A New Locus for Autosomal Dominant Cataract on Chromosome 19: Linkage Analyses and Screening of Candidate Genes

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Purpose. To map and identify the mutated gene for autosomal dominant cataract (ADC) in family ADC4.

Methods. Ophthalmic evaluations were performed on an American family with ADC and a panel of polymorphic DNA sequence-tagged site (STS) markers for known ADC loci and other genome-wide polymorphic markers were used to map the gene; two-point lod scores were calculated. Fine mapping was undertaken in the chromosomal regions of maximum lod scores, and candidate genes were sequenced.

Results. A four-generation American family with ADC was studied. The only phakic individual exhibited white and vacuolated opacities in the cortical region. This ADC locus mapped to several suggestive chromosomal regions. Assuming full penetrance, the highest calculated maximum lod score was 3.91 with *D19S902*. On chromosome 12, we sequenced all exons and the exon–intron borders of the membrane intrinsic protein (*MIP*) gene. On chromosome 19, all exons and the exon–intron borders of genes for lens intrinsic membrane2 (*LIM2*), ferritin light chain (*FTL*), and the human homologue of the *Drosophila sine oculis* homeobox 5 (*SIX5*) were sequenced, and the 3′ untranslated repeat region (UTR) of the dystrophy (*DMPK*) gene and both the 5′ and 3′ UTRs of the *SIX5* genes were amplified; the promoter for *LIM2* was sequenced. For these genes, the sequence matched that in the reference libraries, and the *DMPK* gene had a normal number of CTG repeats.

Conclusions. The mutated gene in ADC4 probably represents a new, not yet identified locus on chromosome 19. In one phakic member, the cortical cataracts were punctate and vacuolated. (*Invest Ophthalmol Vis Sci.* 2006;47:3441–3449) DOI: 10.1167/iovs.05-1035

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Pediatric cataracts are an important and treatable cause of visual impairment in infancy. Because of different definitions of visual impairment and blindness, regional socioeconomic standards and healthcare systems, and study methodology including ascertainment, estimates of the prevalence of blindness and infantile cataract in the United States and worldwide vary. The economic and personal impact of pediatric cataracts is unknown but significant in all cultures, because the predicted number of blind years is greater in children than adults. In developed countries, the prevalence rate varies from 0.63 to 13.6 per 10,000 births[1–4] or infants under the age of 1 year.[5,6] In the United States, SanGiovanni et al.[6] estimated the prevalence of infantile cataracts to be 13.6 per 10,000 infants under the age of 1 year, based on a database collected prospectively from the late 1960s and early 1970s. Spanning the years 1968 to 1998, Bhatti et al.[3] calculated a U.S. rate of 2.03 infants with cataracts per 10,000 births, based on retrospective analyses.

The causes of pediatric cataracts are diverse and include infectious agents and genetic defects. For the autosomal dominant form (ADC), neither the incidence nor the prevalence is known. ADC forms are usually bilateral. In developed countries, bilateral isolated cataracts account for between 44% and 66% of infantile cataracts[3,7]; unilateral, isolated cataracts comprise between 25% and 60%.[3,7] Nearly 90% of bilateral, hereditary cataracts were autosomal dominant, based on a large British study.[7] In Denmark, 46% of bilateral, isolated cataracts were determined to be genetic.[8]

ADC is a clinically and genetically heterogeneous disease. ADCs have been classified clinically on the bases of the morphology, size, color, and location of the opacities in the lens or the name of the investigator describing the cataract or affected family. Although ophthalmologists have developed cataract nomenclature, Francis et al.[9] devised a system for conformity. Wide variations of cataract types among families have been documented including nuclear,[10] anterior polar,[11] posterior polar,[12] coralliform,[13] blue dot cerulean,[14] pulverulent,[15] cortical,[16] zonular,[17] and sutural cataracts.[18] The same phenotype may be caused by mutations of different genes and the identical gene mutation has been reported to cause diverse cataracts in different families. For example, posterior polar cataracts may be caused by mutations of paired-like homeodomain transcription factor 3,[19] a transcription factor on chromosome 10 or the crystallin protein crystallin alpha B[20] on chromosome 11. Conversely, a mutation of the crystallin, beta B2 (475C→T) has been associated with sutural cataract[21] in one family, cerulean cataract[22] in another, and a Coppock-like cataract[23] in a third; morphology was consistent within each family. Despite attempts to categorize hereditary cataracts clinically, there is limited correlation of phenotypes with genetic locus and specific mutation.

ADCs exhibit high penetrance, and many genetic loci have been identified by linkage and mutational analyses. Twenty-four chromosomal regions have been implicated for ADC, and

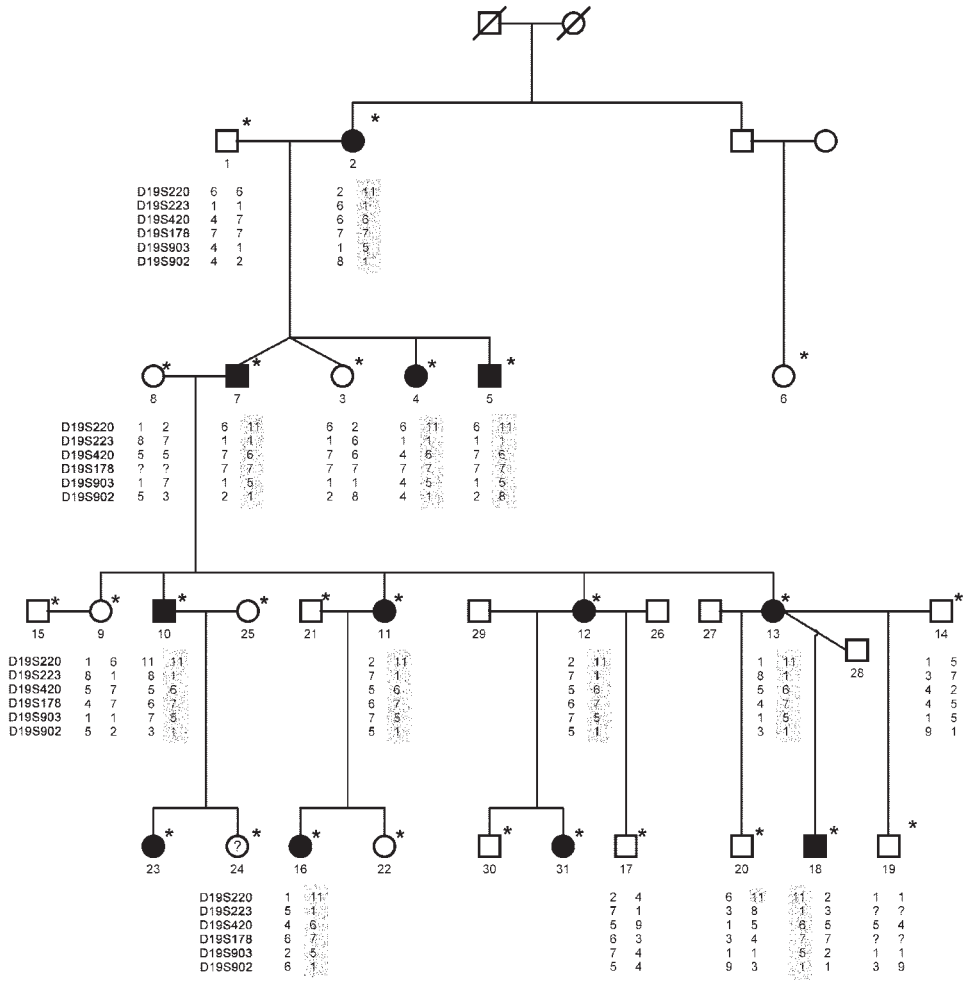

FIGURE 1. Pedigree of ADC4 family with haplotypes in the mapped region of chromosome 19. The pedigree has been modified slightly, to protect the confidentiality of the family. Affected individuals are annotated as *solid symbols*; numbers indicate individuals studied (examined, samples obtained). Haplotypes in the critical region on chromosome 19 are indicated below each individual studied for linkage in this region, and the conserved region is in a *shaded box*. *Individuals from whom DNA was collected.

15 ADC genes have been identified in these regions, including those encoding for membrane proteins connexins (gap junction, alpha 8[24,25] and gap junction, alpha 3[26–29]), membrane junction proteins (major intrinsic protein of lens fiber[30]), crystallins (gamma C,[31] gamma D,[31–37] beta A1,[28,35,38–41] beta B2,[21–23,42] beta B1,[43] alpha B,[20] and alpha A [Xi JH, et al. *IOVS* 2002;43:ARVO E-Abstract 3556],[44,45]), structural proteins (beaded filament structural protein 2),[46–48] intracellular storage proteins (ferritin light chain),[49–58] transcription factors (paired-like homeodomain transcription factor 3,[19,59,60] paired box gene 6,[61,62] and v-mafmusculoaponeurotic fibrosarcoma oncogene homolog (avian)[63]), and heat shock proteins (heat shock transcription factor 4).[64] With few exceptions, the mutations are personal, not supporting a founder effect.

We studied a four-generation family with some members affected with ADC. Ophthalmic evaluations and linkage analyses using genome-wide polymorphic DNA markers were performed, and two-point lod scores were calculated. We undertook fine mapping in the regions of suggestive and statistically significant maximum lod scores and performed multipoint analyses. We screened or sequenced candidate genes.

METHODS

Patients and Clinical Findings

The study adhered to the tenets of the Declaration of Helsinki for research involving human subjects. Informed consent was obtained before examination. A four-generation American family of white ancestry (*ADC4*; Fig. 1) was studied. Individuals 6 and 15 were used for some sequencing studies but not for the linkage analyses. During the study, some new individuals were identified, and one key unaffected individual died. All linkage analyses were performed with sufficient power.

Individuals were examined by slit lamp biomicroscopy or retroillumination (in the field) after pupillary dilation. Affected status was determined by observed opacities or history of cataract extraction before the age of 50 years. The pedigree showed a vertical pattern of inheritance including male-to-male transmission; both genders were similarly affected.

Linkage Analyses

Blood samples were collected in acid citrate dextrose (ACD; BD Vacutainer, Franklin Lakes, NJ), and DNA was extracted. We analyzed polymorphic sequence-tagged site (STS) DNA markers using our 1998 ADC Screening Panel and previously described methodology (Table 1).[39] As the original 1998 Panel had expanded after reports of ADC gene mutations, markers were added and some were analyzed in this family. We used linkage mapping (Prism Linkage Mapping Set, ver. 2.0 and 2.5; Applied Biosystems, Inc. [ABI], Foster City, CA); we performed a genome-wide screening; and we analyzed panels of fluorescent primers for polymorphic STS markers, on average 10 cM apart, as detailed in the user's manual. The PCR genotypes were analyzed on computer (GeneScan and GeneMapper, ver. 3.5.1 software; ABI).

Two point lod scores were calculated using the LIPED algorithm (http://linkage.rockefeller.edu/ provided in the public domain by Rockefeller University, New York, NY).[65] A gene frequency of 0.0001 and full penetrance were assumed for the cataract locus. Two-point lod

TABLE 1. ADC Panel Markers and Lod Scores with *ADC4* Locus

Gene; Protein	Mbp†	Gene/Phenotpe Symbols (OMIM)	Marker		Allele Size Range (bp)	PCR Conditions	Lod Score						
			Locus	Mbp			($\theta_m = \theta_f = 0$)	0.001	0.05	0.1	0.2	0.3	0.4
		CCV	*D1S243*	2.2	142-170	1998 Panel	−∞	−8.78	−2.18	−1.17	−0.39	−0.12	−0.03
		CTPA	*D1S508*	7.5	73-85	1998 Panel	−∞	−8.60	−3.22	−2.18	−1.15	−0.58	−0.23
Gap junction protein alpha 8; connexin 50	144.6	*CZP1/GJA8*	*D1S514*	120.0	145-157	1998 Panel	−∞	−1.50	0.12	0.32	0.42	0.36	0.22
		Nuclear cataracts	*D2S2333*	85.4	246-260	TA	−∞	−14.39	−4.35	−2.70	−1.23	−0.54	−0.17
Crystallin, gamma C, gamma D	208.8	*CRYG*	*D2S72*	204.6	159-173	1998 Panel	−∞	−14.39	−4.33	−2.66	−1.16	−0.45	−0.11
Beaded filament structural protein 2	133.3	*BFSP2*	*D3S1267*	124.5	129-167	TA	−∞	−12.29	−3.89	−2.47	−1.17	−0.52	−0.17
Paired-like homeodomain transcription factor 3	104.0	*PITX3*	*D10S2470*	N/A	243-267	TA	−∞	−2.99	0.21	0.60	0.74	0.58	0.30
Paired box gene 6	31.8	*PAX6*	*PAX6CA/GT*	31.8	272-292	TA	−∞	−17.69	−5.91	−3.91	−2.04	−1.05	−0.42
Crystallin, alpha B	111.3	*CRYAB*	*D11S4176*	93.7	224-254	TA	−∞	−14.69	−4.61	−2.92	−1.37	−0.60	−0.19
Major intrinsic protein of lens fiber	55.1	*MIP*	*D12S90*	56.7	166-182	1998 Panel	−∞	−2.39	0.77	1.11	1.17	0.94	0.54
Gap junction protein alpha 3; connexin 46	19.6	*CZP3/GJA3*	*D13S1236*	21.6	124-132	1998 Panel	−∞	−2.70	−1.00	−0.70	−0.40	−0.22	−0.10
		CCPSO	*D15S117*	56.3	132-150	1998 Panel	−∞	−14.39	−4.35	−2.70	−1.23	−0.54	−0.17
		CTM	*D16S265*	62.1	89-117	1998 Panel	−∞	−11.69	−3.35	−2.00	−0.84	−0.31	−0.07
Heat-shock transcription factor 4	65.8	*HSF4*	*D16S3095*	68.5	150-162	TA	−∞	−4.20	−0.90	−0.42	−0.05	0.06	0.06
		CTM	*D16S518*	76.7	272-290	1998 Panel	−∞	−11.39	−3.05	−1.71	−0.56	−0.09	0.07
		CTAA2	*D17S849*	0.4	251-261	1998 Panel	−∞	−11.99	−3.63	−2.26	−1.06	−0.52	−0.23
Crystallin, beta A1	24.6	*CCZS*	*D17S805*	19.3	216-228	1998 Panel	−∞	−11.69	−3.35	−2.00	−0.84	−0.31	−0.07
		CCA1	*D17S836*	74.8	202-210	1998 Panel	0.30	0.30	0.26	0.21	0.13	0.06	0.02
Ferritin	54.2	*FTL*	*D19S412*	51.7	97-109	TA	*						
		CCP3	*D20S917*	9.2	141-167	TA	*						
Crystallin, alpha A	43.5	*CRYAA*	*D21S171*	44.8	111-133	1998 Panel	−∞	−4.50	−1.18	−0.67	−0.25	0.09	−0.02
Crystallin, beta B2	23.9	*CRYBB2*	*D22S258*	24.3	177-195	1998 Panel	−∞	−12.29	−3.88	−0.04	−1.17	0.52	−0.17
Crystallin, beta B1	25.3	*CRYBB1*	*D22S1167*	25.4	266-278	TA		−8.10	−3.00	−2.10	−1.19	−0.67	−0.29

TA, true allele PCR conditions (Applied Biosystems, Inc.).

* Markers added to panel after ADC4 linkage analyses concluded.

† Mb locations based on NCBI map build 35.1.

scores were calculated for a full range of θ_m and θ_f values. Accurate population-specific allele frequency data are not available for these markers. Therefore, in the regions of interest, we used a range of possible allele frequencies to assess the robustness of the allele frequency assumptions. For these data, the effect on the results was negligible.

The genome-wide coverage was checked by using both the recombination and physical map locations for each marker. We classified lod scores as suggestive or statistically significant. We assessed regions with suggestive lod scores with additional markers and multipoint analyses, and sequenced good candidate genes in the area. We accepted lod scores greater than 3.0 as statistically significant and indicative of significant evidence for linkage with the marker; for statistically significant lod scores, we sequenced all good candidate genes in the region.

Multipoint linkage analyses were undertaken using the FASTLINK[66] implementation of the MLINK and LINKMAP programs (http:www.hgmp.mrc.ac.uk/; provided in the public domain by the Human Genome Mapping Project Resources Centre, Cambridge, UK),[67,68] and Genehunter 2.1 (Rockefeller University).[69] For the Genehunter analyses, it was possible to calculate exact multipoint lod scores using the full pedigree and all 14 markers from chromosome 19, by increasing the "max bits" parameter to 24.

Screening for Candidate Genes

Identification of candidate genes was based on previous reports of mutations of genes causing ADC or on expression and function, using the National Center for Biotechnology Information's Mapviewer.[70]

We sequenced candidate genes in regions suggestive of linkage on chromosomes 12 and 19 including all exons and exon–intron borders of *MIP* on chromosome 12 as well as the lens intrinsic membrane2 (*LIM2*), the homologue of the *Drosophila sine oculis* homeobox 5 gene (*SIX5*), and *FTL* genes on chromosome 19. The 3′ untranslated region of the dystrophia myotonica protein kinase gene (*DMPK*) on chromosome 19 was sized for CTG repeats. In addition, the *LIM2* promoter region and the 5′ and 3′ untranslated regions (UTRs) of the *SIX5* gene were sequenced. Primers were designed for the *LIM2*, *MIP*, and *SIX5* candidate genes based on reference sequences from NCBI[70] and/or Ensembl[71] (Table 2). Previously described primers and conditions were used to amplify the repeat region in the *DMPK* gene (UniSTS:34269) and the exons and intron–exon borders of the *FTL* gene.[72] A minor modification was applied to the *FTL* PCR; the 5′ UTR and exon 1 were amplified in the same reaction using the forward primer 5′-TCCTTGCCACCGCAGATTG-3′ and the reverse primer 5′-GCAGCTGGAGGAAATTA-3′. For *LIM2*, PCR products were sequenced from both directions using a dye terminator cycle sequencing kit (Prism FS; ABI) and an automated fluorescence sequencer (model 373; ABI). For *DMPK*, the 3′ repeat region was amplified (UniSTS:34269) and PCR products were resolved on 2% SFR agarose (Midwest Scientific, St. Louis, MO) gels. For *SIX5* and *MIP*, PCR products were amplified (*Taq* PCR Core kit; Qiagen, Valencia, CA). PCR reactions were run with 25 ng of genomic DNA, 1.5 mM $MgCl_2$, 0.5 mM dNTP, 0.4 μM each primer, and 0.5 units *Taq* polymerase. We sequenced PCR products using dye termination chemistry and a genetic analyzer (Big Dye ver. 3.0 or ver. 1.1 terminator kits and both a 3100 Genetic Analyzer and a 3100-Avant Genetic Analyzer; all ABI). Sequence analyses were performed using Consed.[73] Two unaffected and two affected family members were sequenced for the *MIP* (members 6, 11, 12, and 15) and *FTL* (members 11, 16, 21, and 22) genes. All family members were sequenced for *LIM2* and *SIX5*, and sized for the *DMPK* repeat region. Ferritin level was measured in one affected individual (11) in a commercial laboratory.

Results

Patients and Clinical Findings

Based on office slit lamp biomicroscopy of the only known phakic individual (16), the ADC4 cataracts were irregularly shaped white or spherically shaped vacuolated opacities symmetrically located in the cortical region of lens (Fig. 2). Phenotypic variability is unknown.

Linkage Analyses

Both the focused and genome-wide screen employing 268 markers was completed on the family. We excluded linkage to regions of known ADC loci (Table 1) except for chromosome 12 (maximum lod score of 2.71 with *D12S102* for $\theta_f = \theta_m = 0$); multipoint analysis did not further support a locus in this suggestive region. For the genome-wide screening, a plausible indication of linkage, based on two-point linkage analysis, was found on chromosome 17 (maximum lod score of 1.55 with *D17S1806* for $\theta_m = 0.403$ and $\theta_f = 0.00$); multipoint analyses in this region failed to confirm evidence of linkage. All other chromosomal regions were either excluded by the lod score or by multipoint analysis except for areas on chromosome 19. The maximum lod score was on chromosome 19 (3.91 for *D19S903*, $\theta_f = \theta_m = 0$; Table 3). Therefore, the only remaining region of the genome with evidence for linkage of the cataract and genetic markers is chromosome 19 (data available from the authors by request). Visual inspection of haplotypes (Fig. 1) and multipoint analysis (Fig. 3) indicated that the most likely chromosomal region lies between markers *D19S220* and *D19S902*.

Screening of Candidate Genes

MIP on the long arm of chromosome 12 was the candidate gene on our ADC panel and the marker *D12S102* is 10.07 Mb distal to this candidate gene. On the long arm of chromosome 19, we identified four candidate genes (*LIM2*, *FTL*, *DMPK*, and *SIX5*) within 6.83 Mb distal to 19S902.

For the exons and intron–exon borders sequenced for *MIP*, *LIM2*, *SIX5*, and *FTL*, our sequence was the same in all individuals tested and matched that in the reference libraries. The *LIM2* promoter and the *SIX5* 5′ and 3′ UTRs matched reference sequences. The number of repeat CTG sequence for *DMPK* in ranged from four to nine, below the 50 repeats or greater found in individuals affected with myotonic dystrophy. The ferritin level was 30 ng/mL in affected individual 11, within the reference range of 10 to 291 ng/mL.

Discussion

The clinical features of the cataract in this family are not unique based on the office examination of the one affected phakic member. The prominent vacuoles are suggestive of a water and/or ion transport defect.

We sequenced the *MIP* gene on chromosome 12 that was in the region suggestive of linkage. *MIP* is the predominant membrane protein[74,75] in the lens. The homologous region of human chromosome 12, region q13, is mouse chromosome 10. Mutations of Mip (MP26) cause cataracts in the Fraser (CatFr),[76,77] lens opacity mutations (Lop),[77] hydropic fiber (Hfi),[78] and Tohoku[79] mice. In humans, missense mutations in exon 2 of *MIP* on the long arm of chromosome 12 (12q13) have been the basis of ADC in previously reported families.[30,80]

We identified the most likely region for the ADC gene in this family on chromosome 19 based on a lod score of 3.91 with *D19S903*. Fine mapping narrowed the region of the putative gene to a 10-cM (10-Mb) region on chromosome 19 flanked by *D19S220* and *D19S902*. The long arm of chromosome 19 has several interesting candidate genes that are expressed in the lens and are known to cause cataracts in mice and/or humans. We sequenced the exons and the intron–exon borders of the gene encoding *MIP* on chromosome 12 and genes for *LIM2*, *SIX5*, and *FTL* on chromosome 19 in members of this family;

TABLE 2. Primers for *LIM2, SIX5,* and *MIP*

Exon	PCR Fragment (bp)	Direction	Sequence 5′–3′
LIM2: Chromosome 19			
1	330	F	GTAGGGAGGCTTAAGGGATTTG
		R	GTTCTGAGCAAGGAATAGGCTG
2	313	F	TTCAAGTCCTGGGGATTCAGCTC
		R	TCTGGAATACAGGTGTCCTTGGC
2	178	F	CCAGTTCCTCCCTTCAAGTCCTG
		R	GACCCTGACAGCCGGTACTGC
3	679	F	GGTGTTTATGACACAGAACCAACC
		R	GTACACCAGCTAGTGTCAGATAG
3	426	F	CATTTTCATCTCAGAGGTAGCAG
		R	GTACACCAGCTAGTGTCAGATAG
3	Sequence only	I	CATTTTCATCTCAGAGGTAGCAG
4	287	F	GCTCTCTGAGGGCCTCCAAAATC
		R	GGGACACCCTGTCATCTTCCAC
5	459	F	CCACATGAGTCCCACAGCACTG
		R	TAACAACCTGCCAGGCAGACGG
5	244	F	CTCAGTTCTGGACTGTGGGTTTG
		R	GACCACCCTTACAGCTGTTTCTC
Promoter		F	AGGCTCTGCGACTCAGGTA
		R	AGAACAGGCCACCACCCAT
SIX5: Chromosome 19			
3′ UTR	1274	F	GAGCCCCAGAAATGCGGTTG
		R	CCGCGGCTCTTGCTGGAAGC
5′ UTR	1065	F	CCTCCTCACTTGCGCTGCTC
		R	CTCCCTCGGGCTTTCCCCAG
1	636	F	AAGCGCGGCCAGAGGCGGAG
		R	CAACACCGGGTCGCTGCCAC
	679	F	GCCACGCCGGCCGCTTGAGC
		R	CGGGTGCCTGTCCCGTCCAC
2	954	F	GAGCAGCTGGCTGGCTATG
		R	ACAGCCCCTCCCTCTCCGAGAT
3	770	F	TCTCCACTTCTCTCTGGCTTG
		R	TCAGCAACCGCATTTCTG
MIP Chromosome 12			
1	270	F	AAGGGGACTGTCCACCCAG
		R	TGGGCTCCACTGATGTGGC
1	306	F	GGCTATGGCATTTGGCTTGG
		R	CTGCACCAGTCAGGGAGTC
1	216	F	TCCTCTATAAAGGGGACTGTC
		R	GCCACCTGCAGAACATGCAG
1	300	F	CACTTCTCGTAGTCTCTCTTGCTG
		R	GCTGATCGCAGTTCCCACATGGC
2	263	F	AGGAGGTAACACTGTGGCAG
		R	GAATCCTTGAATGAGAAGTTGC
3	169	F	AAGCTGGGGTGCAGTAGGG
		R	GAGTGCTGGTACAGCAGCC
4	258	F	CAGCGTTGCTGCTCTGTCC
		R	TCAGCTGGAGCTTCTACAGG
4	254	F	GGGAACCTGTTGAACTGAACA
		R	TGGGGAGGAAGGGAAGTTTG
4	201	F	CTCAAGAGTATTTCTGAGAGAC
		R	ACAGTCTCTTTCTTCATCTAGG
4	279	F	GAATATACACATGCTAAGGTGTGG
		R	AGTCTCTCAAGAAATACTCTTGAGC

F, forward; R, reverse; I, Internal.

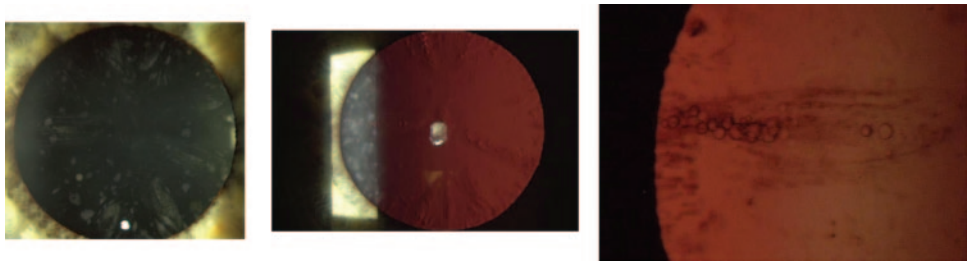

FIGURE 2. Right lens of proband. *Left*: white flecks were evident in the cortical region of the lens (direct illumination). *Center*: vacuoles were visible in the cortical region. *Right*: magnification of vacuoles and white opacities in the cortex. (Courtesy Denice Barsness, CRA, COMT, ROUB, FOPS, California Pacific Medical Center, San Francisco, CA.)

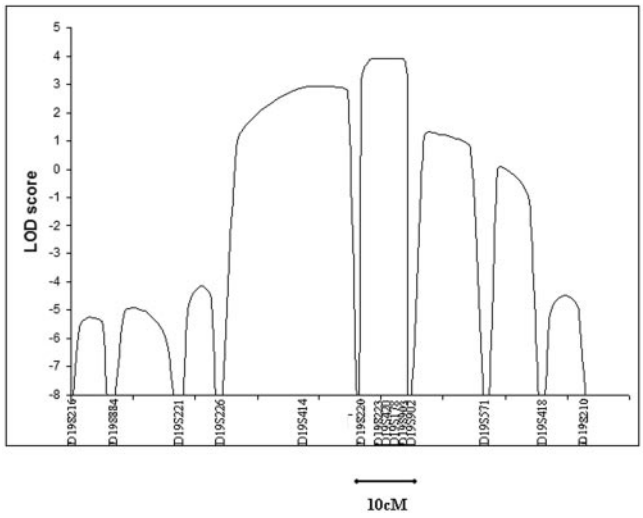

FIGURE 3. Multipoint analysis of mapped regions of chromosome 19.

the exons and the intron–exon borders matched the reference sequence in all. The number of CTG repeats in the 3′ untranslated DM1 region of *DMPK* on chromosome 19 was normal.

LIM2, an ideal candidate as the protein MP-20 (formerly MP-19) is expressed in the lens,[81] is 20 kDa and has four domains within the membrane.[82] Mutations of the gene in the To3 mouse cause a semidominant congenital cataract[83–85]; transgenic mice have cataracts.[86] Although the function of the protein is uncertain, it may play a role in the cellular transition from proliferation.[87] Zhou et al.[88] found similar proteins from primitive species such as *Chlamydia* and suggested important functions such as transport or enzymatic activities. In mouse studies, this protein regulates fiber cell differentiation.[89] Mutations of *LIM2* have been reported to cause an autosomal recessive presenile cataract in one family.[90]

Cataracts may occur as early as the teenage years in individuals with myotonic dystrophy. Myotonic dystrophy (DM1) is caused by an unstable repeat DNA sequence of triplet nucleotides (CTG) in the 3′ noncoding region of the myotonic dystrophy gene (*DMPK*) that encodes a serine-threonine protein kinase. An increased number of CTG repeats cause the disease. A second myotonic dystrophy locus is on chromosome 3. It is likely that there are several mechanisms for the disease. Altered splicing of the *DMPK* transcript may cause retention of the transcript in the nucleus,[91–94] or the *DMPK* RNA CUG repeat may exert a toxic gain-of-function on cellular metabolism.[95] Of importance in cataract formation, the expanded CTG nucleotide repeat may alter expression of neighboring genes. The expansion alters local chromatin structure and suppresses the expression of the *SIX5* gene,[96–98] which is the gene after the 3′ end of the *DMPK* gene. As cataracts develop in mice with one or two defective copies of the *SIX5* gene,[99,100] altered expression of the *SIX5* gene may be the basis of cataracts in myotonic dystrophy. *SIX5* transcripts are expressed in the adult epithelium of the cornea, lens, and ciliary body as well as the retina and sclera but are not expressed in the fetal eye.[101] We postulated that either an unusual clinical manifestation of myotonic dystrophy (cataracts alone) or a mutation of the *SIX5* gene may be the basis for the ADC4 phenotype. However, the sequence of *SIX5* gene and the number of repeats in the 3′ noncoding region of the *DMPK* gene in key members of this family were normal.

Hyperferritinemia is an ADC disorder with elevated serum levels of the light chain of ferritin.[102] Patients are asymptomatic aside from cataracts; however, there are mild abnormalities on liver biopsy. Many mutations of the light-chain ferritin gene have been reported from diverse regions of the world.[49–58,72,103–107] We found normal ferritin DNA sequence in two affected individuals and a normal ferritin level in one.

An autosomal recessive congenital nuclear cataract locus has been mapped recently to the 19q13 region in a large consanguineous Pakistani family[108]; in this family, the most likely region for the gene is between *D19S928* and *D19S425*, based on homozygosity of the region in four affected siblings. The locus in our family probably maps to a more distal region. As Riazuddin et al.[108] note, the distal obligate crossover event in their family is with marker *D19S420*. If this marker is taken as the distal flanking marker in their family, there is a small region of overlap with the mapped region between *D19S213* and *D19S420* (10 Mb) in our family. Although the lod scores in this area of overlap cannot completely exclude the region as

TABLE 3. Lod Scores between *ADC4* Disease Locus and Polymorphic Markers on Chromosome 19

		Lod Score						
Marker	**Mbp**	**($\theta_m = \theta_f = 0$)**	**0.001**	**0.05**	**0.1**	**0.2**	**0.3**	**0.4**
D19S216	4.9	−∞	−5.01	−1.63	−1.07	−0.55	−0.29	−0.12
D19S884	8.1	−∞	−2.91	−1.14	−0.79	−0.44	−0.24	−0.10
D19S221	12.6	−∞	−7.89	−2.79	−1.90	−1.02	−0.53	−0.22
D19S226	14.5	−∞	−5.39	−0.51	0.16	0.57	0.56	0.36
D19S414	36.6	0.60	0.60	0.54	0.47	0.34	0.21	0.10
D19S220	43.1	−∞	0.91	2.32	2.32	1.96	1.39	0.71
D19S223	46.1	1.81	1.80	1.65	1.49	1.13	0.74	0.33
D19S420	48.5	2.71	2.71	2.51	2.30	1.84	1.32	0.71
D19S178	49.1	0.90	0.90	0.84	0.77	0.61	0.44	0.24
D19S903	49.7	3.91	3.91	3.60	3.27	2.56	1.76	0.89
SIX5	51.0							
DMPK	51.0							
D19S902	53.0	−∞	0.91	2.32	2.32	1.98	1.45	0.79
FTL	54.2							
LIM2	56.6							
D19S571	58.0	−∞	−0.60	0.93	1.48	0.96	0.72	0.40
D19S418	60.2	−∞	−5.99	−1.07	−0.35	0.16	0.28	0.20
D19S210	61.7	−∞	−4.67	−1.28	−0.71	−0.24	−0.07	−0.01

Mb locations based on NCBI map, build 35.1.

containing a causative gene in both families, the most likely interpretation is that a different gene is involved in each family.

Based on linkage analyses and sequencing data, our ADC4 family with one member affected with irregularly shaped white or spherically shaped vacuolated cortical opacities probably represents a new locus on the short arm of chromosome 19.

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