Am. J. Hum. Genet. 67:1592–1597, 2000

Report

A Locus for Autosomal Dominant Colobomatous Microphthalmia Maps to Chromosome 15q12-q15

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Congenital microphthalmia is a common developmental ocular disorder characterized by shortened axial length. Isolated microphthalmia is clinically and genetically heterogeneous and may be inherited in an autosomal dominant, autosomal recessive, or X-linked manner. Here, we studied a five-generation family of Sephardic Jewish origin that included 38 members, of whom 7 have either unilateral or bilateral microphthalmia of variable severity inherited as an autosomal dominant trait with incomplete penetrance. After exclusion of several candidate loci, we performed a genome-scan study and demonstrated linkage to chromosome 15q12-q15. Positive LOD scores were obtained with a maximum at the D15S1007 locus (maximum LOD score 3.77, at recombination fraction 0.00). Haplotype analyses supported the location of the disease-causing gene in a 13.8-cM interval between loci D15S1002 and D15S1040.

Congenital microphthalmia (CMIC [MIM 600165]) is an ocular malformation characterized by a small eye attested by shortened axial length (Weiss et al. 1989; Warburg 1993). The reported prevalence of CMIC at birth is ~1.5/10,000 in white populations (Warburg 1993; Bermejo et al. 1998; Busby et al. 1998). Severity of the disease often ranges from mild to extreme microphthalmia (anophthalmia) within a single family, suggesting variable gene expression (Warburg 1993). Also, microphthalmia is often asymmetric or unilateral, suggesting that nongenetic factors or somatic genetic events may also contribute to the phenotype. Some other ocular abnormalities—namely, cataracts, microcornea, sclerocornea, retinal coloboma, and optic-nerve coloboma—are considered to be part of the spectrum of anomalies found in isolated CMIC (Warburg 1993). Nonocular abnormalities are associated with microphthalmia in 80% of cases. Chromosomal abnormalities of virtually all chromosomes may result in syndromic microphthalmia, trisomy 13 being the most frequently observed. Moreover, environmental teratogens such as alcohol, rubella, toxoplasma, or cytomegalovirus may also cause microphthalmia (Warburg 1993).

Although most cases of nonsyndromic microphthalmia are sporadic, a few families with autosomal dominant (Pearce 1986; Vingolo et al. 1994; Fryns 1995; Othman et al. 1998), autosomal recessive (Bateman 1984; Kohn et al. 1988; Ghöse et al. 1991; Warburg 1993; Zlotogora et al. 1994; Bessant et al. 1998, 1999) or, more seldom, X-linked recessive inheritance of the trait (Hoefnagel et al. 1963) have been hitherto reported. Human eye development begins as early as the fourth week of gestation and proceeds through the embryonic and fetal life (for reviews, see Jean et al. 1998; van Heyningen 1998). Many transcription factors and growth factors are involved in mammalian eye development (for reviews, see Freund et al. 1996; Graw 1996; Jean et al. 1998). Recently, mutations in the *CHX10* homeobox gene were identified in two families presenting with nonsyndromic microphthalmia (Percin et al. 2000), and mutations in both alleles of the *RX* gene were identified in a patient with severe congenital microphthalmia (Vo-

Received July 24, 2000; accepted for publication September 21, 2000; electronically published October 13, 2000.

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0002-9297/2000/6706-0027$02.00

ronina and Mathers 2000). Two other loci for human isolated microphthalmia/anophthalmia were previously identified on chromosome 14q32 (Bessant et al. 1998) and 11p (Othman et al. 1998).

Here, we report a study of a five-generation family of Sephardic Jewish origin, including 38 members (fig. 1). Thirty-five individuals were evaluated by ophthalmologic examination by one of the authors (J.-C.Z.) in most cases and by general examination by four of the authors (J.-C.L., A.R.-R., H.P., and P.E.). Inclusion criteria for microphthalmia was reduction of the total axial length <20 mm in at least one eye, determined by use of ultrasonography (table 1). Seven individuals were considered to be affected, since they had either unilateral or bilateral microphthalmia of variable severity. Five affected individuals had an ocular prosthesis in at least one eye. Two individuals, IV:10 and V:2, were designed as of uncertain status, since they had ocular anomalies but normal axial length of both eyes. The disease trait appears to be inherited in an autosomal dominant manner with incomplete penetrance and variable expression. For example, individual IV:10, who carries the mutant allele, has corneal clouding and iridocorneal synechia (Peters' anomaly [MIM 604229]) but no microphthalmia, whereas individuals IV:14 and V:4 have unilateral optic-nerve agenesis associated with other ocular abnormalities. This illustrates that virtually any structure of the eye may be involved in the family described here. Neither associated extraocular anomaly nor mental retardation was observed, except in affected individual IV:17, who has cleft lip and palate. Karyotypes performed on blood lymphocytes in individuals IV:10 and IV:14 were normal. Blood sampling was done in each case after informed consent was obtained by clinicians.

Genomic DNA was extracted from blood leukocytes using the QIAamp Maxi Kit (Qiagen). We first analyzed microsatellite DNA markers mapping to seven candidate loci, using the chemoluminescent detection method (Vignal et al. 1993). We studied linkage to the following genes: *CHX10* (loci D14S63, D14S74, and D14S68), *PAX2* (Sanyanusin et al. 1996; Eccles et al. 1999), *PAX6* (Martha et al. 1993; for review, see Prosser and van Heyningen 1998), *MITF* (locus D3S3633; for review, see Jean et al. 1998), and *HRY* (loci D3S1265 and D3S1314;

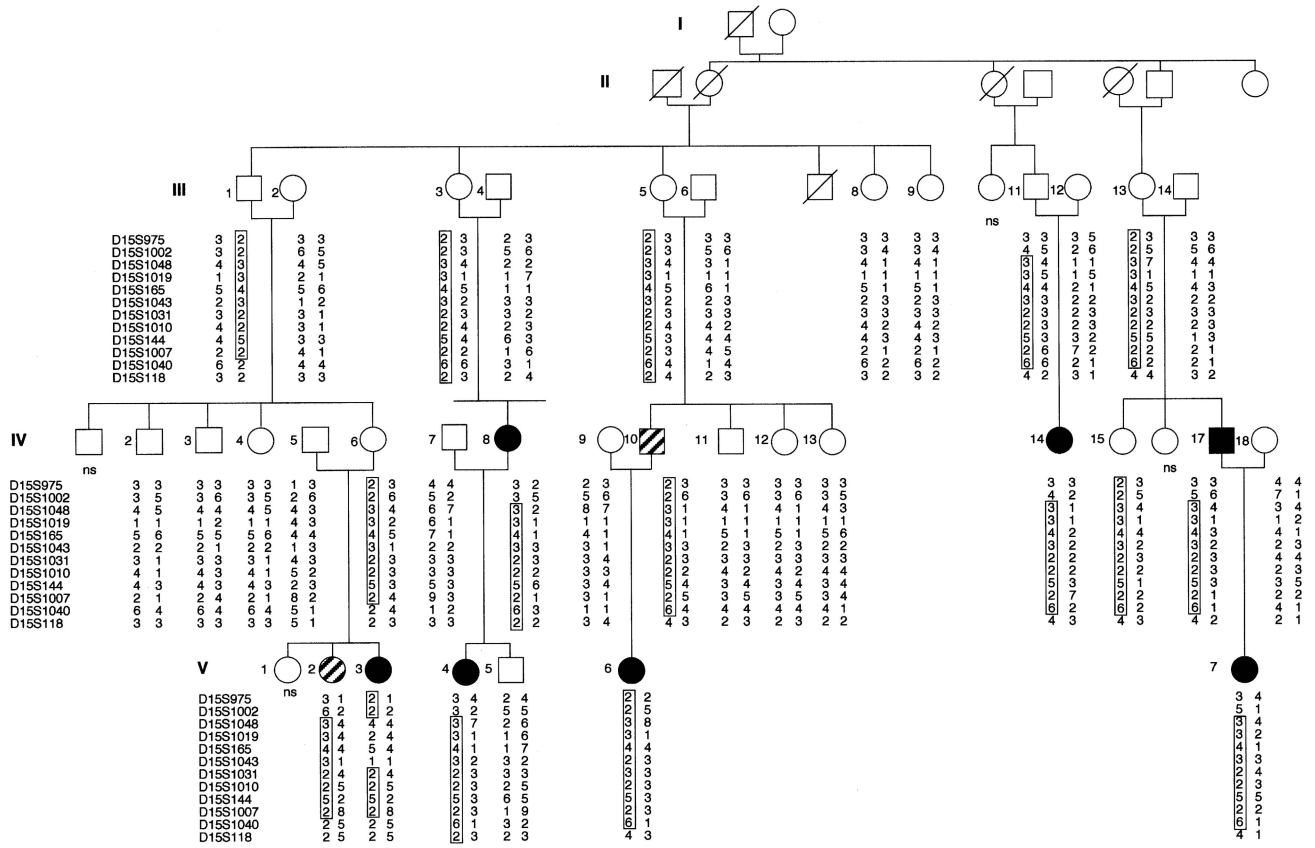

Figure 1 Pedigree of the family studied and haplotypes obtained using 12 microsatellite DNA markers located on chromosome 15q. Blackened symbols indicate affected individuals; hatched symbols represent individuals with uncertain status. NS = not studied. The disease-associated haplotype is boxed.

for review, see Freund et al. 1996) and the following loci: 11p (markers D11S905, D11S4109, D11S4113, and D11S1314; Othman et al. 1998) and 14q32 (markers D14S62, D14S65, and D14S78; Bessant et al. 1998).

Next, we performed a genome-scan analysis using fluorescent microsatellite markers (ABI prism linkage mapping panels LMSV2). PCR amplifications were performed according to the manufacturer's recommended protocols (PE Biosystems). PCR products were denaturated and size-fractionated on a 6% denaturing polyacrylamide gel run on an ABI373 sequencer. GENESCAN and GENOTYPER software was used to determine the size of alleles. Additional fluorescent markers were analyzed—namely, D15S975, D15S1019, D15S1040, and D15S118 from the ABI prism linkage mapping set; HD5; and Généthon markers D15S1043, D15S1031, D15S1010, and D15S144 (Dib et al. 1996).

A two-point LOD-score analysis was computed using the LINKAGE program of the LINKAGE package version 5.2 (Lathrop and Lalouel 1984), under the assumption of an autosomal dominant model with an estimated penetrance of 50% and a frequency of the mutant gene of 1/14,000. Allele frequencies were estimated from family data. For haplotype analysis, we only considered affected individuals and obligate carriers of the disease-causing gene, owing to the incomplete penetrance of the disease.

We first excluded the seven analyzed candidate loci. We found LOD scores consistently <-2 at each of these loci, demonstrating absence of linkage to the disease gene in the family presented here (data not shown). We then performed a genome scan study and found a maximum LOD score (Z_{max}) between the disease locus and microsatellite DNA marker D15S1007 ($Z_{max} = 3.77$ at recombination fraction [θ] 0; table 2). Additional two-point LOD scores obtained with 11 other surrounding markers are shown in table 2. Another marker gave a positive LOD score >3 at $\theta = 0$, and two other markers gave positive LOD scores >1.9 at $\theta = 0$.

Haplotype analysis (fig. 1) showed a telomeric recombination event between markers D15S1007 and D15S1040 in individual III:1, placing the disease-causing gene centomeric to the marker D15S1040. Similarly, recombination events between loci D15S1002 and D15S1048 occurred in individuals III:11, IV:8, and IV:17, indicating that the disease gene is telomeric to locus D15S1002. Thus, in this family, the disease gene lies within a 13.8-cM region on chromosome 15q12-q15, bounded proximally by locus D15S1002 and distally by locus D15S1040. Moreover, two recombinations occurred in affected individual V:3, on the disease-associated chromosome inherited from individual IV:6 (fig. 1)—the first one between loci D15S1002 and D15S1048 and the second one between loci D15S1043 and D15S1031. This result allows the exclusion of a 2.2-cM region, flanked by loci D15S1048 and D15S1043 and located within the 13.8-cM candidate interval. Thus, two genetic intervals—encompassing, respectively, 4.5 cM between loci D15S1002 and D15S1048 and 7.1 cM between loci D15S1043 and D15S1040—are likely to contain the disease-causing gene. To date, we have not been able, by using other microsatellite DNA mark-

Table 1

Clinical Features of Individuals with Affected or Uncertain Status

Individual	Age	Sex	Status	Total Axial Length[a] (mm)	Other Ocular Anomalies
IV:8	34	F	A	RE: 18.0 (microphthalmia)	Sclerocornea
				LE: 21.0	
IV:10[b]	27	M	U	RE: 26.5	Iridocorneal synechy, corneal clouding, ptosis, strabismus, myopia
				LE: 26.5	Myopia
IV:14	12	F	A	RE: Prothesis (anophthalmia)	
				LE: Normal	Iris coloboma, optic-nerve agenesis
IV:17	50	M	A	RE: Normal	
				LE: Prothesis (microphthalmia)	
V:2	12	F	U	RE: 21.5	Remnant pupillar membranes
				LE: 21.5	
V:3	15	F	A	RE: 21.5	
				LE: Prothesis (microphthalmia)	
V:4	13	F	A	RE: 21.0	
				LE: 19.0 (microphthalmia)	Retinal coloboma, optic-nerve agenesis
V:6	3	F	A	RE: Microphthalmia	Corneal clouding
				LE: Prothesis (anophthalmia)	
V:7	18	F	A	RE: Prothesis (anophthalmia)	
				LE: Prothesis (anophthalmia)	

NOTE.—RE = right eye; LE = left eye; A = affected; U = uncertain status.

[a] Not available for eyes with prothesis and was not determined for patient V:6 (right eye). Microphthalmia is defined by total axial length (TAL) <20 mm.

[b] Has normal TAL of both eyes, but has other eye anomalies.

Table 2

Two-Point LOD Scores between Microphthalmia and 12 Chromosome 15q Microsatellite DNA Markers

	LOD Score at θ =						
Marker	0	.01	.05	.1	.2	.3	.4
D15S975	−1.394	−.641	.438	.827	.865	.605	.256
D15S1002	−7.790	−.939	.842	1.357	1.441	1.090	.557
D15S1048	.338	2.501	2.877	2.762	2.179	1.409	.579
D15S1019	.443	2.542	2.902	2.770	2.162	1.388	.590
D15S165	.411	2.574	2.951	2.837	2.256	1.483	.639
D15S1043	−1.514	.003	.544	.657	.586	.401	.189
D15S1031	2.936	2.869	2.598	2.252	1.554	.891	.351
D15S1010	1.906	1.866	1.706	1.503	1.093	.693	.324
D15S144	3.743	3.669	3.370	2.984	2.173	1.339	.576
D15S1007	3.771	3.699	3.404	3.022	2.214	1.364	.565
D15S1040	.188	1.581	1.997	1.947	1.526	.978	.439
D15S118	−1.256	−1.023	−.163	.143	.257	.230	.149

ers (not shown), to exclude the entire D15S1002–D15S1048 interval on the basis of haplotype analysis.

The present study strongly suggests the assignment of a nonsyndromic autosomal dominant microphthalmia gene to chromosomal region 15q12-q15 within a 13.8-cM interval bounded by loci D15S1002 and D15S1040. On the basis of haplotype analysis, a 2.2-cM region defined by loci D15S1048 and D15S1043 and located within the 13.8-cM critical interval was excluded. Indeed, we observed a double recombination in patient V:3 within a 6.8-cM interval defined by loci D15S1002 and D15S1031. The probability of such an event is very low, ~0.5%. However, it is worth noting that both recombination events occurred close to potential hotspots for recombinations (Amos-Landgraf et al. 1999; Christian et al. 1999).

Clinical expression of the disease was extremely variable in individuals carrying the disease-associated haplotype. For example, patients IV:8 and V:4 had unilateral microphthalmia, and patient V:7 had bilateral anophthalmia. Such an intrafamilial variable expression of the disease has been described elsewhere in families with microphthalmia (Warburg 1993; Zlotogora et al. 1994; Fryns 1995; Bessant et al. 1999). More surprisingly, patient IV:10 had no microphthalmia but did have Peters' anomaly, including corneal clouding, iridocorneal synechy, and ptosis, whereas patient IV:14 had unilateral anophthalmia and controlateral isolated optic-nerve agenesis, with a normal ocular globe. The latter observation suggests that anterior segment dysgenesis may be allelic to posterior segment anomalies, at least in the family reported here. Incidentally, individual V:2, who inherited part of the disease-associated haplotype, had remnant pupillar membranes, a feature that may be encountered in normal eyes. It is striking that each of the five carriers of the disease-causing gene in generation III has normal eyes, whereas only 2/6 carriers in generation IV are considered to be unaffected, and 0/4 patients with the entire disease-associated haplotype in generation V are unaffected. The apparently increasing penetrance of the disease trait through successive generations may suggest anticipation, a feature usually associated with trinucleotide-repeat expansion. Alternatively, considering the small number of individuals studied, we cannot exclude that this observation may be fortuitous. The phenomenon of anticipation has been proposed previously, to explain a similar observation of increased penetrance in subsequent generations in a family with iris coloboma (Barros-Nunez et al. 1995).

More than forty transcription factors are expressed during mammalian eye development (Freund et al. 1996; Jean et al. 1998). To our knowledge, none of these genes have been mapped to the candidate interval defined by loci D15S1002 and D15S1040 (Genome Database). Since the homozygous knockout of the Hairy Enhancer of Split homologue 1 (*HES1*) gene in mouse leads to abnormal eye development (Tomita et al. 1996), the *TLE3* gene, which belongs to a family of corepressors coacting with HES proteins, should be considered as a candidate gene. However, the precise genetic location of the *TLE3* gene with respect to our candidate interval remains to be determined (Richard et al. 1994; Liu et al. 1996). At least six expressed-sequenced tags (ESTs), previously obtained from retinal tissues, map within the D15S1002-D15S1040 candidate interval (GeneMap'99 database). One of these ESTs, stSG29857, is expressed in fetal retina and may contain cDNA sequence of a candidate gene.

It is interesting to note that severe syndromic bilateral microphthalmia was associated with an apparently balanced de novo reciprocal translocation 46, XY, t(1;15)(q41;q21.2), suggesting that either the 1q41 or 15q21.2 regions may contain a gene that is important for eye morphogenesis (Smith et al. 1994). On the other hand, interstitial deletions of chromosome 15q13-q15 (Autio et al. 1988), 15q12-q14 (Tonk et al. 1995), and 15q21.2-q22.1 (Martin et al. 1990) were not associated with eye malformation, suggesting that this disorder is not the result of haploinsufficiency of a gene in this region.

Since a large number of genes appear to be involved in vertebrate eye development, the linkage analysis presented here in a large family with autosomal dominant isolated microphthalmia provides an opportunity to focus on a specific area of the genome, namely the proximal long arm of chromosome 15. Efforts are being undertaken with the aim of identifying the disease gene itself.

Acknowledgments

We thank family members for their cooperation; Dr. I. Legal and C. Vaury from the Centre d'Etude du Polymorphisme Hu-

main (CEPH) for multiplex PCR advice; Dr. M. C. Babron (Unité INSERM 535), Dr. M. Sahbatou (CEPH), and the Centre de Ressources Infobiogen (Evry, France) for their help in bioinformatics; and A. Reumert-Kazès for her help in preparing this manuscript. This work was supported by the Hospices Civils de Lyon, the Association Rétina France, the Centre National de la Recherche Scientifique (UMR 5534), and the Université Claude Bernard Lyon I.

Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

Généthon, http://www.genethon.fr
GeneMap'99, http://www.ncbi.nlm.nih.gov/genemap
Genome Database (GDB), The, http://gdbwww.gdb.org
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for microphthalmia [MIM 600165] and for Peter's anomaly [MIM 604229])

References

Amos-Landgraf JM, Ji Y, Gottlieb W, Depinet T, Wandstrat AE, Cassidy SB, Driscoll DJ Rogan PK, Schwartz S, Nicholls RD (1999) Chromosome breakage in the Prader-Willi and Angelman syndromes involves recombination between large, transcribed repeats at proximal and distal breakpoints. Am J Hum Genet 65:370–386

Autio S, Pihko H, Tengstrom C (1988) Clinical features in a de novo interstitial deletion 15q13 to q15. Clin Genet 34: 293–298

Barros-Nunez P, Medina C, Mendoza R, Sanchez-Corona J, Garcia-Cruz D (1995) Unexpected familial recurrenceof iris coloboma: a delayed mutation mechanism? Clin Genet 48: 160–161

Bateman JB (1984) Microphthalmos. Int Ophthalmol Clin 24: 87–107

Bermejo E, Martinez-Frias ML (1998) Congenital eye malformations: clinical-epidemiological analysis of 1,124,654 consecutive births in Spain. Am J Med Genet 75:497–504

Bessant DA, Anwar K, Khaliq S, Hameed A, Ismail M, Payne AM, Mehdi SQ, Bhattacharya SS (1999) Phenotype of autosomal recessive congenital microphthalmia mapping to chromosome 14q32. Br J Ophthalmol 83:919–922

Bessant DA, Khaliq S, Hameed A, Anwar K, Mehdi SQ, Payne AM, Bhattacharya SS (1998) A locus for autosomal recessive congenital microphthalmia maps to chromosome 14q32. Am J Hum Genet 62:1113–1116

Busby A, Dolk H, Collin R, Jones RB, Winter R (1998) Compiling a national register of babies born with anophthalmia/microphthalmia in England 1988–94. Arch Dis Child Fetal Neonatal Ed 79:F168–F173

Christian SL, Fantes JA, Mewborn SK, Huang B, Ledbetter DH (1999) Large genomic duplicons map to sites of instability in the Prader-Willi/Angelman syndrome chromosome region (15q11-q13). Hum Mol Genet 8:1025–1037

Dib C, Fauré S, Fizames C, Samson D, Drouot N, Vignal P, Millasseau P, Marc S, Hazan J, Seboun E, Lathrop M, Gyapay G, Morissette J, Weissenbach J (1996) A comprehensive genetic map of the human genome based on 5,264 microsatellites. Nature 380:152–154

Eccles MR, Schimmenti LA (1999) Renal-coloboma syndrome: a multi-system developmental disorder caused *PAX2* mutations. Clin Genet 56:1–9

Freund C, Horsford DJ, McInnes RR (1996) Transcription factor genes and the developing eye: a genetic perspective. Hum Mol Genet 5:1471–1488

Fryns JP (1995) Autosomal dominant simple microphthalmos: incomplete penetrance and variable expression in a large family. J Med Genet 32:326

Ghöse S, Singh NP, Kaur D, Verma IC (1991) Microphthalmos and anterior segment dysgenesis in a family. Ophthalmic Paediatr Genet 12:177–182

Graw J (1996) Genetic aspects of embryonic eye development in vertebrates. Dev Genet 18:181–197

Hoefnagel D, Keenan ME, Allen FH (1963) Heredofamilial bilateral anophthalmia. Arch Ophthal 69:760–764

Jean D, Ewan K, Gruss P (1998) Molecular regulators involved in vertebrate eye development. Mech Dev 76:3–18

Kohn G, el Shawwa R, el Rayyes E (1988) Isolated "clinical anophthalmia" in an extensively affected Arab kindred. Clin Genet 33:321–324

Lathrop GM, Lalouel JM (1984) Easy calculations of LOD scores and genetic risks on small computers. Am J Hum Genet 36:460–465

Liu Y, Dehni G, Purcell KJ, Sokolow J, Carcangiu ML, Artavanis-Tsakona S, Stifani S (1996) Epithelial expression and chromosomal location of human TLE genes: implications for Notch signaling and neoplasia. Genomics 31:58–64

Martha AD, Ferrell RE, Saunders GF (1993) Dinucleotide repeat polymorphism in the human aniridia (PAX6) gene. Hum Mol Genet 2:1982

Martin F, Platt J, Tawn EJ, Burn J (1990) A de novo interstitial deletion of 15(q21.2q22.1) in a moderately retarded adult male. J Med Genet 27:637–639

Othman MI, Sullivan SA, Skuta GL, Cockrell DA, Stringham HM, Downs CA, Fornes A, Mick A, Boehnke M, Vollrath D, Richards JE (1998) Autosomal dominant nanophthalmos (NNO1) with high hyperopia and angle-closure glaucoma maps to chromosome 11. Am J Hum Genet 63:1411–1418

Pearce WG (1986) Corneal involvement in autosomal dominant coloboma/microphthalmos. Can J Ophthalmol 21: 291–294

Percin EF, Ploder LA,Yu JJ, Arici K, Horsford DJ, Rutherford A, Bapat B, Cox DW, Ducan AMV, Kalnins VI, Kocak-Altintas A, Sowden JC, Traboulsi E, Sarfarazi M, McInnes RR (2000) Human microphthalmia associated with mutations in the retinal homeobox gene CHX10. Nat. Genet 25: 397–401

Prosser J, van Heyningen V (1998) PAX6 mutations reviewed. Hum Mutat 11:93–108

Richard I, Broux O, Chiannilkulchai N, Fougerousse F, Allamand V, Bourg, N, Brenguier L, Devaud C, Pasturaud P, Roudaut C, Lorenzo F, Sebastiani-Kabatchis C, Schultz RA, Polymeropoulos MH, Gyapay G, Auffray C, Beckmann JS (1994) Regional localization of human chromosome 15 loci. Genomics 23:619–627

Sanyanusin P, Norrish JH, Ward TA, Nebel A, McNoe LA, Eccles MR (1996) Genomic structure of the human *PAX2* gene. Genomics 35:258–261

Smith SA, Martin KE, Dodd KL, Young ID (1994) Severe microphthalmia, diaphragmatic hernia and Fallot's tetralogy associated with a chromosome 1;15 translocation. Clin Dysmorphol 3:287–291

Tomita K, Ishibashi M, Nakahara K, Ang SL, Nakanishi S, Guillemot F, Kageyama R (1996) Mammalian hairy and Enhancer of split homolog 1 regulates differentiation of retinal neurons and is essential for eye morphogenesis. Neuron 16:723–734

Tonk V, Wyandt HE, Osella P, Skare J, Wu BL, Haddad B, Milunsky A (1995) Cytogenetic and molecular cytogenetic studies of a case of interstitial deletion of proximal 15q. Clin Genet 48:151–155

van Heyningen V (1998) Developmental eye disease: a genome era paradigm. Clin Genet 54:272–282

Vignal A, Gyapay G, Hazan J, Nguyen S, Dupraz C, Cheron N, Becuwe N, Tranchant M, Weissenbach J (1993) A non-radioactive multiplex procedure for genotyping of microsatellite markers. In: Adolph KW (ed) Methods in molecular genetics: chromosome and gene analysis. Academic Press, Orlando, pp 211–221

Vingolo EM, Steindl K, Forte R, Zompatori L, Iannaccone A, Sciarra A, Del Porto G, Pannarale MR (1994) Autosomal dominant simple microphthalmos. J Med Genet 31:721–725

Voronina VA, Mathers PH (2000) Mutations in the *RX* gene in a patient with anophthalmia. Paper presented at the ARVO Annual Meeting, Fort Lauderdale, FL, April 30–May 5

Warburg M (1993) Classification of microphthalmos and coloboma. J Med Genet 30:664–669

Weiss AH, Kousseff BG, Ross EA, Longbottom J (1989) Simple microphthalmos. Arch Ophthalmol 107:1625–1630

Zlotogora J, Legum C, Raz J, Merin S, BenEzra D (1994) Autosomal recessive colobomatous microphthalmia. Am J Med Genet 49:261–262