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A Missense Mutation in the Human Connexin50 Gene (*GJA8*) Underlies Autosomal Dominant "Zonular Pulverulent" Cataract, on Chromosome 1q

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Summary

***CZP1*, a locus for autosomal dominant "zonular pulverulent" cataract, previously had been linked with the Duffy blood-group–antigen locus on chromosome 1q. Here we report genetic refinement of the *CZP1* locus and show that the underlying mutation is present in *GJA8*, the gene for connexin50. To map the *CZP1* locus we performed linkage analysis using microsatellite markers on two distantly related branches of the original Ev. pedigree, which now spans eight generations. Significantly positive two-point LOD score (*Z*) values were obtained for markers *D1S2669* (maximum *Z* [Z_{max}] = 4.52; maximum recombination frequency [θ_{max}] = 0) and *D1S514* (Z_{max} = 4.48; θ_{max} = 0). Multipoint analysis gave Z_{max} = 5.22 (θ_{max} = 0) at marker *D1S2669*. Haplotyping indicated that *CZP1* probably lies in the genetic interval *D1S2746*–(20.6 cM)–*D1S2771*. Sequence analysis of the entire protein-coding region of the *GJA8* gene from the pedigree detected a C→T transition in codon 88, which introduced a novel *Mnl*I restriction-enzyme site that also cosegregated with the cataract. This missense mutation is predicted to result in the nonconservative substitution of serine for a phylogenetically conserved proline (P88S). These studies provide the first direct evidence that *GJA8* plays a vital role in the maintenance of human lens transparency and identify the genetic defect believed to underlie the first inherited disease to be linked to a human autosome.**

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Introduction

Inherited cataract is a genetically heterogeneous lens disease that most often presents as a congenital, autosomal dominant Mendelian trait showing considerable inter- and intrafamilial clinical variation and high penetrance (Francois 1982; Merin 1991; Lund et al. 1992; Scott et al. 1994). At least nine independent loci for autosomal dominant cataract (ADC) have been mapped on human chromosomes 1p (Eiberg et al. 1995; Ionides et al. 1997), 1q (Renwick and Lawler 1963; OMIM 1997), 2q (Lubsen et al. 1987; Rogaev et al. 1996), 13q (Mackay et al. 1997), 16q (Marner et al. 1989), 17p (Berry et al. 1996), 17q11-q12 (Padma et al. 1995), 17q24 (Armitage et al. 1995), and 22q (Kramer et al. 1996).

Mutations in crystallin genes, which encode >90% of lens cytoplasmic proteins, have been identified at two of these ADC loci. Novel activation of the γE-crystallin pseudogene, on 2q, has been associated with the "Coppock-like" cataract (Brackenhoff et al. 1994), and a premature chain-termination mutation in the βB2-crystallin gene, on 22q, has been associated with "cerulean" cataract (Litt et al. 1997). In addition, the βA3/A1 crystallin gene, on 17q11β-q12, represents a strong candidate for "zonular sutural" cataract (Padma et al. 1995). Dominant mutations in the βB2-, γE-, and ζ-crystallin genes have also been associated with inherited cataract in the Philly mouse (Chambers and Russell 1991), the eye-lens–obsolescence mouse (Cartier et al. 1992), and the guinea-pig (Rodriguez et al. 1992), respectively. The discovery, however, of dominant cataract-causing mutations in the mouse genes for lens major intrinsic protein (Shiels and Bassnett 1996) and for lens intrinsic membrane protein 2 (Steele et al. 1997) indicates that lens genes other than those for crystallins may also be involved in human inherited cataract.

More than 30 years ago, a gene for "zonular pulverulent" cataract (CZP1; formerly "CAE1" [MIM 116200]) was shown to cosegregate in an autosomal dominant manner with the Duffy blood-group antigen in a six-generation English kindred (Renwick and Lawler 1963). Subsequently, the Duffy gene (*FY*) was linked to

chromosome 1 (Donahue et al. 1968), making CZP1 the first inherited disease to be linked to a human autosome (Renwick 1970). More recently, *FY* has been cytogenetically localized to 1q22-q23 (Mathew et al. 1994), and *GJA8,* the gene for gap-junction protein alpha-8 (MIM 600897), which encodes a connexin protein (Cx50) that is ~50 kD and that is primarily and abundantly expressed in the lens (White et al. 1992), has also been assigned to human chromosome 1 (Church et al. 1995). In addition, the mouse homologue for *GJA8* (*Gja8*) has been mapped to a chromosome 3 region that is reported to be syntenic with human chromosome 1q12-q21 (Kerscher et al. 1995). Thus, the predicted chromosomal location and the lens preferred expression of *GJA8* suggest that it is a likely candidate gene for CZP1. In order to directly test this hypothesis, we have performed linkage analysis to genetically refine the *CZP1* locus and have followed this by sequence analysis to identify the underlying mutation in the *GJA8* gene.

Subjects and Methods

Pedigree and Diagnosis

Using the registers at Moorfields Eye Hospital and Great Ormond Street Hospital (both in London), we traced two distantly related branches (fig. 1) of the original Ev. cataract family first described, in four generations, by Nettleship (1909) and then, in six generations, by Renwick and Lawler (1963). Although all of the affected family members traced in this study had undergone lens surgery, hospital records confirmed that the cataract usually either was present at birth or developed in infancy and that there was no family history of other ocular or systemic abnormalities. Autosomal dominant inheritance of the cataract was supported by the presence of affected individuals in each of the eight generations, equal numbers of affected males and females, and male-to-male transmission.

Historically, the Ev. cataract has been described as "lamellar" (Nettleship 1909) and then, after the invention of the slit lamp, either as zonular pulverulent with innumerable powdery opacities located in the nuclear (central) and perinuclear (lamellar) zones of the lens (Renwick and Lawler 1963) or as total nuclear cataract (Renwick 1970). It has been assumed (Waardenburg 1961) that the zonular pulverulent cataract of the Ev. pedigree is identical to Doyne's "discoid" cataract, which presents as a circular spotted disk in the center of the lens (Adams 1942) and is characteristic of the genealogically unrelated Coppock pedigree first described by Nettleship and Ogilvie (1906). Indeed the Coppock and Ev. cataracts have become synonymous; however, the former is confined to the tiny embryonic lens, whereas the latter involves the larger fetal lens,

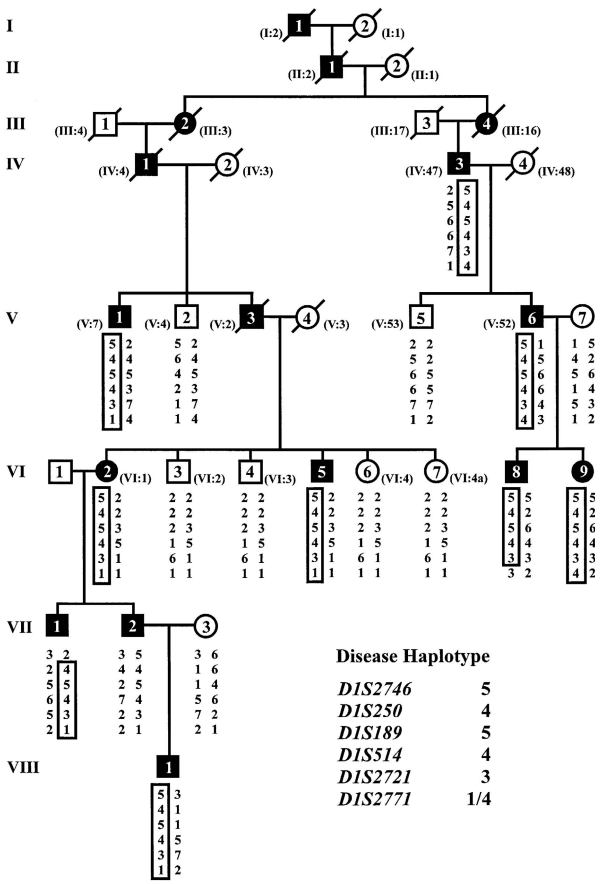

Figure 1 Abridged pedigree of the CZP1 (Ev.) family used in this study, showing segregation of six microsatellite markers on chromosome 1q, listed in descending order from the centromere. Squares and circles symbolize males and females, respectively; and unblackened and blackened symbols denote unaffected and affected individuals, respectively. Bracketed numbers denote individuals from the original Ev. pedigree constructed by Renwick and Lawler (1963).

which is more comparable in size to the nucleus of the adult lens. In addition, there is no conclusive evidence that the Coppock cataract is also linked to *FY* (Renwick 1970; also see MIM 116200).

Genotyping and Linkage Analysis

PCR-based genotyping using Généthon microsatellite markers (Dib et al. 1996) followed by linkage analysis, by means of the LINKAGE package of programs (Lathrop et al. 1984; Atwood and Bryant 1988), was performed essentially as described elsewhere (Mackay et al. 1997).

Sequencing

Exon 2 of the *GJA8* gene was amplified from genomic DNA by PCR using primers for codons 1–7 and 428–stop (table 1). PCR conditions were as follows: 1

Table 1

PCR Primers Used for Mutation Screening of the GJA8 Coding Exon

Codon	Direction	Sequence
1–7	Forward	5′-TATGGGCGACTGGAGTTTCCT
77–83	Forward	5′-CTCTGGGTGCTGCAGATCATC
97–103	Reverse	5′-CTCCATGCGGACGTAGTGCAC
102–108	Reverse	5′-TGCTTTTGCGCTTCTCCTCCA
169–175	Forward	5′-CACTACTTCCTGTACGGGTTC
209–215	Reverse	5′-CACAGAGGCCACAGACAACAT
257–263	Forward	5′-GTCTCCTCCATCCAGAAAGCC
312–318	Reverse	5′-CTCTTGGTAGCCCCGGGACAA
428–stop	Reverse	5′-TCATACGGTTAGATCGTCTGA

cycle at 94°C for 5 min; 30 cycles at 94°C for 1 min, 60°C for 1 min, and 72°C for 1 min; and then 1 cycle at 72°C for 5 min. PCR products of appropriate size were purified from agarose gels by means of the QIAquick gel-extraction kit (Qiagen) and then were TA subcloned by means of the pGEM-T vector system II (Promega). Plasmid DNA was purified by means of the QIAprep spin miniprep kit (Qiagen), and insert DNA was sequenced by means of the DyeDeoxy-terminator *Taq* FS cycle sequencing kit (Perkin-Elmer) and an ABI 377 automated sequencer. T7 and SP6 primers were used to sequence the 5′ and 3′ ends of the insert, and internal primers for codons 77–83, 102–108, 169–175, 209–215, 257–263, and 312–318 (table 1) were used to obtain overlapping sequence in both directions.

Restriction Analysis

Flanking primers for codons 77–83 and 97–103 (table 1) were used to amplify the novel *Mnl*I site in affected individuals and to exclude the 28 other *Mnl*I sites within the coding exon of the wild-type *GJA8* gene. PCR products of appropriate size (81 bp) were purified by means of the QIAquick PCR kit and then were digested with *Mnl*I (0.2 U/ml) at 37°C for 1 h, and the resulting restriction fragments (39 bp and 42 bp) were separated in 4% agarose gels stained with ethidium-bromide. The exon 2 fragment (1.3 kb) used for sequencing above was digested with *Sfi*I (1 U/ml) at 50°C for 2 h, and the resulting restriction fragments (620 bp and 680 bp) were separated in 1% agarose–ethidium bromide gels.

Results

CZP1 *Linkage Analysis*

Eighteen members of the pedigree, including 10 affected individuals, 6 unaffected individuals, and 2 spouses (fig. 1), were genotyped by means of 13 microsatellite markers from the Généthon $(AC)_n$ map (Dib et al. 1996) of chromosome 1. The two-point maximum LOD score (Z_{max}) (table 2) was obtained with marker *D1S2669* (Z_{max} = 4.52; maximum recombination fraction [θ_{max}] = 0). Multipoint analysis using markers *D1S2746, D1S2669, D1S442,* and *D1S2771* (fig. 2) yielded Z_{max} = 5.22 (θ_{max} = 0) at *D1S2669*. These microsatellite marker–derived Z_{max} values compare favorably with that determined elsewhere (Z_{max} = 3.78; θ_{max} = 0) with the Duffy blood-group alloantigen markers (Renwick and Lawler 1963).

Haplotype analysis (fig. 1) detected one affected male (VI-8) who was recombinant with regard to marker *D1S2771* and another affected male (VII-1) who was recombinant with regard to marker *D1S2746*. Notably, the disease allele at *D1S2771* differs in each family branch descended from affected females III-2 (allele 1) and III-4 (allele 4), suggesting that a recombination event

Table 2

Two-Point *Z* Values for Linkage between *CZP1* and Chromosome 1q Markers

Marker	Genetic Distance[a] (cM)	LOD Score at Recombination of .00	.01	.05	.10	.20	.30	.40	Z_{max}	θ_{max}
D1S2746	1.1	−∞	1.19	1.66	1.65	1.31	.84	.34	1.68	.07
D1S250	.6	3.52	3.46	3.19	2.84	2.10	1.31	.52	3.52	.00
D1S189	2.2	3.34	3.27	3.02	2.69	2.00	1.27	.52	3.34	.00
D1S2669	1.3	4.52	4.43	4.09	3.65	2.72	2.24	.76	4.52	.00
D1S514	1.1	4.48	4.40	4.07	3.64	2.73	1.77	.77	4.48	.00
D1S2696	1.1	3.49	3.44	3.22	2.91	2.21	1.44	.65	3.49	.00
D1S442	1.2	1.07	1.04	.95	.84	.62	.41	.20	1.07	.00
D1S2345	3.3	2.23	2.16	1.90	1.57	.90	.30	.00	2.23	.00
D1S305	1.6	2.34	2.28	2.05	1.76	1.17	.62	.20	2.34	.0
D1S2721	1.7	3.83	3.75	3.42	2.99	2.08	1.15	.35	3.83	.00
D1S506	2.7	1.11	1.09	.99	.86	.59	.33	.11	1.11	.00
D1S2635	2.7	.93	.92	.86	.76	.53	.31	.13	.93	.00
D1S2771		−∞	-1.84	-.57	-.14	.11	.12	.07	.13	.25

[a] Between the marker directly to the left and that directly below it; values are sex-averaged and are from Dib et al. (1996).

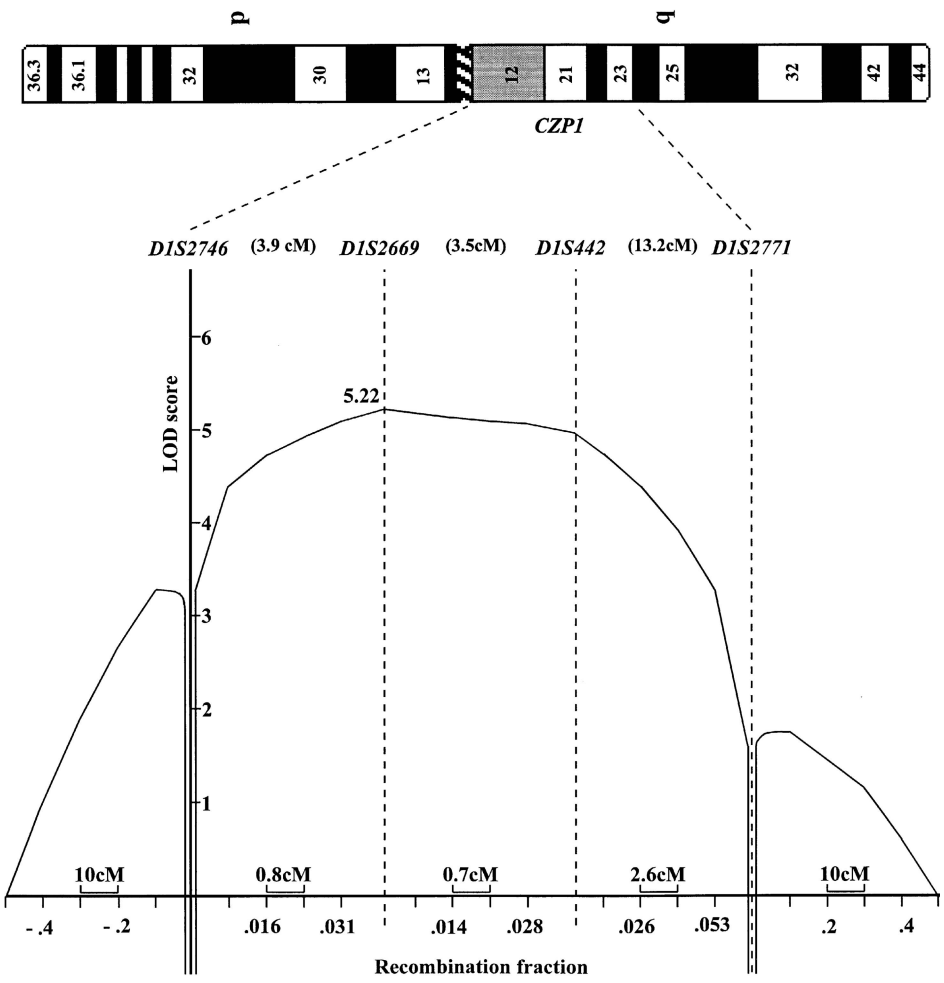

Figure 2 Multipoint linkage analysis between the *CZP1* locus and chromosome 1q microsatellite markers. An idiogram of human chromosome 1 shows the predicted cytogenetic location of *CZP1*, on the basis of both linkage to *FY* at 1q22-q23 (Mathew et al. 1994) and synteny of 1q12-q21 with *Gja8* on mouse chromosome 3 (Kerscher et al. 1995).

had also occurred in an ancestor of those individuals genotyped in this study. However, no individuals recombinant for the cataract locus and five other markers located between *D1S2746* and *D1S2771* were observed. Thus, the combined LOD-score value and haplotype data indicated that *CZP1* probably lies in the genetic interval *D1S2746*–(20.6 cM)–*D1S2771* (fig. 2).

GJA8 *Sequence Analysis*

In search of the CZP1 mutation, we amplified the single protein-coding exon of the *GJA8* gene from all 18 haplotyped members of the family who are depicted in figure 1. Sequence analysis of the resulting ~1.3-kb fragments revealed four significant changes from the published human *GJA8* sequence (Church et al. 1995). First, a C→G transversion at nucleotide 330 resulted in the conservative change of aspartate (GAC) to glutamate (GAG) at codon 110 (D110E). Second, an additional codon for alanine (GCG) was detected at nucleotides 331–333 (A111), extending the published human GJA8 protein sequence from 432 to 433 amino acids. Both E110 and A111 were also found to be conserved in the other known GJA8 sequences, from mouse (White et al. 1992), sheep (Yang and Louis 1996), and chicken (Jiang et al. 1994). Furthermore, these changes were present in both affected and unaffected members of the pedigree, indicating that neither D110E nor A111 is the CZP1 mutation. Third, an A→G transition at nucleotide 673 resulted in both the nonconservative substitution of glycine (GGC) for serine (AGC) at codon 225 (S225G) and the introduction of a unique *Sfi*I restriction-enzyme site ($GGCCN_4\downarrow NGGCC$). Restriction analysis confirmed that this change was present in both affected and unaffected members of the pedigree, and it was also detected in 25 unrelated normal individuals (data not shown), effectively excluding S225G as the CZP1 mu-

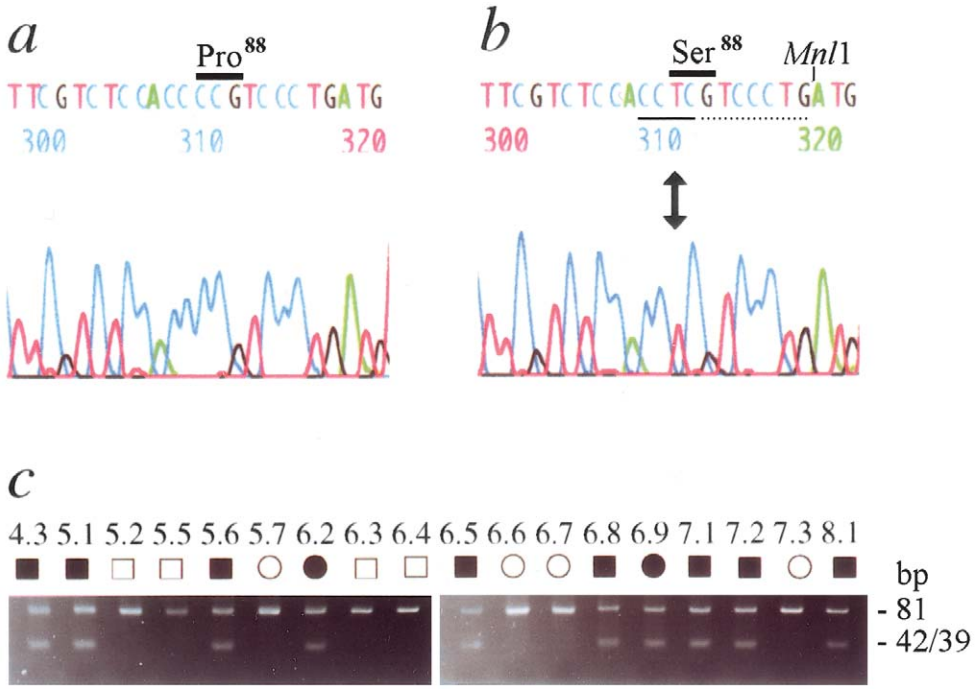

Figure 3 Sequence analysis of the *CJA8* gene from the CZP1 pedigree shown in figure 1. *a,* Wild-type allele showing a phylogenetically conserved proline (CCG) at codon 88. *b, CZP1* allele showing a C→T transition (*arrow*) that results in the substitution of serine (TCG) at codon 88. *c,* Restriction-fragment-length analysis showing gain of an *Mnl*I site ($CCTCN_{7/7}$ in *b*) that cosegregates with affected individuals (*blackened symbols*) heterozygous for the P88S mutation (81 bp and 39/42 bp) but not with unaffected individuals and spouses (81 bp).

tation. Finally, a C→T transition at nucleotide 262 resulted in both a nonconservative substitution of serine for proline at codon 88 (P88S) and the introduction of an *Mnl*I restriction site (fig. 3). Restriction analysis confirmed that this change was present only in affected members of the pedigree (fig. 3), and it was not detected in 102 unrelated normal individuals (data not shown), indicating that P88S is the CZP1 mutation rather than a GJA8 polymorphism.

Discussion

Using a combination of linkage and sequence analyses we have genetically refined the *CZP1* locus to a 20-cM interval between markers *D1S2746* and *D1S2771* on the long arm of chromosome 1 and have identified a P88S missense mutation in *GJA8,* the gene for Cx50, that cosegregates with the cataract. Our data give a genetic-map location for *GJA8* and constitute the first report implicating a connexin gene in human inherited cataract.

The connexin-gene family encodes gap-junction–channel proteins that mediate the intercellular transport of small (<1 kD) biomolecules, including ions, metabolites, and second messengers in diverse vertebrate tissues such as the brain, heart, liver, and lens (for a recent review, see Kumar and Gilula 1997). At least eight genes for connexins of varying molecular mass (~26–50 kD) have been identified in humans, and mutations in the genes for Cx26 (*GJB2*), Cx32 (*GJB1*), and Cx43 (*GJA1*) have been associated with certain forms of sensorineural deafness (Kelsell et al. 1997; Zelante et al. 1997), Charcot-Marie-Tooth neuropathy (Bergoffen et al. 1993), and visceroatrial heterotaxia (Britz-Cunningham et al. 1995), respectively.

The P88S mutation identified here is centrally located within the putative second transmembrane domain (M2) of Cx50. Sequence comparison of all the known vertebrate connexins shows that this M2 proline is strictly conserved at either codon 87, codon 88, or codon 89, across species including the zebrafish, frog, chicken, and mouse (GenBank accession numbers 1008909, 117709, 544115, and 117716 http:/ncbi.nln.nih.gov/entrez/). In vitro mutagenesis of this phylogenetically conserved proline, supports the view that it functions in voltage gating of gap -junctions (Suchyna et al. 1993). Significantly, inherited P87S (Bort et al. 1997; Janssen et al. 1997) and P87A (Nelis et al. 1997) mutations in the human *Cx32* gene have been associated with Schwann-cell dysfunction and peripheral nerve degeneration in X-linked dominant Charcot-Marie-Tooth disease. These obser-

vations raise the possibility that mutation of the M2 proline may impair voltage-dependent opening and closing of gap junctions in electrically excitable tissues. However, both the physiological significance of such voltage gating in the noninnervated lens and its role in cataractogenesis remain to be established.

Note added in proof.—During the preparation of the manuscript of this article, Geyer et al. (1997) reported cytogenetic mapping of the human *Cx50* gene to band region 1q21.1, and White et al. (1997) reported that Cx50-deficient mice develop cataract.

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References

Adams PH (1942) Doyne's discoid cataract (Coppock). Br J Ophthalmol 26:152–153

Armitage MM, Kivlin JD, Ferrell RE (1995) A progressively early onset cataract gene maps to human chromosome 17q24. Nat Genet 9:37–40

Attwood J, Bryant SA (1988) A computer program to make analysis with LIPED and LINKAGE easier to perform and less prone to input errors. Ann Hum Genet 52:259

Bergoffen J, Scherer SS, Wang S, Oronzi Scott M, Bone LJ, Paul DL, Chen K, et al (1993) Connexin mutations in X-linked Charcot-Marie-Tooth disease. Science 262: 2039–2042

Berry V, Ionides ACW, Moore AT, Plant C, Bhattacharya SS, Shiels A (1996) A locus for autosomal dominant anterior polar cataract on chromosome 17p. Hum Mol Genet 5: 415–419

Bort S, Nelis E, Timmerman V, Sevilla T, Cruz-Martinez A, Martinez F, Millan JM, et al (1997) Mutational analysis of the MPZ, PMP22 and Cx32 genes in patients of Spanish ancestry with Charcot-Marie-Tooth disease and hereditary neuropathy with liability to pressure palsies. Hum Genet 99: 746–754

Brakenhoff RH, Henskens HAM, van Rossum MWPC, Lubsen NH, Schoenmakers JGG (1994) Activation of the γE-crystallin pseudogene in the human hereditary Coppock-like cataract. Hum Mol Genet 3:279–283

Britz-Cunningham SH, Shah MM, Zuppan CW, Fletcher WH (1995) Mutations of the connexin43 gap-junction gene in patients with heart malformations and defects of laterality. N Engl J Med 332:1323–1329

Cartier M, Breitman ML, Tsui L-C (1992) A frameshift mutation in the gE-crystallin gene of the Elo mouse. Nat Genet 2:42–45

Chambers C, Russell P (1991) Deletion mutation in an eye lens β-crystallin. J Biol Chem 266:6742–6746

Church RL, Wang J-H, Steele E (1995) The human lens intrinsic membrane protein MP70 (CX50) gene: clonal analysis and chromosome mapping. Curr Eye Res 14:215–221 (erratum: 14:979–981)

Dib C, Faure S, Fizames C, Samson D, Drouot N, Vignal A, Millasseau P, et al (1996) A comprehensive genetic map of the human genome based on 5,264 microsatellites. Nature 380:152–154

Donahue RP, Bias WB, Renwick JH, McKusick VA (1968) Probable assignment of the Duffy blood group locus to chromosome 1 in man. Proc Natl Acad Sci USA 61:949–955

Eiberg H, Lund AM, Warburg M, Rosenberg T (1995) Assignment of congenital cataract Volkmann type (CCV) to chromosome 1p36. Hum Genet 96:33–38

Francois J (1982) Genetics of cataract. Ophthalmologica 184: 61–71

Geyer DD, Church RL, Steele EC, Heinzmann C, Kojis TL, Klisak I, Sparkes RS, et al (1997) Regional mapping of the human MP70 (Cx50; connexin 50) gene by fluorescence in situ hybridization to 1q21.1. Mol Vis 3:13 (http://www.emory.edu/molvis/v3/geyer)

Ionides ACW, Berry V, Mackay DS, Moore AT, Bhattacharya SS, Shiels A (1997) A locus for autosomal dominant posterior polar cataract on chromosome 1p. Hum Mol Genet 6:47–51

Janssen EAM, Kemp S, Hensels GW, Sie OG, de Die-Smulders CEM, Hoogendijk JE, de Visser M, et al (1997) Connexin32 gene mutations in X-linked dominant Charcot-Marie-Tooth disease (CMTX1). Hum Genet 99:501–505

Jiang JX, White TW, Goodenough DA, Paul DL (1994) Molecular cloning and functional characterization of chick lens fiber connexin 45.6. Mol Biol Cell 5:363–373

Kelsell DP, Dunlop J, Stevens HP, Lench NJ, Liang JN, Parry G, Mueller RF, et al (1997) Connexin 26 mutations in hereditary non-syndromic sensorineural deafness. Nature 387: 80–83

Kerscher S, Church RL, Boyd Y, Lyon MF (1995) Mapping of four genes encoding eye lens-specific structural, gap junction and integral membrane proteins: *Cryba1* (crystallinβA3/A1), *Crybb2* (Crystallinβb2), *Gja8* (MP70) and *Lim2* (MP19). Genomics 29:445–450

Kramer P, Yount J, Mitchell T, LaMorticella D, Carrero-Valenzuela R, Lovrien E, Maumenee I, et al (1996) A second locus for cerulean cataract maps to the beta-crystallin region on chromosome 22. Genomics 35:539–542

Kumar NM, Gilula NB (1997) The gap junction communication channel. Cell 84:381–388

Lathrop GM, Lalouel JM, Julier C, Ott J (1984) Strategies for multipoint linkage analysis in humans. Proc Natl Acad Sci USA 81:3443–3446

Litt M, Carrero-Valenzuela R, LaMorticella DM, Schultz DW, Mitchell TN, Kramer P, Maumenee IH (1997) Autosomal

dominant cerulean cataract is associated with a chain termination mutation in the human β-crystallin gene CRYBB2. Hum Mol Genet 6:665-668

Lubsen NH, Renwick JH, Tsui L-C, Breitman ML, Schoenmakers JGG (1987) A locus for a human hereditary cataract is closely linked to the γ-crystallin gene family. Proc Natl Acad Sci USA 84:489-492

Lund AM, Eiberg H, Rosenberg T, Warburg M (1992) Autosomal dominant congenital cataract: linkage relations: clinical and genetic heterogeneity. Clin Genet 41:65–69

Mackay D, Ionides A, Berry V, Moore A, Bhattacharya S, Shiels A (1997) A new locus for dominant "zonular pulverulent" cataract, on chromosome 13. Am J Hum Genet 60:1474–1478

Marner E, Rosenberg T, Eiberg H (1989) Autosomal dominant congenital cataract: morphology and genetic mapping. Acta Ophthalmol 67:151–158

Mathew S, Chaudhuri A, Murty VVVS, Pogo AO (1994) Confirmation of Duffy blood group antigen locus (FY) at 1q22-q23 by fluorescence in situ hybridization. Cytogenet Cell Genet 67:68

Merin S (1991) Inherited cataracts. In: Merin S (ed) Inherited eye disease: diagnosis and clinical management. Marcel Dekker, New York, pp 86–120

Nelis E, Simokovic S, Timmerman V, Lofgren A, Backhovens H, De Jonghe P, Martin J-J, et al (1997) Mutation analysis of the connexin 32 (Cx32) gene in Charcot-Marie-Tooth neuropathy type 1: identification of five new mutations. Hum Mutat 9:47–52

Nettleship E (1909) Seven new pedigrees of hereditary cataract. Trans Ophthalmol Soc UK 29:188–211

Nettleship E, Ogilvie FM (1906) A peculiar form of hereditary congenital cataract. Trans Ophthalmol Soc UK 26:191–207

Online Mendelian inheritance in man (OMIM) (1997) Johns Hopkins University, Baltimore. http://www.ncbi.nlm.nih.gov.omim/

Padma T, Ayyagari R, Murty JS, Basti S, Fletcher T, Rao GN, Kaiser-Kupfer M, et al (1995) Autosomal dominant zonular cataract with sutural opacities localized to chromosome 17q11-q12. Am J Hum Genet 57:840–845

Renwick JH (1970) Eyes on chromosomes. J Med Genet 7: 239–243

Renwick JH, Lawler SD (1963) Probable linkage between a congenital cataract locus and the duffy blood group locus. Ann Hum Genet 27:67–84

Rodriguez IR, Gonzalez P, Zigler JS, Borras T (1992) A guinea-pig hereditary cataract contains a splice-site deletion in a crystallin gene. Biochim Biophys Acta 1180:44–52

Rogaev EI, Rogaeva EA, Korovaitseva GI, Farrar LA, Petrin AN, Keryanov SA, Turaeva S, et al (1996) Linkage of polymorphic congenital cataract to the γ-crystallin gene locus on human chromosome 2q33-q35. Hum Mol Genet 5: 699–703

Scott MH, Hejtmancik JF, Wozencraft LA, Reuter LM, Parks MM, Kaiser-Kupfer MI (1994) Autosomal dominant congenital cataract–interocular phenotypic variability. Ophthalmology 101:866–871

Shiels A, Bassnett S (1996) Mutations in the founder of the MIP gene family underlie cataract development in the mouse. Nat Genet 12:212–215

Steele EC, Kerscher S, Lyon MF, Glenister PH, Favor J, Wang JH, Church RL (1997) identification of a mutation in the MP19 gene, LIM2, in the cataractous mouse mutant To3. Mol Vis 3:5 (http://www.emory.edu/molvis/v3/steele)

Suchyna TM, Xu LX, Gao F, Fourtner CR, Nicholson BJ (1993) Identification of a proline residue as a transduction element involved in voltage gating of gap junctions. Nature 365:847–849

Waardenburg PJ (1961) The lens. In: Waardenburg PJ, Franceschetti A, Klein D (eds) Genetics and ophthalmology. Vol 1. Blackwell Scientific, Oxford; Royal VanGorcum, Assen; CC Thomas, Springfield, IL, pp 863–865

White TW, Bruzzone R, Goodenough DA, Paul DL (1992) Mouse Cx50, a functional member of the connexin family of gap junction proteins, is the lens fiber protein MP70. Mol Biol Cell 3:711–720

White TW, Goodenough DA, Paul D (1997) Ocular abnormalities in connexin50 knockout mice. Mol Biol Cell 8:93

Yang D-I, Louis CF (1996) Molecular cloning of sheep connexin49 and its identity with MP70. Curr Eye Res 15: 307–314

Zelante L, Gasparini P, Estivill X, Melchionda S, D'Agruma L, Govea N, Mila M, et al (1997) Connexin26 mutations associated with the most common form of non-syndromic neurosensory autosomal recessive deafness (DFNB1) in Mediterraneans. Hum Mol Genet 6:1605–1609