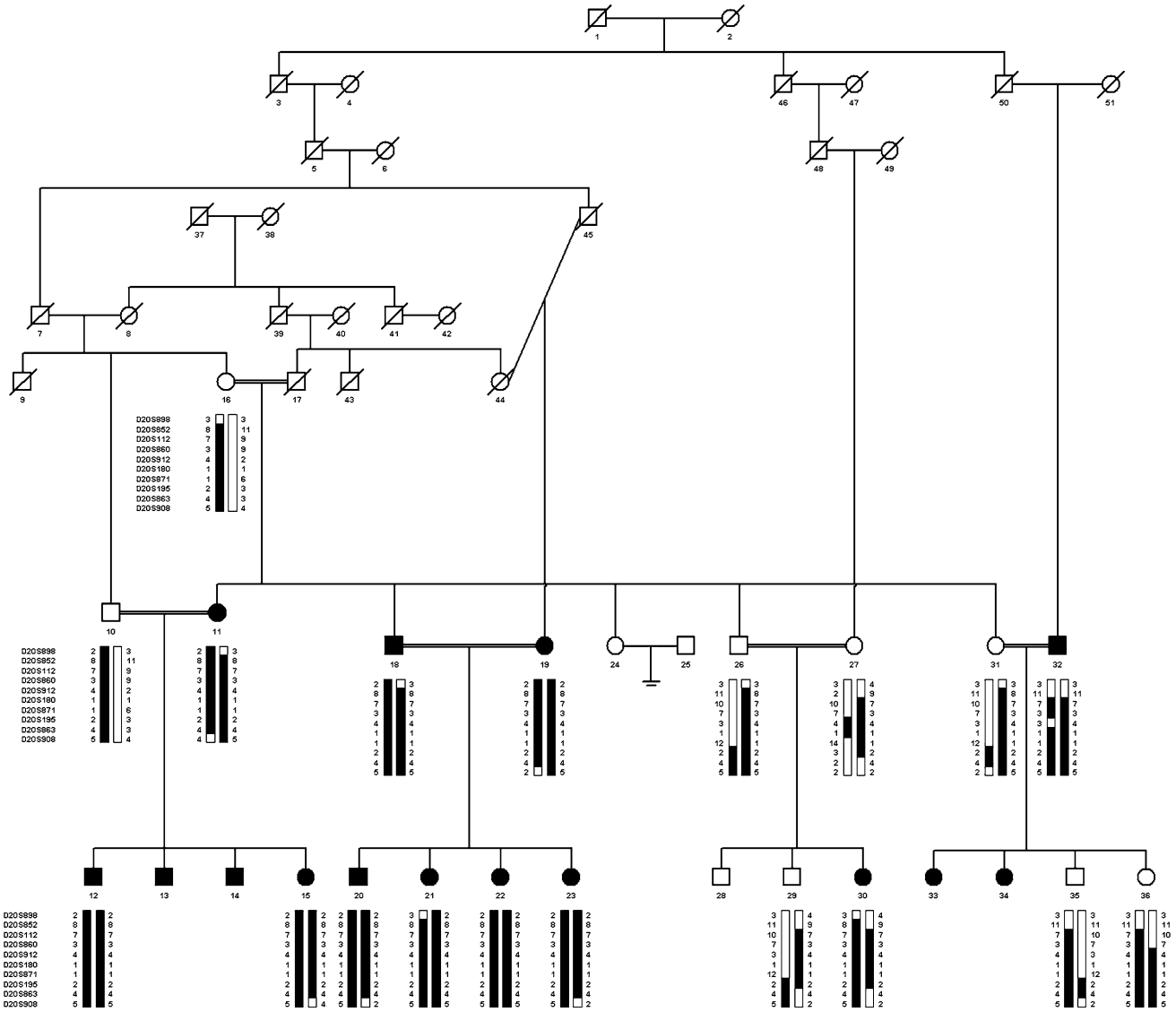

Fig. 1 Pedigree and Haplotype analysis of family 30023 with selected markers on 20q. *Squares* represent males and *circles* females, *blackened symbols* correspond to affected individuals and *clear symbols* describe normal individuals, a *double line* between symbols shows consanguineous marriage. *Filled bars* indicate the ancestral haplotype common to affected individuals. Only individuals with haplotypes shown were studied

Mutation analysis

For sequence analysis of *BFSP1* at the National Eye Institute, NIH, MD, primers were designed flanking the exon–intron boundaries so as to amplify the coding region of *BFSP1* as described in Table 3. Amplifications were carried out in 20 µl reactions containing 80 ng of genomic DNA, 10 pmol forward and reverse primers. 200 nM dNTP, 1X PCR buffer, 2.5 mM $MgCl_2$ and 0.2 U Taq DNA Polymerase (PE Applied Biosystems, Foster city, California). Thermal cycling conditions consisted of an initial denaturation at 95°C for 5 min followed by 35 cycles of denaturation for 40 s at 95°C, annealing for 40 s at 58°C and extension for a minute at 72°C. A final extension was performed for 7 min at 72°C. The PCR product was purified using Ampure Agencourt purification reagents (Beckman, Beverly, MA) with a Beckman NX MC Automated Workstation. To confirm the deletion of exon 6, sequencing was performed using a primer pair that amplifies a fragment extending from intron 5 to exon 7 which resulted in 973 bp product in the mutant allele (Table 3). PCR conditions were the same as described above. The 973 bp band was excised from a 0.7% agarose gel, DNA was purified by a gel extraction kit (QIA Quick; Qiagen, Valencia, CA), and bidirectional sequencing was carried out as described above (Table 1).

Table 1 Primers used for sequencing BFSP1 gene

Exon	Forward sequence	Reverse sequence	Product size (bp)
Exon 1	5′-GGGCCTCCGGTGTTTATTTA-3′	5′-ATCGACAGGGGACCAGAGAC-3′	589
Exon 2	5′-AAAGGAGAGGGCATCGTACC-3′	5′-AACCTGCACTTCCACCATTC-3′	238
Exon 3	5′-CAGGTGGTCTGTGTGCTCAT-3′	5′-TCGGCTTACCTGATCAAACC-3′	249
Exon 4	5′-TGTCCATTCCTGTTCTCATCT-3′	5′-GCCCTTCCCTGGGAGTCT-3′	250
Exon 5	5′-ACCTTCTCTGCCCTTTTCCT-3′	5′-CACCTCCATGAAACATGTGG-3′	227
Exon 6	5′-CCTTTTCCTGGTGAGGTCTG-3′	5′-GGCACACAATAGGCACTCAA-3′	366
Exon 7	5′-CTTGCCCCTGACCTCTGTT-3′	5′-AAGAGAGCCGCTTGGTTTTT-3′	199
Exon 8	5′-TTCCAACCAGCGTATTTTCTTT-3′	5′-TCAGGGCCTTCCAGCTCT-3′	699
Exon 8	5′-CTCTCCTGAGTCACCCAAGC-3′	5′-CTCATGAAGCTGACCCACCT-3′	688
Intron5 –exon7[a]	5′-CATCTTCCAGGGTGTCCAGT-3′	5′-AAGAGAGCCGCTTGGTTTTT-3′	4316 [a]

[a] The wild type gene is expected to yield a 4316p band where as the mutant gene yields a 973 bp

Results

Clinical findings

Clinical features of affected individuals are shown in Table 2. Lenses of affected individuals developed opacities that matured by early childhood. The cataract was first documented at 5 years of age in all individuals except for individual 23 in whom it was first documented at 2 years of age. Individuals 15, 19 and 23 showed fluffy cotton-like cortical opacities with occasional grape like cysts in the anterior cortex (Fig. 2). As the other affected individuals had undergone surgery in childhood their phenotype was not available. The unaffected family members' lenses appeared clear. Individuals 16 and 10 developed nuclear cataracts at 50 years of age and were considered unaffected for linkage analysis. Examination of individual 10 reveals nuclear sclerotic cataracts (Fig. 2, current age 65 years). The corneal diameter and the axial length measurement were normal and no other eye abnormalities were detected in these individuals.

Linkage analysis

In the initial genome wide scan lod scores greater than 1.5 at $\theta = 0$ are obtained with 11 markers: D9S171 (1.8), D11S904 (1.8), D11S908 (2.1), D14S276 (2.1), D14S74 (1.7), D17S1868 (2.7), D18S478 (1.7), D20S186 (2.0), D20S112 (4.9), D20S195 (2.0) and D22S423 (1.7). Markers closely flanking the suggestive markers on chromosomes 9, 11, 14, 17, 18 and 22 show obligate recombination, giving large negative lod scores and decreasing the likelihood that these represent true

Table 2 Clinical details of the family members

S. no.	Study no.	Age (years)	Sex	Age of onset (years)		Best corrected vision before surgery		Best corrected vision after surgery	
				RE	LE	RE	LE	RE	LE
1	10	65	M	50		6/24	NA	6/24	6/36
2	11	50	F	5		NA	NA	LP	6/24
3	12	35	M	5		NA	NA	1/60	1/60
4	15	21	F	10		NA	6/36	5/60	ND
5	16	71	F	50		NA	NA	NA	NA
6	18	43	M	5		NA	NA	No vision	2/60
7	19	36	F	5		NA	1/60	NA	NA
8	20	18	M	6		NA	NA	NA	NA
9	21	15	F	5		NA	NA	6/12p	1/60
10	22	12	F	5		NA	NA	6/12p	1/60
11	23	8	F	2		HM	HM	6/18	6/18
12	26	40	M	–		6/6	6/6	–	–
13	27	30	F	–		6/6	6/6	–	–
14	29	15	M	–		6/6	6/6	–	–
15	30	12	F	6		NA	NA	6/12p	6/12p
16	31	40	F	–		6/6	6/6	–	–
17	32	40	M	13	30	NA	NA	2/60	6/18p
18	35	15	M	–		6/6	6/6	–	–
19	36	12	F	–		6/6	6/6	–	–

NA information not available, *ND* surgery not yet done, *HM* hand motion, *LP* light perception, *p* partial. Age of onset denotes the earliest age at which the cataract was documented

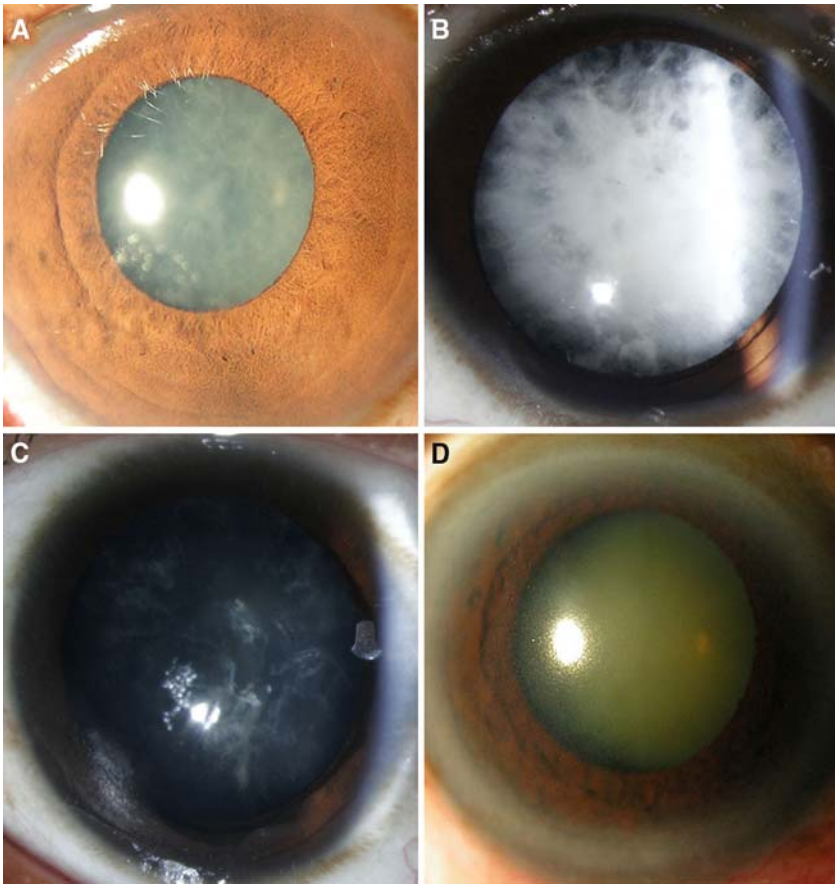

Fig. 2 Slit-lamp image of individual **a** 23 (5 years), **b** 19 (33 years), **c** 15 (19 years) showing cortical cataract and **d** 10 (65 years) showing nuclear cataract

linkage (data not shown). Results of fine mapping at 1–2 cM intervals with additional markers on chromosome 20 are shown in Table 3. Significant evidence of linkage is shown by markers D20S112 and D20S860. Obligate recombination events giving large negative lod scores are seen with markers D20S898 (-5.8 at $\theta = 0$) and D20S912 ($-\infty$ at $\theta = 0$).

Haplotypes

Examination of haplotypes in affected family members shows inheritance of a common homozygous haplotype for markers D20S180, D20S871, D20S195 and D20S863, consistent with the consanguineous matings in the pedigree. Critical centromeric recombinations are seen in affected individuals 11 and 18, offspring of individual 16, at marker D20S898 and affected individual 32 at markers D20S852 and D20S912. Telomeric recombination is observed in affected individuals 11 and 19 at marker D20S908. Critical recombination events are also seen in unaffected individuals 26, 27 and 36. These occur in individual 26 at marker D20S871, individual 27 at markers D20S852 and D20S863 and in individual 36 at marker D20S860. In addition, unaffected individuals inherited the homozygous risk haplotype for markers D20S912, D20S180, D20S871, D20S195,

Table 3 Two point LOD score of chromosome 20 markers

Marker	MB	cM	0	0.01	0.05	0.1	0.2	0.3	0.4
D20S898	15.22	35.8	−5.68	−1.73	−0.47	−0.02	0.22	0.21	0.11
D20S852	15.37	36.8	1.32	2.23	2.53	2.38	1.74	1.01	0.36
D20S112	17.39	39.3	4.96	4.85	4.42	3.86	2.71	1.55	0.57
BFSP1	17.4								
D20S860	18.28	40.6	5.40	5.30	4.86	4.29	3.09	1.86	0.76
D20S912	20.8	46.1	−∞	2.65	2.99	2.83	2.17	1.37	0.60
D20S180	22.07	47.0	2.19	2.14	1.94	1.69	1.18	0.70	0.29
D20S871	23.28	48.1	−∞	3.31	3.58	3.34	2.52	1.56	0.67
D20S195	28.57	50.2	2.07	2.02	1.82	1.60	1.16	0.71	0.30
D20S863	30.04	50.7	1.50	1.45	1.29	1.11	0.77	0.47	0.19
D20S908	37.24	53.6	−∞	−4.03	−1.50	−0.61	−0.03	0.09	0.06

Intermarker distances were obtained from NCBI (http://www.ncbi.nlm.nih.gov), cM were taken from the Genethon Map

D20S863 and D20S908, suggesting that the locus does not lie in this interval. Co-segregation with the cataract phenotype is observed for markers D20S112 and D20S860 in all the affected individuals. Overall, these results narrowed the linked region to a 9.3 cM (5.43 Mb) region flanked by markers D20S852 and D20S912 (Fig. 1). The beaded filament structural protein 1 gene *BFSP1* is included in this region and was a logical candidate gene for mutational analysis based on its expression in the lens and role in beaded filaments.

Sequencing

BFSP1 has eight coding exons that encode a 665 amino acid residue protein (Genbank ref. no. NM_001195). Primers used for amplifying the exons and their flanking regions are described in Table 3. PCR amplification of exon 6 of *BFSP1* yields the predicted 366 bp band in unaffected individuals including obligate carriers of the mutation. However, amplification of DNA from affected members of the family yields no product, consistent with absence of exon 6 from both copies of this gene (Fig. 3a). In order to investigate this further, PCR amplification of the region between Intron5 and exon7 was carried out using the primers shown in Table 1. This yields a 973 bp product in affected family members and carriers but no PCR product in control individuals, probably because the large size of the included region in controls, 4316 bp, prevented efficient amplification (Fig. 3b). Sequencing of the 973 bp product shows a 3343 bp deletion encompassing exon 6, c.736-1384_c.957-66 del (Fig. 4). Affected family members are homozygous for the deletion and unaffected family members predicted to be carriers by linkage analysis are heterozygous for the change as shown by PCR of the junctional fragment as above. This deletion does not occur in 50 ethnically matched control individuals (100 chromosomes). Direct sequencing of the other exons in the affected individuals showed no changes. Ten additional families were subjected to a genome wide scan and none of these mapped to this locus.

Discussion

We report for the first time a mutation in *BFSP1* associated with autosomal recessive cataracts in humans. The 3.3 kb deletion identified in this family results in deletion of exon6 in its entirety. The mutant *BFSP1* protein predicted to result from the gene lacking exon 6 would comprise an initial 245aa similar to those of the wild type protein, and then six additional new

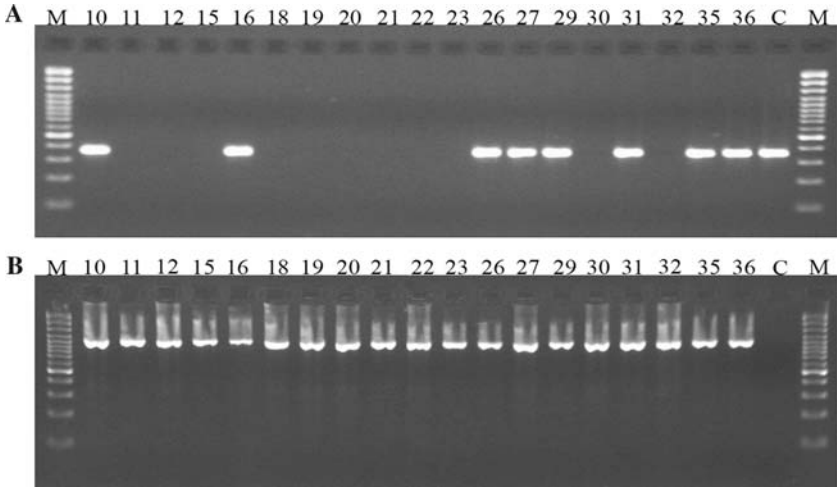

Fig. 3 **a** Agarose gel electrophoresis of PCR products of exon6. All affected individuals show no amplification due to homozygous deletion of this region. The unaffected heterozygous individuals show the respective product size (366 bp), **b** PCR amplification of the region between Intron5 and exon7. This yields a 973 bp product in affected family members and carriers but no PCR product in control individual. M-100 bp ladder

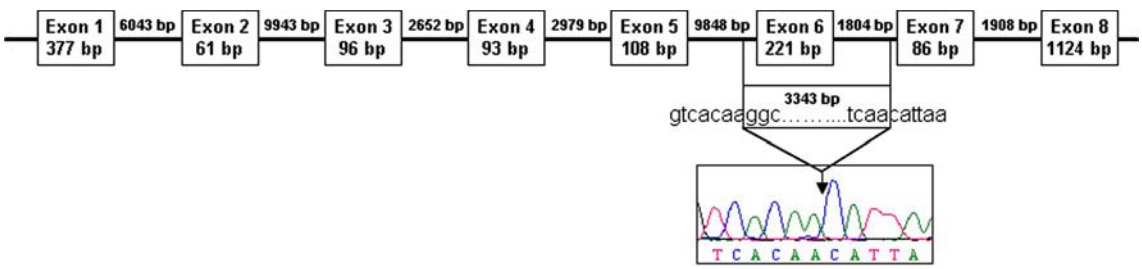

Fig. 4 Exonic organization of BFSP1 and the electropherogram of affected individual 23 showing the 3.3 kb deletion

amino acids due to the frame shift followed by a premature stop codon resulting in absence of the final 414 amino acids of the normal BFSP1 protein, p.Thr246fs. Thus, this deletion is predicted by Genbank (Q12934) to result in the loss of a part of the rod and second coil and the entire tail region of the protein, which suggests that the mutant bfsp1 protein might not participate efficiently in filament formation (Gu et al. 2004a, b). However, it is likely that the mutant mRNA undergoes nonsense-mediated decay (Hentze and Kulozik 1999), which would be consistent with the autosomal recessive inheritance pattern seen in this family. The cataract phenotype in this family is interesting in that while homozygous deletion of exon 6 of *BFSP1* is associated with juvenile onset cortical cataracts, two individuals heterozygous for the mutation developed nuclear sclerosis of the lens at approximately 50 years of age. It is possible that the fiber cells actually do accumulate the truncated protein to some degree, and as the lens ages this results in nuclear cataract. Being hemizygous for *BFSP1* might also be mildly deleterious and result in a presenile onset nuclear sclerotic cataract, or the occurrence of these two cataracts in carriers of the mutation in this family might simply be happenstance.

BFSP1 and *BFSP2* are cytoskeletal proteins that are only distantly related to other members of this gene family. Beaded filaments, which these proteins form, are unique to the lens (Hess et al. 1996), although a low level of BFSP1 transcripts have been noted in cDNA libraries from other tissues, including the liver (NCBI UniGene EST Profile Viewer). In mice, both BFSP1 and BFSP2 protein expression are absent in lens epithelial cells and first appear in the anterior end of the fiber cells after fiber cell elongation has begun. There is a gradual transition in the distribution of the beaded filament protein from being membrane associated to becoming cytoplasmic as the lens matures (Blankenship et al. 2001). This finding is consistent with gene knockout studies in mice. Lenses that lacked BFSP1 failed to form beaded filaments in fiber cells, whereas elimination of *BFSP2* resulted in the reduction in the levels of *BFSP1* as well. This was interpreted to mean that beaded filaments were not needed for normal lens fetal development or fiber cell differentiation, but they appear necessary for long-term maintenance of lens clarity. This was evident from light scattering of the lens in the mice that lacked either protein and the opacity worsened with age, although the *BFSP2* knockout mice show a milder cataract phenotype (Alizadeh et al. 2002, 2003).

In humans, congenital cataracts resulting from a deletion mutation (E233del) in *BFSP2* have been shown to be inherited in an autosomal dominant manner have a more adverse effect compared to the deletion of the gene in mice (Jakobs et al. 2000). The same mutation (E233del) has been reported in a large Chinese family and was shown to be associated with early childhood cataract and myopia (Zhang et al. 2004). It is notable that no affected individuals in family 30023 studied here are myopic. A missense mutation in exon 4 of *BFSP2* (R278W) has also been found to cause juvenile onset cataract with a variable phenotype (Conley et al. 2000). The juvenile onset of the cataract described here is consistent with these reports as well as with the phenotype shown by the *BFSP1* and *BFSP2* knockout mice.

In conclusion, autosomal recessive cataracts in an Indian family map to a 5.43 Mb interval on chromosome 20q flanked by markers D20S852 and D20S912 and including the *BFSP1* gene. Sequencing of *BFSP1* shows deletion of exon 6 in all affected members of the family, demonstrating for the first time association of human cataracts with a mutation in the gene encoding beaded filament structural protein 1.

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