Inherited Congenital Cataract: A Guide to Suspect the Genetic Etiology in the Cataract Genesis

Olga Messina-Baas^a Sergio A. Cuevas-Covarrubias^b

Departments of ^aOphthalmology and ^bMedical Genetics, Facultad de Medicina, Hospital General de México, UNAM, Mexico City, Mexico

Keywords

Clinical heterogeneity · Clinical variability · Congenital cataract · Genetic heterogeneity

Abstract

Cataracts are the principal cause of treatable blindness worldwide. Inherited congenital cataract (CC) shows all types of inheritance patterns in a syndromic and nonsyndromic form. There are more than 100 genes associated with cataract with a predominance of autosomal dominant inheritance. A cataract is defined as an opacity of the lens producing a variation of the refractive index of the lens. This variation derives from modifications in the lens structure resulting in light scattering, frequently a consequence of a significant concentration of high-molecular-weight protein aggregates. The aim of this review is to introduce a guide to identify the gene involved in inherited CC. Due to the manifold clinical and genetic heterogeneity, we discarded the cataract phenotype as a cardinal sign; a 4-group classification with the genes implicated in inherited CC is proposed. We consider that this classification will assist in identifying the probable gene involved in inherited CC.

© 2017 S. Karger AG, Basel

Cataracts cause half of all cases of blindness and one-third of the visual impairment cases worldwide. The term cataract comes from the Latin word “cataracta” that itself derives from the Greek “katarráktēs” and refers to a waterfall. Apparently, Constantine the African (a Carthaginian monk from the Monte Cassino monastery and a member of the Salerno school of translators) borrowed this term for lens opacity from the translation of Arab medical writings into Latin. Cataract is a term that is still used today [Chance, 1939]. Since cataracts are the most common cause of vision loss in the world, surgical management of this has been documented since ancient times. Possibly, the first written evidence is from 600 years B.C.: “Uttara-Tantra of Sushruta Samshita,” wherein the recline method technique is described [Bhishagratna, 2005].

A cataract is defined as an opacity of the lens resulting from a variation of the refractive index of the lens. This variation derives from changes in the lens structure resulting in light scattering, frequently due to a significant concentration of high-molecular-weight protein aggregates. Congenital cataract (CC), one of the leading causes of treatable blindness worldwide, has a prevalence of 1–15/10,000 live births with a greater presence in developing countries than in developed countries [Apple et al., 2000;

Fig. 1. Some examples of inherited cataracts: anterior subcapsular (A), fetal nuclear (B), punctate in lens cortex (C), and embryonic nuclear Y-sutural (D).

Gilbert and Foster, 2001]. Inherited CC is a clinically and genetically heterogeneous disease normally associated with the breakdown of the lens architecture. Inherited CC presents all types of inheritance patterns in a syndromic and nonsyndromic form with more than 100 causative genes (<http://cat-map.wustl.edu/>). For example, hereditary CC may be inherited as autosomal dominant, autosomal recessive, or X-linked traits, with autosomal dominant being the most prevalent form of inheritance pattern. Hereditary CC shows an important intrafamilial and interfamilial variability; the same mutation in one gene can result in distinct cataract phenotypes, whereas expression of different genes can produce the same cataract pattern. Clinical variability can even be observed in the same patient [Hejtmancik and Smaoui, 2003].

Several terms have been used to describe the different types of hereditary CC in the literature. CC classification has not been homogenous. In some cases, the description corresponds to the name of the author who first described the cataract, i.e., Marner cataract, a cataract with sutural opacities [Marner et al., 1989]; to the name of the affected

family such as Coppock cataract, an embryonic nuclear cataract [Nettleship and Ogilvie, 1906]; the Volkman cataract, a central or zonular variety with opacities in the embryonic, fetal, and juvenile nucleus [Eiberg 1995], or to the affected community such as the Hutterite cataract [Boone et al., 2015]. In other cases, anatomic localization is used to establish the cataract definition, i.e., subcapsular, nuclear, sutural, cortical, fetal, embryonic, or capsular cataract (Fig. 1).

There are excellent reviews of inherited cataracts in the literature. The purpose of this review is to provide a guide to the suspected genetic causes of inherited CC. Due to the great clinical and genetic heterogeneity, we separated the genes implicated in the process of cataractogenesis into 4 groups (Tables 1–4). These groups contain the genes involved in syndromic cataracts, the genes implicated in syndromic cataracts but with reports of congenital cataracts only, the genes that present cataracts only, and finally, the genes with cataract and eye anomalies. We consider that this classification will assist in identifying the probable gene involved in inherited CC.

Table 1. Syndromic cataract genes

Locus	Gene	Inheritance	OMIM	Disease	Gene product
1p36.32	<i>PEX10</i>	AR	614870	neonatal adrenoleukodystrophy, Zellweger syndrome	protein of peroxisomal matrix
1p36.22	<i>PEX14</i>	AR	614887	Zellweger syndrome	peroxisomal import machinery
1p36.1p34	<i>HSPG2</i>	AR	224410/25800	Schwartz-Jampel syndrome type 1/dyssegmental dysplasia	perlecan protein
1p36p35	<i>GALE</i>	AR	230350	galactose epimerase deficiency	UDP-galactose-4-epimerase
1p34.1	<i>POMGNT1</i>	AR	253280	muscular dystrophy-dystroglycanopathy	type 2 transmembrane protein that resides in the Golgi apparatus
1p22p21	<i>ABCD3</i>	AR	616278	Zellweger syndrome 2	member of the superfamily of ATP-binding cassette transporters
1p21	<i>COL11A1</i>	AD	604841/154780	Stickler syndrome type 2, Marshall syndrome	one of the 2 alpha chains of type XI collagen
1q41	<i>IARS2</i>	AR	616007	cataracts, growth hormone deficiency, sensory neuropathy, sensorineural hearing loss, skeletal dysplasia	Aminoacyl-tRNA synthetase
1q41	<i>RAB3GAP2</i>	AR	212720/614225	Martsolf syndrome, Warburg micro syndrome	RAB3 protein regulates exocytosis of neurotransmitters and hormones
1q42	<i>GNPAT</i>	AR	222765	rhizomelic chondrodysplasia punctata type 2	enzyme in synthesis of ether phospholipids
2p14p16	<i>PEX13</i>	AR	614883	Zellweger syndrome	peroxisomal membrane protein
2q21.3	<i>RAB3GAP1</i>	AR	600118	Warburg micro syndrome	catalytic subunit of a Rab GTPase activating protein
2q24q31	<i>LRP2</i>	AR	222448	Donnai-Barrow syndrome	low density lipoprotein-related protein 2
2q33qter	<i>CYP27A1</i>	AR	213700	cerebrotendinous xanthomatosis	member of the cytochrome P450 superfamily
2q37	<i>KCNJ13</i>	AD	193230	snowflake vitreoretinal degeneration	member of the inwardly rectifying potassium channel family
3p21.1	<i>COL7A1</i>	AR	226600	epidermolysis bullosa dystrophica	alpha chain of type VII collagen
3p14.3	<i>FLNB</i>	AD, AR	150250/272460	Larsen syndrome/spondylocarpotarsal synostosis syndrome	member of the filamin family
3q21q22	<i>CNBP</i>	AD	602668	myotonic dystrophy type 2	a nucleic-acid binding protein with 7 zinc-finger domains
3q25	<i>SLC33A1</i>	AR	614482	congenital cataracts, hearing loss, neurodegeneration	required for the formation of O-acetylated (Ac) gangliosides
4p16.1	<i>HMX1</i>	AR	612109	oculoauricular syndrome	transcription factor that belongs to the H6 family of homeobox proteins
4p15.32	<i>CC2D2A</i>	AR	612285	Joubert syndrome 9	play a critical role in cilia formation
4p12q12	<i>SRD5A3</i>	AR	612713	Kahirazi syndrome	steroid 5-alpha reductase family
4q32q35	<i>ETFDH</i>	AR	231680	glutaric acidemia	component of the electron-transfer system in mitochondria
4q35.1	<i>TRAPPC11</i>	AR	615356	muscular dystrophy limb girdle 2S	a subunit of the TRAPP (transport protein particle) tethering complex
5q12.1	<i>ERCC8</i>	AR	216400	Cockayne syndrome type A	a WD repeat protein
5q14.3	<i>VCAN</i>	AD	143200	Wagner syndrome 1	a member of the aggrecan/versican proteoglycan family
5q31	<i>SIL1</i>	AR	248800	Marinesco-Sjögren syndrome	resident endoplasmic reticulum N-linked glycoprotein
6p24	<i>TFAP2A</i>	AD	113620	branchiooculofacial syndrome	a transcription factor
6p23	<i>GCM2</i>	AD	146200	hypoparathyroidism familial isolated	a homolog of the <i>Drosophila</i> glial cells missing gene
6p21.3	<i>NEU1</i>	AR	256550	sialidosis type 2	a lysosomal enzyme that cleaves terminal sialic acid residues
6q21q23.2	<i>GJA1</i>	AD	164200	oculodentodigital dysplasia	a member of the connexin gene family
6q22q24	<i>PEX7</i>	AR	215100	rhizomelic chondrodysplasia punctata type 1	cytosolic receptor for the set of peroxisomal matrix enzymes
6q24.2	<i>PEX3</i>	AR	614882	Zellweger syndrome	involved in peroxisome biosynthesis and integrity
7p15.3	<i>FAM126A</i>	AR	610532	hypomyelinating leukodystrophy 5	part in the beta-catenin/Lef signaling pathway
7q21.2	<i>PEX1</i>	AR	214100	Zellweger syndrome	a member of the AAA ATPase family
7q31.1	<i>CAV1</i>	AD	606721	partial lipodystrophy, congenital cataracts, neurodegeneration syndrome	main component of the caveolae plasma membranes
7q34	<i>AGK</i>	AR	212350	Sengers syndrome	a mitochondrial membrane protein involved in lipid and glycerolipid metabolism
8p21.1	<i>ESCO2</i>	AR	268300	Roberts syndrome	acetyltransferase activity may be required for the establishment of sister chromatid cohesion
8q13.3	<i>EYA1</i>	AD	601653	branchiootorenal syndrome 1	a member of the eyes absent (EYA) family of proteins
8q21.1	<i>PXMP3</i>	AR	614866	Zellweger syndrome	an integral peroxisomal membrane protein required for peroxisome biogenesis
8q21q22	<i>CNGB3</i>	AR	262300	achromatopsia 3	the beta subunit of a cyclic nucleotide-gated ion channel
8q24.3	<i>RECQL4</i>	AR	268400	Rothmund Thompson syndrome	DNA helicase that belongs to the RecQ helicase family
9p13.13	<i>GALT</i>	AR	230400	galatosemia	galactose-1-phosphate uridyl transferase
9p24	<i>VLDLR</i>	AR	224050	cerebellar hypoplasia and mental retardation with or without quadrupedal locomotion 1	low-density lipoprotein receptor
9q31q33	<i>FKTN</i>	AR	253800	muscular dystrophy-dystroglycanopathy	a putative transmembrane protein localized to the cis-Golgi compartment
9q34	<i>LMX1B</i>	AD	161200	nail-patella syndrome	a member of LIM-homeodomain family of proteins
9q34.1	<i>POMT1</i>	AR	236670	muscular dystrophy-dystroglycanopathy A1	an O-mannosyltransferase
10q11.23	<i>ERCC6</i>	AR	214150/133540	cerebrooculofacioskeletal syndrome I/Cockayne syndrome type B	a DNA-binding protein that is important in transcription-coupled excision repair
10q23.31	<i>PTEN</i>	AD	158350	Cowden disease	a tumor suppressor
10q24.3	<i>ALDH18A1</i>	AD/AR	616603/219150	cutis laxa AD/cutis laxa AR	a member of the aldehyde dehydrogenase family
10q26	<i>OAT</i>	AR	258870	gyrate atrophy of choroid and retina	mitochondrial enzyme ornithine aminotransferase

Table 1 (continued)

Locus	Gene	Inheritance	OMIM	Disease	Gene product
11p15.3p15.1 11q13.4	<i>PTH</i> <i>LRP5</i>	AD/AR AR, AD	146200 601813/607634	familial isolated hypoparathyroidism exudative vitreoretinopathy 4/osteopetrosis, autosomal dominant 1	a member of the parathyroid family of proteins a transmembrane low-density lipoprotein receptor
11q13.2q13.5	<i>DHCR7</i>	AR	270400	Smith-Lemli-Opitz syndrome	an enzyme that removes the C(7-8) double bond in the B ring of sterols
11q13.4	<i>CLPB</i>	AR	616271	3-methylglutaconic aciduria with cataracts, neurologic involvement, neutropenia	member of the ATPases associated with diverse cellular activities (AAA+) superfamily
11q14.2	<i>FZD4</i>	AD	133780	retinopathy of prematurity	a member of the frizzled gene family
11q22.3	<i>MMP1</i>	AR	226600	epidermolysis bullosa dystrophic	a member of the peptidase M10 family of matrix metalloproteinases
11q22.1q23.2	<i>CRYAB</i>	AD	608810	myofibrillar myopathy	members of the small heat shock protein (HSP20) family
11q23.3	<i>SC5DL</i>	AR	607330	lathosterolosis	enzyme of cholesterol biosynthesis
11q25	<i>JAM3</i>	AR	613730	hemorrhagic destruction of brain, subependymal calcification	immunoglobulin superfamily gene member
12q13.12	<i>TUBA1A</i>	AD	611603	lissencephaly	microtubule constituents of the tubulin superfamily
12p13.3	<i>PEX5</i>	AR	214110	Zellweger syndrome	protein essential for the assembly of functional peroxisomes
12q24	<i>MVK</i>	AR	610377	mevalonic aciduria	peroxisomal enzyme mevalonate kinase
13q12	<i>GJB6</i>	AD	129500	Clouston syndrome	one of the connexin proteins
13q12.3	<i>B3GALTL</i>	AR	261540	Peters-plus syndrome	a beta-1,3-glucosyltransferase that transfers glucose to O-linked fucosylglycans on thrombospondin type-1 repeats
13q14.3	<i>ITM2B</i>	AD	117300	cerebral amyloid angiopathy	a transmembrane protein
13q34	<i>COL4A1</i>	AD	607595	cerebral small vessel disease	a type IV collagen alpha protein
14q21.1	<i>SEC23A</i>	AR	607812	craniofacial dysplasia	a member of the SEC23 subfamily of the SEC23/SEC24 family
14q24	<i>POMT2</i>	AR	613150	muscular dystrophy-dystroglycanopathy	an O-mannosyltransferase
15q15	<i>BUB1B</i>	AR	257300	mosaic variegated aneuploidy syndrome 1	a kinase involved in spindle checkpoint function
15q21.1	<i>FBN1</i>	AD	608328	Weill-Marchesani syndrome	a member of the fibrillin family of proteins
15q25	<i>POLG</i>	AD/AR	157640	progressive external ophthalmoplegia with mitochondrial DNA deletions 1	the catalytic subunit of mitochondrial DNA polymerase
16p13.3p13.2	<i>GFER</i>	AR?	613076	progressive mitochondrial myopathy, sensorineural hearing loss, developmental delay	structural and functional homolog of the yeast <i>scERV1</i> gene
16q21	<i>NOD2</i>	AD	186580	Blau syndrome	a member of the Nod1/Apaf-1 family
16q23	<i>ADAMTS18</i>	AR	267750	Knobloch syndrome	a member of the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) protein family
16q22q23	<i>MAF</i>	AD	601088	Aymé-Gripp syndrome	a DNA-binding, leucine zipper-containing transcription factor
17p13.3	<i>YWHAE</i>	AD	247200	Miller-Dieker lissencephaly syndrome	member of the 14-3-3 family of proteins which mediate signal transduction by binding to phosphoserine-containing proteins
17q12	<i>PEX12</i>	AR	614859	Zellweger syndrome	member of the peroxin-12 family
17q21	<i>WNT3</i>	AR	273395	tetraamelia syndrome	secreted signaling proteins implicated in oncogenesis
17q21.33	<i>XYLT2</i>	AR	605822	spondyloocular syndrome	an isoform of xylosyltransferase, which belongs to a family of glycosyltransferases
18q12.3	<i>EPG5</i>	AR	242840	Vici syndrome (immunodeficiency, cleft lip/palate, cataract, hypopigmentation, absent corpus callosum)	a large coiled-coil domain-containing protein that functions in autophagy
18q23	<i>CTDP1</i>	AR	604168	congenital cataracts, facial dysmorphism, neuropathy	a protein which interacts with the carboxy-terminus of the RAP74 subunit of transcription initiation factor TFIIF
19q13.1	<i>MAN2B1</i>	AR	248500	alpha-mannosidosis	an enzyme that hydrolyzes terminal, nonreducing alpha-D-mannose residues in alpha-D-mannosides
19q13.3	<i>DMPK</i>	AD	160900	myotonic dystrophy 1	a serine-threonine kinase
19q13.32	<i>FKRP</i>	AR	613153	muscular dystrophy-dystroglycanopathy	a protein which is targeted to the medial Golgi apparatus and is necessary for posttranslational modification of dystroglycan
20p11.21q12	<i>ABHD12</i>	AR	612674	polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, cataract	an enzyme that catalyzes the hydrolysis of 2-arachidonoyl glycerol
20q13.13q13.2	<i>SALL4</i>	AD	607323	Duane-radial ray syndrome	a zinc finger transcription factor thought to play a role in the development of abducens motor neurons
20q13.3	<i>GNAS</i>	AD	103580/ 612462/ 612463	pseudohypoparathyroidism type 1A/ pseudohypoparathyroidism type 1C/ pseudohypoparathyroidism	multiple transcript variants encoding different isoforms
21q22.3	<i>COL18A1</i>	AR	267750	Knobloch syndrome 1	alpha chain of type XVIII collagen
22q11.21	<i>PEX26</i>	AR	614872	Zellweger syndrome	member of the peroxin-26 gene family
22q12.2	<i>NF2</i>	AD	101000	neurofibromatosis type 2	a protein similar to ezrin, radixin, moesin family of proteins
22q12.3	<i>LARGE</i>	AR	613154	muscular dystrophy-dystroglycanopathy	a member of the N-acetylglucosaminyltransferase gene family
22q13.1	<i>MYH9</i>	AD	153640	Fechtner syndrome	a conventional non-muscle myosin

Table 1 (continued)

Locus	Gene	Inheritance	OMIM	Disease	Gene product
Xp11.4	<i>BCOR</i>	XL	300166	microphthalmia syncromic 2	an interacting corepressor of BCL6
Xp11.23	<i>PQBPI</i>	XL	309500	Renpenning syndrome	a nuclear polyglutamine-binding protein that is involved with transcription activation
Xp11.23p11.22	<i>EBP</i>	XL	302960	chondrodysplasia punctata 2	an integral membrane protein of the endoplasmic reticulum
Xp22.3	<i>ARSE</i>	XL	302950	chondrodysplasia punctata 1	a member of the sulfatase family
Xp22.3	<i>HCCS</i>	XL	309801	linear skin defects with multiple congenital anomalies	an enzyme that covalently links a heme group to the apoprotein of cytochrome c
Xp22	<i>AIC</i>	XL	304050	Aicardi syndrome	unknown
Xp22.13	<i>NHS</i>	XL	302350	Nance-Horan syndrome	a protein containing 4 conserved nuclear localization signals
Xq22	<i>GLA</i>	XL	301500	Fabry disease	a homodimeric glycoprotein that hydrolyzes the terminal alpha-galactosyl moieties from glycolipids and glycoproteins
Xq22	<i>COL4A5</i>	XL	301050	Alport syndrome	one of the 6 subunits of type IV collagen
Xq25q26.1	<i>OCRL</i>	XL	309000	Lowe oculocerebrorenal syndrome	an inositol polyphosphate 5-phosphatase
Xq28	<i>IKBK</i>	XL	308300	incontinentia pigmenti	regulatory subunit of the inhibitor of kappaB kinase complex

AD, autosomal dominant; AR, autosomal recessive; XL, X linked.

Table 2. Syndromic genes only with cataract

Locus	Gene	OMIM	Cataract inheritance	Syndrome inheritance	Syndrome	Reference of only cataract affection
4p16.1	<i>WFS1</i>	614296	AD	AD	Wolfram-like syndrome (no cataract is associated with this syndrome)	Berry et al., 2013
7q34	<i>AGK</i>	212350	AR	AR	Sengers syndrome	Aldahmesh et al., 2012
8q13.3	<i>EYA1</i>	601653	AD	AD	brachio-oto-renal syndrome-1, nystagmus	Azuma et al., 2000
11q22.1q23.2	<i>CRYAB</i>	608810	AR/AD	AD	myofibrillar myopathy (alpha-B crystallinopathy)	Berry et al., 2001; Liu et al., 2006; Devi et al., 2008; Chen et al., 2009; Safieh et al., 2009; Sun et al., 2011b; Xia et al., 2014b; Jiaox et al., 2015; Khan et al., 2015; Ma AS et al., 2016
13q34	<i>COL4A1</i>	607595	AD	AD	familial porencephaly, brain small vessel disease with hemorrhage/Axenfeld-Rieger anomalies, hereditary angiopathy with nephropathy, aneurysms, and muscle cramps	Xia et al., 2014a
15q21.1	<i>FBNI</i>	608328	AD	AD	Marfan syndrome, Weill-Marchesani syndrome	Li D et al., 2016
16q22q23	<i>MAF</i>	601088	AD	AD	Aymé-Gripp syndrome	Jamieson et al., 2002; Vanita et al., 2006; Hansen et al., 2007, 2009; Narumi et al., 2014; Sun et al., 2014; Ma AS et al., 2016
Xp22.13	<i>NHS</i>	302350	XL	XL	Nance-Horan syndrome	Ramprasad et al., 2005; Florijn et al., 2006; Sharma et al., 2008; Coccia et al., 2009; Sun et al., 2014; Li D et al., 2016; Ma AS et al., 2016

AD, autosomal dominant; AR, autosomal recessive; XL, X linked.

Embryological Development of the Lens

Briefly, from mouse studies, the lens development starts at day 22 of gestation (4 mm embryonic stage) from the surface ectoderm. *Pax6* and *Sox2* genes, in the optic vesicle, induce the surface ectoderm to form the lens placode, which invaginates and forms the lens vesicle [Kamachi et al., 2001; Kondoh et al., 2004]. By day 40 of gestation (10 mm stage), the lens vesicle is completely separated from the surface ectoderm. Group B1 SOX proteins

(SOX1, SOX2, and SOX3) activate γ -crystallin genes in the mouse lens, producing the crystallins, water-soluble proteins that comprise over 90% of the proteins of the lens [Hoehenwarter et al., 2006]. Elongating cells of the posterior end of the lens vesicle form the primary fibers, which become the embryonic nucleus in the mature lens. In the final phase of lens differentiation, several fibroblast growth factors seem to be required [McAvoy and Chamberlain, 1989; Lovicu and Overbeek, 1998]. The lens continues growing after birth, with the new secondary fibers

Table 3. Only cataract genes

Locus	Gene	Inheritance	Cataract phenotype	Other phenotype	Gene product	Reference
1p36	<i>EPHA2</i>	AR/AD	nuclear, posterior, cortical, total, posterior polar, subcapsular and cortical, zonular	a few reports with microcornea or delay development ^{a, b}	ephrin receptor subfamily of the protein-tyrosine kinase family	Shiels et al., 2008; Zhang et al., 2009a; Kaul et al., 2010; Aldahmesh et al., 2012; Dave et al., 2013; Shentu et al., 2013; Gillespie et al., 2014; Reis et al., 2014; Sun et al., 2014; Bu et al., 2016; Li D et al., 2016
2q33q35	<i>CRYGD</i>	AD	punctate, progressive		account for approximately one-third of total lens proteins	Héon et al., 1999; Stephan et al., 1999; Kmoch et al., 2000; Santhiya et al., 2002; Nandrot et al., 2003; Burdon et al., 2004; Mackay et al., 2004; Shentu et al., 2004; Xu et al., 2004; Gu et al., 2005; Zenteno et al., 2005; Gu et al., 2006; Messina-Baas et al., 2006; Hansen et al., 2007; Plotnikova et al., 2007; Zhang et al., 2007; Devi et al., 2008; Li et al., 2008; Khan et al., 2009; Santana et al., 2009; Zhang et al., 2009b; Roshan et al., 2010; Wang et al., 2010; Sun et al., 2011b; Wang et al., 2011b; Vanita et al., 2012; Jia et al., 2013; Reis et al., 2013; Gillespie, et al., 2014; Mackay et al., 2014; Zhai et al., 2014; Zhuang et al., 2015; Gao et al., 2016; Ma AS et al., 2016; Yang et al., 2016
2q33q35	<i>CRYGC</i>	AD	central zonular pulverulent (Coppock-like)	some cases with microphthalmia and microcornea	constitute the major proteins of vertebrate eye lens	Héon et al., 1999; Ren et al., 2000; Santhiya et al., 2002; Gonzalez-Huerta et al., 2007; Devi et al., 2008; Yao et al., 2008; Zhang et al., 2009b; Kumar et al., 2011; Guo et al., 2012; Li et al., 2012; Kondo et al., 2013; Reis et al., 2013; Gillespie et al., 2014; Prokudin et al., 2014; Li D et al., 2016; Ma AS et al., 2016
2q33q35	<i>CRYGB</i>	AD	anterior polar and lamellar		account for approximately one-third of total lens proteins	AlFadhli et al., 2012
2q33q35	<i>CRYGA</i>	sporadic	total		major protein components of the vertebrate eye lens	Li D et al., 2016
3p21.31	<i>FYCO1</i>	AR	posterior capsular, nuclea		plays a role in microtubule plus end-directed transport of autophagic vesicles	Chen et al., 2011; Aldahmesh et al., 2012; Gillespie et al., 2014; Khan et al., 2015
3q21q22	<i>BFSP2</i>	AD/AR	nuclear, pulverulent, cortical, Y-sutural, lamellar, opalescent, spok-like opacities, sutural		conforms the cytoskeletal element referred to as the beaded filament	Conley et al., 2000; Jakobs et al., 2000; Zhang et al., 2004; Zhang et al., 2006; Cui et al., 2007; Ma et al., 2008; Aldahmesh et al., 2011, 2012; Gillespie et al., 2014; Liu et al., 2014; Li D et al., 2016
3q25qter	<i>CRYGS</i>	AD	central pulverulent, opalescent, sutural, lamellar, Coppock		is expressed late abundantly in the ocular lens	Sun et al., 2005; Devi et al., 2008; Vanita et al., 2009; Sun et al., 2011a; Yang et al., 2013
5q22	<i>WDR36</i>	sporadic	posterior polar, nuclear		a member of the WD repeat protein family	Li D et al. 2016
6p24.2	<i>GCNT2</i>	AR	central, nuclear, polar	adult i blood group	enzyme responsible for formation of the blood group I antigen	Yu et al., 2001; Inaba et al., 2003; Pras et al., 2004; Wussuki-Lior et al., 2011; Aldahmesh et al., 2012; Borck et al., 2012; Happ et al., 2016
6p21.31	<i>LEMD2</i>	AR	Hutterite type		a transmembrane protein of the inner nuclear membrane that is involved in nuclear structure organization	Boone et al., 2015
9p22.1	<i>RRAGA</i>	AD	nuclear		a Ras-related GTP-binding A	Chen et al., 2016
9q13q22	<i>CTPL1</i>	AR	progressive pulverulent		unknown	Héon et al., 2001; Forsheew et al., 2005
9q22.33	<i>TDRD7</i>	AR	polar		a member of the Tudor family of proteins	Lachke et al., 2011; Li D et al., 2016
10p13	<i>VIM</i>	AD	pulverulent		a member of the intermediate filament family	Müller et al., 2009; Ma AS et al., 2016

Table 3 (continued)

Locus	Gene	Inheritance	Cataract phenotype	Other phenotype	Gene product	Reference
12q13	<i>MIP</i>	AD	lamellar, sutural, cerulean, punctate, nuclear, pulverulent, snail-like, cortical, Y-sutural		a member of the water-transporting aquaporins as well as the original member of the MIP family of channel proteins	Berry et al., 2000; Geyer et al., 2006; Gu et al., 2007; Lin et al., 2007; Jiang et al., 2009; Wang et al., 2010; Wang et al. 2011a; Xiao et al., 2011; Yang et al., 2011b; Reis et al., 2013; Senthil Kumar et al., 2013; Zeng et al., 2013; Ding et al., 2014; Sun et al., 2014; Yu et al., 2014; Shentu et al., 2015; Song et al., 2015; Ma AS et al., 2016; Qin et al., 2016
13q11q12	<i>GJA3</i>	AD	nuclear, pulverulent, Y-sutural, lamellar, lamellar sutural, pearl box, coralliform, punctate, Coppock-like		gap junction protein alpha 3	Mackay et al., 1999; Rees et al., 2000; Jiang et al., 2003; Bennett et al., 2004; Burdon et al., 2004; Li et al., 2004; Devi et al., 2005; Ma et al., 2005; Addison et al., 2006; Hansen et al., 2006, 2009; Guleria et al., 2007; Santhiya et al., 2010; Zhou Z et al., 2010; Bennett and Shiels, 2011; Ding et al., 2011; Sun et al., 2011a; Yang et al., 2011a; Yao et al., 2011b; Wang and Zhu, 2012; Zhang et al., 2012; Guo et al., 2013; Ponnamp et al., 2013; Zhou et al., 2013; Gillespie et al., 2014; Hu et al., 2014; Yang Z et al., 2015; Yuan et al., 2015; Li B et al., 2016; Ma AS et al., 2016; Ma MF et al., 2016; Wang et al., 2016
16p13.2	<i>TMEM114</i>	AD			a glycosylated transmembrane protein	Jamieson et al., 2007
16q21	<i>HSF4</i>	AD/AR	cortical lamellar, zonular, anterior polar, nuclear, sutural		heat-shock transcription factor	Bu et al., 2002; Smaoui et al., 2004; Forsheew et al., 2005; Ke et al., 2006; Sajjad et al., 2008; Hansen et al., 2009; Gillespie et al., 2014; Lv et al., 2014; Liu et al., 2015; Behnam et al., 2016; Li D et al., 2016
17q11.2q12	<i>CRYBA1</i>	AD/AR	zonular sutural, pulverulent, sutural nuclear, lamellar, floriform, Y-sutural, nuclear, polymorphic		crystallin structure proteins	Kannabiran et al., 1998; Bateman et al., 2000; Burdon et al., 2004; Ferrini et al., 2004; Reddy et al., 2004; Qi et al., 2004; Lu et al., 2007; Devi et al., 2008; Gu et al., 2010; Zhu et al., 2010; Sun et al., 2011b; Yang Z et al., 2011; Yang et al., 2012; Yu et al., 2012; Gillespie et al., 2014; Zhang et al., 2014; Khan et al., 2015
17q12	<i>UNC45B</i>	AD	posterior subcapsular and central		a co-chaperone required for folding and accumulation of type II myosins	Hansen et al., 2014
17q24	<i>GALK1</i>	AR		galactokinase deficiency	galactokinase 1	Stambolian et al., 1995; Asada et al., 1999; Kalaydjieva et al., 1999; Kolosha et al., 2000; Hunter et al., 2001; Reich et al., 2002; Yasmeen et al., 2010; Singh et al., 2012; Chacon-Camacho et al., 2014; Gillespie et al., 2014
19p13.2	<i>LONP1</i>	AR	nuclear		a mitochondrial matrix protein that belongs to the Lon family of ATP-dependent proteases	Khan et al., 2015
19q13.13	<i>WDR87</i>	AR	total white		WD repeat domain 87	Khan et al., 2015
19q13.2	<i>PRX</i>	AD	nuclear		a protein involved in peripheral nerve myelin upkeep	Yuan et al., 2016
19q13.33	<i>FTL</i>	AD	iron flecks, nuclear, Y-sutural, stellate, sunflower, pulverulent, crystallin, breadcrumb-like nuclear, cortical opacities	hyperferritinemia	the light subunit of the ferritin protein	http://www.hgmd.cf.ac.uk/ac/gene.php?gene=FTL
19q13.4	<i>LIM2</i>	AR	congenital	galactokinase deficiency	an eye lens-specific protein found at the junctions of lens fiber cells	Ponnamp et al., 2008
19q33	<i>SIPA1L3</i>	AR			the signal-induced proliferation associated 1 family of genes	Greenlees et al., 2015
20p11.23p12.1	<i>BFSP1</i>	AR	cortical progressive, juvenile onset, nuclear		a lens-specific intermediate filament-like protein named filensin	Ramachandran et al., 2007; Wang et al., 2013; Li D et al., 2016; Ma AS et al., 2016
20q11.22	<i>CHMP4B</i>	AD	posterior subcapsular		a member of the chromatin-modifying protein/charged multivesicular body protein family	Shiels et al., 2007

Table 3 (continued)

Locus	Gene	Inheritance	Cataract phenotype	Other phenotype	Gene product	Reference
21q22.3	<i>LSS</i>	AR	total	?	catalyzes the conversion of (S)-2,3-oxidosqualene to lanosterol	Zhao et al., 2015
22q11.23	<i>CRYBB3</i>	AR/AD	nuclear, cortical		crystallin protein	Riazuddin et al., 2005; Hansen et al., 2009; Reis et al., 2013; Li D et al., 2016; Ma AS et al., 2016
22q11.23	<i>CRYBB2</i>	AD	subcapsular, zonular, nuclear, coronary, lamellar, sutural, cerulean, pulverulent, polymorphic, cortical		crystallin protein	Litt et al., 1997; Gill et al., 2000; Vanita et al., 2001; Santhiya et al., 2004; Yao et al., 2005; Bateman et al., 2007; Pauli et al., 2007; Devi et al., 2008; Li et al., 2008; Hansen et al., 2009; Lou et al., 2009; Mothobi et al., 2009; Wang et al., 2009; Santhiya et al., 2010; Wang et al., 2011b; Yao et al., 2011a; Weisschuh et al., 2012; Chen et al., 2013; Faletra et al., 2013; Garnai et al., 2014; Gillespie et al., 2014; Sun et al., 2014; Ma AS et al., 2016; Messina-Baas et al., 2016
22q12.1	<i>CRYBB1</i>	AR/AD	nuclear		crystallin protein	Willoughby et al., 2005; Cohen et al., 2007; Wang et al., 2007; Yang et al., 2008; Meyer et al., 2009; Wang et al., 2011b; Khan et al., 2012; Reis et al., 2013; Wu et al., 2013; Ma AS et al., 2016

For abbreviations, see Table 2. ^a Gillespie et al., 2014. ^b Aldahmesh et al., 2012.

generated from the equatorial cells of the lens epithelium (germinative zone). The lens epithelial cells synthesize crystallins and lose their nuclei to become mature lens fibers. Disruption of this delicate process due to toxic, metabolic, infectious, or genetic agents results in CC.

Syndromic and Nonsyndromic Cataracts

A rough division of hereditary cataracts comprises 2 parts: syndromic and nonsyndromic cataracts. If only the lens is implicated in the pathological process, it is defined as nonsyndromic cataracts. If there are more organs implicated, it results in syndromic cataracts. Around 100 genes throughout the genome are in the OMIM database explaining the different syndromes caused by different genes, either associated with cataracts or as part of them (Table 1). Nevertheless, genetically it is sometimes difficult to establish this difference because clinically one gene defect can result in either lens affection or systemic disease. Some examples of this variance (Table 2) are found in the affected *AGK* gene, which results in either an isolated cataract or in Senger syndrome (OMIM 212350) [Aldahmesh et al., 2012]; the *MAF* gene, in which a molecular defect can result in cataracts or in Aymé-Gripp syndrome (OMIM 601088) [Narumi et al., 2014; Sun et al., 2014; Ma AS et al., 2016], or in the *NHS* gene alteration which can lead to isolated cataracts or Nance-Horan syndrome (OMIM 302350) [Coccia et al., 2009; Li D et al., 2016]. The scope of this review does not include syn-

dromic cataracts. It is only briefly referenced because some genes (*WFS1*, *AGK*, *EYA1*, *CRYAB*, *COL4A1*, *FBN1*, *MAF*, and *NHS*) are also described in previous reports with CC and no other anomalies (Table 2).

Nonsyndromic Cataracts

Around 35 genes have been strongly associated with inherited CC only and with no other systemic anomalies; they show autosomal dominant and autosomal recessive inheritance patterns (Table 3). However, in some of these cases (*EPHA2*, *BFSP2*, *HSF4*, *CRYBA1*, *CRYBB1*, and *CRYBB3*), hereditary CC can present both patterns of autosomal inheritance (dominant or recessive). A great variety of functions is described in all affected genes that produce nonsyndromic inherited CC. Protein functions encompass structural to enzymatic processes including channels, phagosomes, RNA processing, transcription factors, and regulation of intracellular signaling (Table 3).

The cataract phenotype by itself is not an efficient indicator of the affected gene or mutation, since identical cataracts can result from mutations at different loci and may have several inheritance patterns. Conversely, various cataract types can be found in the same gene affection, presenting clinical heterogeneity. In addition, some nonsyndromic cataracts could include the presence of lens opacities only or lens opacities with ocular abnormalities and with no systemic affection, i.e., microcornea, aniridia, vitreoretinopathology, microphthalmia, anophthalmia, iris hypoplasia, or rod-cone dystrophy (Table 4).

Table 4. Cataract genes and eye anomalies

Locus	Gene	Inheritance	Cataract phenotype	Other phenotype	Gene product	Reference
1p32	<i>FOXE3</i>	AR/AD	cerulean, congenital	microphthalmia, sclerocornea, aphakia, optic disc coloboma, aniridia plus, glaucoma, vitreoretinal dysplasia (almost all reports)	the forkhead family of transcription factors	Semina et al., 2001; Ormestad et al., 2002; Valleix et al., 2006; Iseri et al., 2009; Ali et al., 2010; Anjum et al., 2010; Bremond-Gignac et al., 2010; Reis et al., 2010; Doucette et al., 2011; Gillespie et al., 2014; Li D et al., 2016
1q21.1	<i>GJA8</i>	AD/AR	nuclear, punctiform, pulverulent, jellyfish-like, star-shaped, full moon, Y-sutural, balloon-like, lamellar, zonular, nuclear, triangular, perinuclear	microcornea, glaucoma (about half of the reports)	a transmembrane connexin protein	Shiels et al., 1998; Berry et al., 1999; Polyakov et al., 2001; Willoughby et al., 2003; Zheng et al., 2005; Arora et al., 2006, 2008; Devi and Vijayalakshmi, 2006; Vanita et al., 2006; Hansen et al., 2007; Ponnam et al., 2007; Lin et al., 2008; Schmidt et al., 2008; Vanita et al., 2008; Yan et al., 2008; Graw et al., 2009; Hansen et al., 2009; Wang et al., 2009; Gao et al., 2010; Hu et al., 2010; He et al., 2011; Kumar et al., 2011; Sun et al., 2011a; Wang L et al., 2011; Li et al., 2013; Ponnam et al., 2013; Reis et al., 2013; Su et al., 2013; Chen et al., 2014; Ge et al., 2014; Gillespie et al., 2014; Mackay et al., 2014; Prokudin et al., 2014; Sun et al., 2014; Zhu et al., 2014; Chen et al., 2015; Liang et al., 2015; Yang Z et al., 2015; Ma AS et al., 2016; Min et al., 2016; Yu et al., 2016
9q21.12	<i>TRPM3</i>	AD		open-angle glaucoma	family of transient receptor potential channels	Bennett et al., 2014
11p13	<i>PAX6</i>	AD		aniridia "plus" (iris and foveal hypoplasia, nystagmus, cataract, corneal abnormalities, glaucoma)	a homeobox and paired domain-containing protein that binds DNA	LOVD PAX6 Homepage
11q13	<i>BEST1</i>	AD	pulverulent-like	vitreoretinchoroidopathy, microcornea, rod-cone dystrophy, cataract, posterior staphyloma	a member of the bestrophin gene family	Boon et al., 2009
14q24.3	<i>VSX2</i>	AR		microphthalmia, anophthalmia, iris coloboma	a homeobox protein originally described as a retina-specific transcription factor	Ferda Percin et al., 2000
15q22.32	<i>NR2E3</i>	AD, AR		retinitis pigmentosa-37, enhanced S-cone syndrome	a family of nuclear receptor transcription factors	Edwards et al., 2008
15q25.1	<i>MIR184</i>	AD	congenital, early-onset anterior polar	endothelial dystrophy, iris hypoplasia, cataract and stromal thinning (EDICT) syndrome, keratoconus. Corneal anomalies	microRNAs involved in post-transcriptional regulation of gene expression	Iliff et al., 2012; Bykhovskaya et al., 2015
17p13.1	<i>GUCY2D</i>	AR		Leber congenital amaurosis-1	a retina-specific guanylate cyclase	Gradstein et al., 2016
21q22.3	<i>CRYAA</i>	AR/AD	nuclear, laminar, posterior polar, punctate, spike-like, ring-like, fan-shaped, disc-like, Y-sutural, zonular, lamellar, polymorphic, perinuclear	microcornea, iris coloboma, axial elongation, macular hypoplasia, corneal opacity	chaperone-like small heat-shock protein family	Litt et al., 1998; Pras et al., 2000; Mackay et al., 2003; Graw et al., 2006; Santhiya et al., 2006; Vanita et al., 2006; Beby et al., 2007; Hansen et al., 2007; Khan et al., 2007; Devi et al., 2008; Gu et al., 2008; Richter et al., 2008; Hansen et al., 2009; Santana et al., 2009; Zhang et al., 2009a; Li et al., 2010; Sun et al., 2011a; Su et al., 2012; Wang and Zhu, 2012; Kondo et al., 2013; Laurie et al., 2013; Reis et al., 2013; Yang et al., 2013; Kong et al., 2015; Liang et al., 2015; Javadiyan et al., 2016; Li D et al., 2016; Ma AS et al., 2016
22q12.1	<i>CRYBA4</i>	AD	congenital nuclear, lamellar	microcornea, microphthalmia	soluble proteins in the human lens	Billingsley et al., 2006; Zhou G et al., 2010
For abbreviations, see Table 2.

Fig. 2. The structure of CRYGD, from <https://swissmodel.expasy.org/>.

Crystallins

Crystallins are divided in α , β , and γ and constitute around 90% of the soluble proteins of the lens with an asymmetric and biphasic distribution [Augusteyn, 2010]. α -crystallins (α A-crystallin and α B-crystallin) belong to the chaperone-like small heat shock protein family (sHSPs). They block the formation of stress protein aggregates to avoid toxic effects [Clark et al., 2012]. The sHSPs are large, polydisperse, and do not crystallize, thus playing an important role in the lens. It is likely that the high refractive index of a lens with no compromise of transparency is due to the ability to form extended lattices of the water-insoluble α -crystallin [Slingsby et al., 2013]. Outside of the lens, α -crystallin is expressed principally in the retina, the muscle, and the brain. In the retina, it seems to be implicated in cytoprotection, cell survival, inflammation, and autophagy [Kannan et al., 2012]. A great diversity of mutations associated with cataracts has been reported in the *CRYAA* and *CRYAB* genes, whose products are α A-crystallin and α B-crystallin, respectively. In approximately half of the cases, *CRYAA* gene defects are associated with eye anomalies,

whereas *CRYAB* gene defects are associated with myofibrillar myopathy (Tables 1, 4); in both cases, the rest of the reports connect lens opacities with great clinical heterogeneity (Table 4). Most cases show an autosomal dominant pattern, and in a few cases, a recessive autosomal inheritance.

The β - and γ -crystallins consist of 4 similarly folded Greek key motifs organized into 2 domains. The Greek key motif is a structure of 4 β -sheets, folded in an anti-parallel form that generates a folded compact domain [Richardson, 1977]. The values and gradients in the refractive index of lens proteins seem to be related to the Greek key motif [Zhao et al., 2011]. The central portion and the embryonic nuclear region of the lens are rich in β - and γ -crystallins. In humans, γ -crystallins comprise from γ A to γ F. Now, γ S-crystallin (β S-crystallin) is also included in this group; γ E and γ F are pseudogenes. Interestingly, *CRYBA*, *CRYBB*, *CRYGA*, *CRYGB*, *CRYGC*, *CRYGD*, and *CRYGS* gene mutations are only associated with inherited CC and no other systemic or eye anomalies (Table 3). In Figure 2, the normal CYGD crystallin structure is shown.

Fig. 3. The structure of EPHA2, from <https://swissmodel.expasy.org/>.

EPH2

The *EPHA2* (ephrin receptor A2) gene encodes a transmembrane tyrosine kinase receptor (epithelial cell) which contains an extracellular ligand-binding domain and is expressed in the human lens [Pasquale, 2010]. *EPH2*, with its ligands ephrin-A1 or ephrin-A5, has a role in cell adhesion and cell repulsion [Miao and Wang, 2009]. Inhibition of *EPHA2* induces apoptosis and abrogates tumorigenic growth of tumor cells [Amato et al., 2014]. Apparently, the downstream signaling of activated *EPHA2* promotes the antioxidative capacity of lens epithelial cells to eradicate the overproduction of reactive oxygen species [Yang J et al., 2015]. It is probable that the loss of *EPHA2* function could affect the structural stability of the cell, cell-to-cell crosstalk, protein folding and transcriptional activation [Park et al., 2013]. Thus, the cytoprotective and antiapoptotic functions of *EPHA2* in the lens indicate the possible role of *EPHA2* in avoiding lens opacity. Practically, all mutations reported in the *EPH2* gene are associated exclusively with inherited CC and no other anomalies (some cataracts are age related, as well). Only one study reports microcornea with mild dysmorphic features [Gillespie et al., 2014]. Both autosomal recessive and domi-

nant patterns as well as clinical heterogeneity are present (Table 3). Figure 3 shows the structure of the EPH2 protein.

GJA3 and GJA8

The *GJA3* (gap junction alpha-3) gene encodes connexin 46, whereas the *GJA8* (gap junction alpha-8) gene encodes connexin 50, gap junction channel proteins that play an important role in lens cell homeostasis. Connexin proteins have 4 transmembrane domains, 3 intracellular regions, and 2 extracellular loops. Six connexin subunits form 1 connexon. Connexin 46 and connexin 50 are expressed in the lens fiber cells and are essential for the coupling of mature fibers in the central core of the lens [Gong et al., 1997; Martinez-Wittinghan et al., 2004]. Connexins allow the interchange of ions and low-molecular-weight molecules between contiguous cells. Connexin 46 and connexin 50 are the major components of human lens fiber cells, and their molecular defects result in about 20% of nonsyndromic cataract reports [Shiels et al., 2010]. *GJA3* gene mutations produce only cataracts with no other manifestations, unlike *GJA8* that includes the presence of microcornea in half of the reports (Tables 3, 4). The structure of connexin 46 is shown in Figure 4.

Fig. 4. The structure of GJA3, from <https://swissmodel.expasy.org/>.

MIP

The *MIP* (major intrinsic protein) gene encodes aquaporin 0 (AQP0), the most abundant protein in the fiber cell membrane that functions as a water channel and belongs to the superfamily of AQPs [Shiels et al., 2001]. AQPs create a microcirculation in the avascular lens to nourish central fiber cells, maintaining their transparency and homeostasis [Gao et al., 2013]. AQP0 accounts for about 45% of the total plasma proteins [Bassnett et al., 2009]. Homozygous or heterozygous loss of AQP0 will reduce the water permeability of lens fiber cells producing lens opacities in mice [Shiels et al., 2001]. Apart from the intermolecular contacts between AQP0 monomers, AQP0 interacts with other proteins in lens fiber cells as crystallins and connexins [Liu and Liang 2008; Liu et al. 2011]. Mutations in the *MIP* gene result only in cataracts with no other manifestations, and all of them are inherited in an autosomal dominant pattern (Table 3). The structure of the AQP0 channel is shown in Figure 5.

FYCO1

FYCO (FYVE and coiled-coil domain containing 1), a PI(3)P-, Rab7-, and LC3-binding protein, mediates microtubule plus end-directed vesicle transport of autophagosomes, a required process for autolysosome formation

[Pankiv et al., 2010]. FYCO1 is expressed in the lens epithelium and fiber cells (principally in nuclear fibers) in newborn mice, suggesting that autophagy is important in lens fiber cell differentiation [Brennan et al., 2012]. When FYCO1 is lacking, phagosomes stay p40phox⁺ longer and produce more reactive oxygen. This represents FYCO1's participation in the immunity role of regulating the phagosome maturation process and production of reactive oxygen, processes necessary for handling extracellular pathogens [Ma et al., 2014]. All mutations reported in the *FYCO1* gene are inherited in an autosomal recessive pattern and have no other systemic or eye anomalies (Table 3). Figure 6 shows the structure of the FYCO1 protein.

BFSP1 and BFSP2

BFSP1 (filesin, CP115) and BFSP2 (phakinin, CP49), lens-specific proteins, are the principal components of beaded filaments, which are unique cytoskeletal lens structures [Alizadeh et al., 2003]. *BFSP1* and *BFSP2* genes (beaded filament structural protein 1 and 2) encode these proteins. Apparently, the beaded filament is required to maintain cell morphology, 3-dimensional membrane architecture and lens transparency during fetal development and fiber cell differentiation [Alizadeh et al., 2002]. Both genes are associated with cataracts with no other

Fig. 5. The structure of MIP, from <https://swissmodel.expasy.org/>.

Fig. 6. The structure of FYCO1, from <https://swissmodel.expasy.org/>.

Fig. 7. The structure of BFSP1, from <https://swissmodel.expasy.org/>.

anomalies: the *BFS1* gene inherited in an autosomal recessive pattern and the *BFS2* gene inherited in autosomal dominant and recessive patterns. Figure 7 shows the BFSP1 structure.

Nonsyndromic Cataracts with Eye Anomalies

In some cases, nonsyndromic cataracts are associated with eye anomalies; about 15 genes have been reported in the literature with this condition (Tables 3, 4), but only a few genes have consistently presented this association (*BEST1*, *VSX2*, *NR2E3*, *MIR184*, and *GUCY2D*). The rest of the genes (*CRYGB*, *CRYGA*, *FYCO1*, *BFSP2*, *CRYGS*, *WDR36*, *GCNT2*, *RRAGA*, *CTPL1*, *TDRD7*, *VIM*, *MIP*, *GJA3*, *TMEM114*, *HSF4*, *CRYBA1*, *UNC45B*, *LONP1*, *SIPA1L3*, *WDR87*, *LIM2*, *BFSP1*, *CHMP4B*, and *LSS*) have also been reported with inherited CC exclusively. The principal eye anomalies correspond to microcornea, aniridia, microphthalmia, or vitreoretinal dysplasia.

IRE, GALK1 and GCNT2

The hyperferritinaemia-cataract syndrome (OMIM 600886), an autosomal dominant condition, presents high serum ferritin levels and bilateral CCs. Mutations in the I-ferritin gene that encodes the iron-responsive element (IRE) results in hyperferritinaemia-cataract syndrome

(<http://www.hgmd.cf.ac.uk/ac/gene.php?gene=FTL>). The IRE in the ferritin mRNAs is a structure in the 5'-untranslated region. The increase of iron diminishes the binding of trans-acting iron-regulatory proteins with the ferritin mRNA structure, resulting in increased ferritin mRNA translation. Mutations in the IRE block this IRE-mediated regulation of ferritin production with the subsequent hyperferritinemia [Brooks et al., 2002]; this gene defect produces CC. Galactokinase 1 converts galactose into galactose-1-phosphate, when galactokinase deficiency is present, the accumulating galactose is converted to galactitol by aldose reductase and the cataractogenesis is observed. In this case, only CC with no other manifestations is present (Table 3). The human blood i and I antigens are linear and branched repeats of N-acetyllactosamine, respectively. The I-branching beta-1,6-N-acetylglucosaminyltransferase enzyme catalyzes the conversion of the i to the I antigen. Null phenotype of I (the adult i phenotype) is associated with CC. The gene defect in the I locus leads to the formation of CC with no other clinical manifestations (Table 3).

Diagnosis of Inherited Cataracts

As previously described, hereditary CC is a difficult condition to diagnose genetically due to more than 100 genes that have been associated with it. This task is even more difficult if no specific inherited pattern is observed in the pedigree. When systemic anomalies are present in the clinical symptomatology, syndromic cataracts are a possible diagnosis. The presence of cataracts with no other alterations reduces the genes involved to 35. Fortunately, the new molecular tools are very useful in identifying the gene affection with the support of clinical data. Next-generation sequencing (NGS) certainly represents an excellent tool for analyzing inherited cataracts. Some physicians believe the technique should not be used in cases of monogenic diseases due to high costs and the fact that it generates volumes of data which can be difficult to interpret. The analysis would be easier to interpret if the potentially affected gene is preselected. NGS enables identifying mutations throughout the human genome by facilitating the genetic diagnosis of hereditary diseases, of course including CCs, and has opened a new pathway in genetic diagnosis.

Disclosure Statement

The authors report no conflicts of interest.

References

- Addison PK, Berry V, Holden KR, Espinal D, Rivera B, et al: A novel mutation in the connexin 46 gene (*GJA3*) causes autosomal dominant zonular pulverulent cataract in a Hispanic family. *Mol Vis* 12:791–795 (2006).
- Aldahmesh MA, Khan AO, Mohamed J, Alkuraya FS: Novel recessive *BFSP2* and *PITX3* mutations: insights into mutational mechanisms from consanguineous populations. *Genet Med* 11:978–981 (2011).
- Aldahmesh MA, Khan AO, Mohamed JY, Hijazi H, Al-Owain M, et al: Genomic analysis of pediatric cataract in Saudi Arabia reveals novel candidate disease genes. *Genet Med* 14:955–962 (2012).
- AlFadhli S, Abdelmoaty S, Al-Hajeri A, Behbehani A, Alkuraya F: Novel crystallin gamma B mutations in a Kuwaiti family with autosomal dominant congenital cataracts reveal genetic and clinical heterogeneity. *Mol Vis* 18:2931–2936 (2012).
- Ali M, Buentello-Volante B, McKibbin M, Rocha-Medina JA, Fernandez-Fuentes N, et al: Homozygous *FOXE3* mutations cause non-syndromic, bilateral, total sclerocornea, aphakia, microphthalmia and optic disc coloboma. *Mol Vis* 16:1162–1168 (2010).
- Alizadeh A, Clark JI, Seeberger T, Hess J, Blankenship T, et al: Targeted genomic deletion of the lens-specific intermediate filament protein CP49. *Invest Ophthalmol Vis Sci* 43:3722–3727 (2002).
- Alizadeh A, Clark J, Seeberger T, Hess J, Blankenship T, FitzGerald PG: Targeted deletion of the lens fiber cell-specific intermediate filament protein filensin. *Invest Ophthalmol Vis Sci* 44:5252–5258 (2003).
- Amato KR, Wang S, Hastings AK, Youngblood VM, Santapuram PR, et al: Genetic and pharmacologic inhibition of *EPHA2* promotes apoptosis in NSCLC. *J Clin Invest* 124:2037–2049 (2014).
- Anjum I, Eiberg H, Baig SM, Tommerup N, Hansen L: A mutation in the *FOXE3* gene causes congenital primary aphakia in an autosomal recessive consanguineous Pakistani family. *Mol Vis* 16:549–555 (2010).
- Apple DJ, Ram J, Foster A, Peng Q: Elimination of cataract blindness: a global perspective entering the new millennium. *Surv Ophthalmol* 45 Suppl 1:S1–196 (2000).
- Arora A, Minogue PJ, Liu X, Reddy MA, Ainsworth JR, et al: A novel *GJA8* mutation is associated with autosomal dominant lamellar pulverulent cataract: further evidence for gap junction dysfunction in human cataract. *J Med Genet* 43:e2 (2006).
- Arora A, Minogue PJ, Liu X, Addison PK, Russell-Eggitt I, et al: A novel connexin50 mutation associated with congenital nuclear pulverulent cataracts. *J Med Genet* 45:155–160 (2008).
- Asada M, Okano Y, Imamura T, Suyama I, Hase Y, Isshiki G: Molecular characterization of galactokinase deficiency in Japanese patients. *J Hum Genet* 44:377–382 (1999).
- Augusteyn RC: On the growth and internal structure of human lens. *Exp Eye Res* 90:643–654 (2010).
- Azuma N, Hirakiyama A, Inoue T, Asaka A, Yamada M: Mutations of a human homologue of the *Drosophila* eyes absent gene (*EYA1*) detected in patients with congenital cataracts and ocular anterior segment anomalies. *Hum Mol Genet* 9:363–366 (2000).
- Bassnett S, Wilmarth PA, David LL: The membrane proteome of the mouse lens fiber cell. *Mol Vis* 15:2448–2463 (2009).
- Bateman JB, Geyer DD, Flodman P, Johannes M, Sikela J, et al: A new betaA1-crystallin splice junction mutation in autosomal dominant cataract. *Invest Ophthalmol Vis Sci* 41:3278–3285 (2000).
- Bateman JB, von-Bischhoffshaunsen FR, Richter L, Flodman P, Burch D, Spence MA: Gene conversion mutation in crystallin, beta-B2 (*CRYBB2*) in a Chilean family with autosomal dominant cataract. *Ophthalmology* 114:425–432 (2007).
- Beby F, Commeaux C, Bozon M, Denis P, Edery P, Morlé L: New phenotype associated with an Arg116Cys mutation in the *CRYAA* gene: nuclear cataract, iris coloboma, and microphthalmia. *Arch Ophthalmol* 125:213–216 (2007).
- Behnam M, Imagawa E, Chaleshtori AR, Ronasian F, Salehi M, et al: A novel homozygous mutation in *HSF4* causing autosomal recessive congenital cataract. *J Hum Genet* 61:177–179 (2016).
- Bennett TM, Shiels A: A recurrent missense mutation in *GJA3* associated with autosomal dominant cataract linked to chromosome 13q. *Mol Vis* 17:2255–2262 (2011).
- Bennett TM, Mackay DS, Knopf HL, Shiels A: A novel missense mutation in the gene for gap-junction protein alpha3 (*GJA3*) associated with autosomal dominant “nuclear punctate” cataracts linked to chromosome 13q. *Mol Vis* 10:376–382 (2004).
- Bennett TM, Mackay DS, Siegfried CJ, Shiels A: Mutation of the melastatin-related cation channel, TRPM3, underlies inherited cataract and glaucoma. *PLoS One* 9:e104000 (2014).
- Berry V, Mackay D, Khaliq S, Francis PJ, Hameed A, et al: Connexin 50 mutation in a family with congenital “zonular nuclear” pulverulent cataract of Pakistani origin. *Hum Genet* 105:168–170 (1999).
- Berry V, Francis P, Kaushal S, Moore A, Bhat-tacharya S: Missense mutations in *MIP* underlie autosomal dominant “polymorphic” and lamellar cataracts linked to 12q. *Nat Genet* 25:15–17 (2000).
- Berry V, Francis P, Reddy MA, Collyer D, Vithana E, et al: Alpha-B crystallin gene (*CRYAB*) mutation causes dominant congenital posterior polar cataract in humans. *Am J Hum Genet* 69:1141–1145 (2001).
- Berry V, Gregory-Evans C, Emmett W, Waseem N, Raby J, et al: Wolfram gene (*WFS1*) mutation causes autosomal dominant congenital nuclear cataract in humans. *Eur J Hum Genet* 21:1356–1360 (2013).
- Bhishagratna K: An English translation of the *SushrutaSamhitā*: Based on original Sanskrit text, with a full and comprehensive introduction, additional texts, different readings, notes, comparative views, index, glossary and plates, in Chowkhamba Sanskrit Series Office, vol 3:XVII, pp 206–210 (Calcutta, Varanasi 2005).
- Billingsley G, Santhiya ST, Paterson AD, Ogata K, Wodak S, et al: *CRYBA4*, a novel human cataract gene, is also involved in microphthalmia. *Am J Hum Genet* 79:702–709 (2006).
- Boon CJ, Klevering BJ, Leroy BP, Hoyng CB, Keunen JE, den Hollander AI: The spectrum of ocular phenotypes caused by mutations in the *BEST1* gene. *Prog Retin Eye Res* 28:187–205 (2009).
- Boone PM, Yuan B, Gu S, Ma Z, Gambin T, et al: Hutterite-type cataract maps to chromosome 6p21.32–p21.31, cosegregates with a homozygous mutation in *LEMD2*, and is associated with sudden cardiac death. *Mol Genet Genomic Med* 4:77–94 (2015).
- Borck G, Kakar N, Hoch J, Friedrich K, Freudenberger J, et al: An Alu repeat-mediated genomic *GCNT2* deletion underlies congenital cataracts and adult i blood group. *Hum Genet* 131:209–216 (2012).
- Brémond-Gignac D, Bitoun P, Reis LM, Copin H, Murray JC, Semina EV: Identification of dominant *FOXE3* and *PAX6* mutations in patients with congenital cataract and aniridia. *Mol Vis* 16:1705–1711 (2010).
- Brennan LA, Kantorow WL, Chauss D, McGreal R, He S, et al: Spatial expression patterns of autophagy genes in the eye lens and induction of autophagy in lens cells. *Mol Vis* 18:1773–1786 (2012).
- Brooks DG, Manova-Todorova K, Farmer J, Lobmayr L, Wilson RB, et al: Ferritin crystal cataracts in hereditary hyperferritinemia cataract syndrome. *Invest Ophthalmol Vis Sci* 43:1121–1126 (2002).
- Bu J, He S, Wang L, Li J, Liu J, Zhang X: A novel splice donor site mutation in *EPHA2* caused congenital cataract in a Chinese family. *Indian J Ophthalmol* 64:364–368 (2016).
- Bu L, Jin Y, Shi Y, Chu R, Ban A, Eiberg H, et al: Mutant DNA-binding domain of *HSF4* is associated with autosomal dominant lamellar and Marner cataract. *Nat Genet* 31:276–278 (2002).
- Burdon KP, Wirth MG, Mackey DA, Russell-Eggitt IM, Craig JE, et al: A novel mutation in the Connexin 46 gene causes autosomal dominant congenital cataract with incomplete penetrance. *J Med Genet* 41:e106 (2004).
- Bykhovskaya Y, Caiado Canedo AL, Wright KW, Rabinowitz YS: C.57C>T mutation in *MIR184* is responsible for congenital cataracts and corneal abnormalities in a five-generation family from Galicia, Spain. *Ophthalmic Genet* 36:244–247 (2015).

- Chacon-Camacho OF, Buentello-Volante B, Velázquez-Montoya R, Ayala-Ramirez R, Zenteno JC: Homozygosity mapping identifies a *GALK1* mutation as the cause of autosomal recessive congenital cataracts in 4 adult siblings. *Gene* 534:218–221 (2014).
- Chance B: *Clio Medica: A Series of Primers on the History of Medicine*, vol XX, Krumbhaar EB (ed), Cloth (Paul B. Hoeber Inc., New York 1939).
- Chen C, Sun Q, Gu M, Liu K, Sun Y, Xu X: A novel Cx50 (*GJA8*) p.H277Y mutation associated with autosomal dominant congenital cataract identified with targeted next-generation sequencing. *Graefes Arch Clin Exp Ophthalmol* 253:915–924 (2015).
- Chen J, Ma Z, Jiao X, Fariss R, Kantorow WL, et al: Mutations in *FYCO1* cause autosomal-recessive congenital cataracts. *Am J Hum Genet* 88:827–838 (2011).
- Chen JH, Qiu J, Chen H, Pang CP, Zhang M: Rapid and cost-effective molecular diagnosis using exome sequencing of one proband with autosomal dominant congenital cataract. *Eye (Lond)* 28:1511–1516 (2014).
- Chen JH, Huang C, Zhang B, Yin S, Liang J, et al: Mutations of RagA GTPase in mTORC1 pathway are associated with autosomal dominant cataracts. *PLoS Genet* 12:e1006090 (2016).
- Chen Q, Ma J, Yan M, Mothobi ME, Liu Y, Zheng F: A novel mutation in *CRYAB* associated with autosomal dominant congenital nuclear cataract in a Chinese family. *Mol Vis* 15:1359–1365 (2009).
- Chen W, Chen X, Hu Z, Lin H, Zhou F, et al: A missense mutation in *CRYBB2* leads to progressive congenital membranous cataract by impacting the solubility and function of β B2-crystallin. *PLoS One* 8:e81290 (2013).
- Clark AR, Lubsen NH, Slingsby C: sHSP in the eye lens: crystallin mutations, cataract and proteostasis. *Int J Biochem Cell Biol* 44:1687–1697 (2012).
- Coccia M, Brooks SP, Webb TR, Christodoulou K, Wozniak IO, et al: X-linked cataract and Nance-Horan syndrome are allelic disorders. *Hum Mol Genet* 18:2643–2655 (2009).
- Cohen D, Bar-Yosef U, Levy J, Gradstein L, Belfair N, et al: Homozygous *CRYBB1* deletion mutation underlies autosomal recessive congenital cataract. *Invest Ophthalmol Vis Sci* 48:2208–2213 (2007).
- Conley YP, Erturk D, Keverline A, Mah TS, Keralava A, et al: A juvenile-onset, progressive cataract locus on chromosome 3q21-q22 is associated with a missense mutation in the beaded filament structural protein-2. *Am J Hum Genet* 66:1426–1431 (2000).
- Cui X, Gao L, Jin Y, Zhang Y, Bai J, et al: The E233del mutation in *BFSP2* causes a progressive autosomal dominant congenital cataract in a Chinese family. *Mol Vis* 13:2023–2029 (2007).
- Dave A, Laurie K, Staffieri SE, Taranath D, Mackey DA, et al: Mutations in the *EPHA2* gene are a major contributor to inherited cataracts in South-Eastern Australia. *PLoS One* 8:e72518 (2013).
- Devi RR, Vijayalakshmi P: Novel mutations in *GJA8* associated with autosomal dominant congenital cataract and microcornea. *Mol Vis* 12:190–195 (2006).
- Devi RR, Reena C, Vijayalakshmi P: Novel mutations in *GJA3* associated with autosomal dominant congenital cataract in the Indian population. *Mol Vis* 11:846–852 (2005).
- Devi RR, Yao W, Vijayalakshmi P, Sergeev YV, Sundaresan P, Hejtmancik JF: Crystallin gene mutations in Indian families with inherited pediatric cataract. *Mol Vis* 14:1157–1170 (2008).
- Ding X, Wang B, Luo Y, Hu S, Zhou G, et al: A novel mutation in the connexin 46 (*GJA3*) gene associated with congenital cataract in a Chinese pedigree. *Mol Vis* 17:1343–1349 (2011).
- Ding X, Zhou N, Lin H, Chen J, Zhao C, et al: A novel *MIP* gene mutation analysis in a Chinese family affected with congenital progressive punctate cataract. *PLoS One* 9:e102733 (2014).
- Doucette L, Green J, Fernandez B, Johnson GJ, Parfrey P, Young TL: A novel, non-stop mutation in *FOXE3* causes an autosomal dominant form of variable anterior segment dysgenesis including Peters anomaly. *Eur J Hum Genet* 19:293–299 (2011).
- Edwards AO: Clinical features of the congenital vitreoretinopathies. *Eye (Lond)* 22:1233–1242 (2008).
- Eiberg H, Lund AM, Warburg M, Rosenberg T: Assignment of congenital cataract Volkmann type (CCV) to chromosome 1p36. *Hum Genet* 96:33–38 (1995).
- Faletta F, d'Adamo AP, Pensiero S, Athanasakis E, Catalano D, et al: A novel *CRYBB2* missense mutation causing congenital autosomal dominant cataract in an Italian family. *Ophthalmic Genet* 34:115–117 (2013).
- Ferda Percin E, Ploder LA, Yu JJ, Arici K, Horsford DJ, et al: Human microphthalmia associated with mutations in the retinal homeobox gene *CHX10*. *Nat Genet* 25:397–401 (2000).
- Ferrini W, Schorderet DF, Othenin-Girard P, Uffer S, Héon E, Munier FL: *CRYBA3/A1* gene mutation associated with suture-sparing autosomal dominant congenital nuclear cataract: a novel phenotype. *Invest Ophthalmol Vis Sci* 45:1436–1441 (2004).
- Florijn RJ, Loves W, Maillette de Buy Wenniger-Prick LJ, Mannens MM, Tijmes N, et al: New mutations in the *NHS* gene in Nance-Horan Syndrome families from the Netherlands. *Eur J Hum Genet* 14:986–990 (2006).
- Forshaw T, Johnson CA, Khaliq S, Pasha S, Willis C, et al: Locus heterogeneity in autosomal recessive congenital cataracts: linkage to 9q and germline *HSF4* mutations. *Hum Genet* 117:452–459 (2005).
- Gao J, Wang H, Sun X, Varadaraj K, Li L, et al: The effects of age on lens transport. *Invest Ophthalmol Vis Sci* 54:7174–7187 (2013).
- Gao M, Huang S, Li J, Zou Y, Xu P, et al: A novel pathogenic mutation of *CRYGD* gene in a congenital cataract family (in Chinese). *Zhonghua Yi Xue Yi Chuan Xue Za Zhi* 4:515–518 (2016).
- Gao X, Cheng J, Lu C, Li X, Li F, et al: A novel mutation in the connexin 50 gene (*GJA8*) associated with autosomal dominant congenital nuclear cataract in a Chinese family. *Curr Eye Res* 35:597–604 (2010).
- Garnai SJ, Huyghe JR, Reed DM, Scott KM, Liebmann JM, et al: Congenital cataracts: de novo gene conversion event in *CRYBB2*. *Mol Vis* 20:1579–1593 (2014).
- Ge XL, Zhang Y, Wu Y, Lv J, Zhang W, et al: Identification of a novel *GJA8* (Cx50) point mutation causes human dominant congenital cataracts. *Sci Rep* 4:4121 (2014).
- Geyer DD, Spence MA, Johannes M, Flodman P, Clancy KP, et al: Novel single-base deletion mutation in major intrinsic protein (*MIP*) in autosomal dominant cataract. *Am J Ophthalmol* 141:761–763 (2006).
- Gilbert C, Foster A: Childhood blindness in the context of VISION 2020 – the right to sight. *Bull World Health Organ* 79:227–232 (2001).
- Gill D, Klose R, Munier FL, McFadden M, Priston M, et al: Genetic heterogeneity of the Cop-pock-like cataract: a mutation in *CRYBB2* on chromosome 22q11.2. *Invest Ophthalmol Vis Sci* 41:159–165 (2000).
- Gillespie RL, O'Sullivan J, Ashworth J, Bhaskar S, Williams S, et al: Personalized diagnosis and management of congenital cataract by next-generation sequencing. *Ophthalmology* 121:2124–2137 (2014).
- Gong X, Li E, Klier G, Huang Q, Wu Y, et al: Disruption of alpha3 connexin gene leads to proteolysis and cataractogenesis in mice. *Cell* 91:833–843 (1997).
- Gonzalez-Huerta LM, Messina-Baas OM, Cuevas-Covarrubias SA: A family with autosomal dominant primary congenital cataract associated with a *CRYGC* mutation: evidence of clinical heterogeneity. *Mol Vis* 13:1333–1338 (2007).
- Gradstein L, Zolotushko J, Sergeev YV, Lavy I, Narkis G, et al: Novel *GUCY2D* mutation causes phenotypic variability of Leber congenital amaurosis in a large kindred. *BMC Med Genet* 17:52 (2016).
- Graw J, Klopp N, Illig T, Preising MN, Lorenz B: Congenital cataract and macular hypoplasia in humans associated with a de novo mutation in *CRYAA* and compound heterozygous mutations in P. *Graefes Arch Clin Exp Ophthalmol* 244:912–919 (2006).
- Graw J, Schmidt W, Minogue PJ, Rodriguez J, Tong JJ, et al: The *GJA8* allele encoding CX50I247M is a rare polymorphism, not a cataract-causing mutation. *Mol Vis* 15:1881–1885 (2009).
- Greenlees R, Mihelec M, Yousoof S, Speidel D, Wu SK, et al: Mutations in *SIPA1L3* cause eye defects through disruption of cell polarity and cytoskeleton organization. *Hum Mol Genet* 24:5789–5804 (2015).
- Gu F, Li R, Ma XX, Shi LS, Huang SZ, Ma X: A missense mutation in the gammaD-crystallin gene *CRYGD* associated with autosomal dominant congenital cataract in a Chinese family. *Mol Vis* 12:26–31 (2006).

- Gu F, Zhai H, Li D, Zhao L, Li C, et al: A novel mutation in major intrinsic protein of the lens gene (*MIP*) underlies autosomal dominant cataract in a Chinese family. *Mol Vis* 13:1651–1656 (2007).
- Gu F, Luo W, Li X, Wang Z, Lu S, et al: A novel mutation in AlphaA-crystallin (*CRYAA*) caused autosomal dominant congenital cataract in a large Chinese family. *Hum Mutat* 29:769 (2008).
- Gu J, Qi Y, Wang L, Wang J, Shi L, et al: A new congenital nuclear cataract caused by a missense mutation in the gammaD-crystallin gene (*CRYGD*) in a Chinese family. *Mol Vis* 11:971–976 (2005).
- Gu Z, Ji B, Wan C, He G, Zhang J, et al: A splice site mutation in *CRYBA1/A3* causing autosomal dominant posterior polar cataract in a Chinese pedigree. *Mol Vis* 16:154–160 (2010).
- Guleria K, Sperling K, Singh D, Varon R, Singh JR, Vanita V: A novel mutation in the connexin 46 (*GJA3*) gene associated with autosomal dominant congenital cataract in an Indian family. *Mol Vis* 13:1657–1665 (2007).
- Guo Y, Su D, Li Q, Yang Z, Ma Z, et al: A nonsense mutation of *CRYGC* associated with autosomal dominant congenital nuclear cataracts and microcornea in a Chinese pedigree. *Mol Vis* 18:1874–1880 (2012).
- Guo Y, Yuan L, Yi J, Xiao J, Xu H, et al: Identification of a *GJA3* mutation in a Chinese family with congenital nuclear cataract using exome sequencing. *Indian J Biochem Biophys* 50:253–258 (2013).
- Hansen L, Yao W, Eiberg H, Funding M, Riise R, et al: The congenital ‘ant-egg’ cataract phenotype is caused by a missense mutation in connexin46. *Mol Vis* 12:1033–1039 (2006).
- Hansen L, Eiberg H, Rosenberg T: Novel *MAF* mutation in a family with congenital cataract-microcornea syndrome. *Mol Vis* 13:2019–2022 (2007).
- Hansen L, Mikkelsen A, Nürnberg P, Nürnberg G, Anjum I, et al: Comprehensive mutational screening in a cohort of Danish families with hereditary congenital cataract. *Invest Ophthalmol Vis Sci* 50:3291–3303 (2009).
- Hansen L, Comyn S, Mang Y, Lind-Thomsen A, Myhre L, et al: The myosin chaperone *UNC45B* is involved in lens development and autosomal dominant juvenile cataract. *Eur J Hum Genet* 22:1290–1297 (2014).
- Happ H, Weh E, Costakos D, Reis LM, Semina EV: Case report of homozygous deletion involving the first coding exons of *GCNT2* isoforms A and B and part of the upstream region of *TFAP2A* in congenital cataract. *BMC Med Genet* 17:64 (2016).
- He W, Li X, Chen J, Xu L, Zhang F, et al: Genetic linkage analyses and *Cx50* mutation detection in a large multiplex Chinese family with hereditary nuclear cataract. *Ophthalmic Genet* 32:48–53 (2011).
- Hejtmancik JF, Smaoui N: Molecular genetics of cataract. *Dev Ophthalmol* 37:67–82 (2003).
- Héon E, Priston M, Schorderet DF, Billingsley GD, Girard PO, et al: The gamma-crystallins and human cataracts: a puzzle made clearer. *Am J Hum Genet* 65:1261–1277 (1999).
- Héon E, Paterson AD, Fraser M, Billingsley G, Priston M, et al: A progressive autosomal recessive cataract locus maps to chromosome 9q13-q22. *Am J Hum Genet* 68:772–777 (2001).
- Hoehenwarter W, Klose J, Jungblut PR: Eye lens proteomics. *Amino Acids* 30:369–389 (2006).
- Hu S, Wang B, Zhou Z, Zhou G, Wang J, et al: A novel mutation in *GJA8* causing congenital cataract-microcornea syndrome in a Chinese pedigree. *Mol Vis* 16:1585–1592 (2010).
- Hu Y, Gao L, Feng Y, Yang T, Huang S, et al: Identification of a novel mutation of the gene for gap junction protein $\alpha 3$ (*GJA3*) in a Chinese family with congenital cataract. *Mol Biol Rep* 41:4753–4758 (2014).
- Hunter M, Angelicheva D, Levy HL, Pueschel SM, Kalaydjieva L: Novel mutations in the *GALK1* gene in patients with galactokinase deficiency. *Hum Mutat* 17:77–78 (2001).
- Iliff BW, Riazuddin SA, Gottsch JD: A single-base substitution in the seed region of miR-184 causes EDICT syndrome. *Invest Ophthalmol Vis Sci* 53:348–353 (2012).
- Inaba N, Hiruma T, Togayachi A, Iwasaki H, Wang XH, et al: A novel I-branching beta-1,6-N-acetylglucosaminyltransferase involved in human blood group I antigen expression. *Blood* 101:2870–2876 (2003).
- Iseri SU, Osborne RJ, Farrall M, Wyatt AW, Mirza G, et al: Seeing clearly: the dominant and recessive nature of *FOXE3* in eye developmental anomalies. *Hum Mutat* 30:1378–1386 (2009).
- Jakobs PM, Hess JF, FitzGerald PG, Kramer P, Weleber RG, Litt M: Autosomal-dominant congenital cataract associated with a deletion mutation in the human beaded filament protein gene *BFSP2*. *Am J Hum Genet* 66:1432–1436 (2000).
- Jamieson RV, Perveen R, Kerr B, Carette M, Yardley J, et al: Domain disruption and mutation of the bZIP transcription factor, *MAF*, associated with cataract, ocular anterior segment dysgenesis and coloboma. *Hum Mol Genet* 11:33–42 (2002).
- Jamieson RV, Farrar N, Stewart K, Perveen R, Mihelec M, et al: Characterization of a familial t(16;22) balanced translocation associated with congenital cataract leads to identification of a novel gene, *TMEM114*, expressed in the lens and disrupted by the translocation. *Hum Mutat* 28:968–977 (2007).
- Javadiyan S, Craig JE, Souzeau E, Sharma S, Lower KM, et al: Recurrent mutation in the crystallin alpha A gene associated with inherited paediatric cataract. *BMC Res Notes* 9:83 (2016).
- Jia X, Zhang F, Bai J, Gao L, Zhang X, et al: Combinational analysis of linkage and exome sequencing identifies the causative mutation in a Chinese family with congenital cataract. *BMC Med Genet* 14:107 (2013).
- Jiang H, Jin Y, Bu L, Zhang W, Liu J, Cui B, et al: A novel mutation in *GJA3* (connexin46) for autosomal dominant congenital nuclear pulverulent cataract. *Mol Vis* 9:579–583 (2003).
- Jiang J, Jin C, Wang W, Tang X, Shentu X, et al: Identification of a novel splice-site mutation in *MIP* in a Chinese congenital cataract family. *Mol Vis* 15:38–44 (2009).
- Jiaox X, Khan SY, Irum B, Khan AO, Wang Q, et al: Missense mutations in *CRYAB* are liable for recessive congenital cataracts. *PLoS One* 10:e0137973 (2015).
- Kalaydjieva L, Perez-Lezaun A, Angelicheva D, Onengut S, Dye D, et al: A founder mutation in the *GK1* gene is responsible for galactokinase deficiency in Roma (Gypsies). *Am J Hum Genet* 65:1299–1307 (1999).
- Kamachi Y, Uchikawa M, Tanouchi A, Sekido R, Kondoh H: Pax6 and SOX2 form a co-DNA-binding partner complex that regulates initiation of lens development. *Genes Dev* 15:1272–1286 (2001).
- Kannabiran C, Rogan PK, Olmos L, Basti S, Rao GN, et al: Autosomal dominant zonular cataract with sutural opacities is associated with a splice mutation in the betaA3/A1-crystallin gene. *Mol Vis* 4:21 (1998).
- Kannan R, Sreekumar PG, Hinton DR: Novel roles for alpha-crystallins in retinal function and disease. *Prog Retin Eye Res* 31:576–604 (2012).
- Kaul H, Riazuddin SA, Shahid M, Kousar S, Butt NH, et al: Autosomal recessive congenital cataract linked to *EPHA2* in a consanguineous Pakistani family. *Mol Vis* 16:511–517 (2010).
- Ke T, Wang QK, Ji B, Wang X, Liu P, et al: Novel *HSP4* mutation causes congenital total white cataract in a Chinese family. *Am J Ophthalmol* 142:298–303 (2006).
- Khan AO, Aldahmesh MA, Meyer B: Recessive congenital total cataract with microcornea and heterozygote carrier signs caused by a novel missense *CRYAA* mutation (R54C). *Am J Ophthalmol* 144:949–952 (2007).
- Khan AO, Aldahmesh MA, Ghadhfan FE, Al-Mesfer S, Alkuraya FS: Founder heterozygous P23T *CRYGD* mutation associated with cerulean (and coralliform) cataract in 2 Saudi families. *Mol Vis* 15:1407–1411 (2009).
- Khan AO, Aldahmesh MA, Mohamed JY, Alkuraya FS: Clinical and molecular analysis of children with central pulverulent cataract from the Arabian Peninsula. *Br J Ophthalmol* 96:650–655 (2012).
- Khan AO, Aldahmesh MA, Alkuraya FS: Phenotypes of recessive pediatric cataract in a cohort of children with identified homozygous gene mutations (An American Ophthalmological Society Thesis). *Trans Am Ophthalmol Soc* 113:T7 (2015).
- Kmoch S, Brynda J, Asfaw B, Bezouska K, Novák P, et al: Link between a novel human gammaD-crystallin allele and a unique cataract phenotype explained by protein crystallography. *Hum Mol Genet* 9:1779–1786 (2000).
- Kolosh V, Anoa E, de Cespedes C, Gitzelmann R, Shih L, et al: Novel mutations in 13 probands with galactokinase deficiency. *Hum Mutat* 15:447–453 (2000).

- Kondo Y, Saito H, Miyamoto T, Lee BJ, Nishiyama K, et al: Pathogenic mutations in two families with congenital cataract identified with whole-exome sequencing. *Mol Vis* 19: 384–389 (2013).
- Kondoh H, Uchikawa M, Kamachi Y: Interplay of Pax6 and SOX2 in lens development as a paradigm of genetic switch mechanisms for cell differentiation. *Int J Dev Biol* 48:819–827 (2004).
- Kong XD, Liu N, Shi HR, Dong JM, Zhao ZH, et al: A novel 3-base pair deletion of the *CRYAA* gene identified in a large Chinese pedigree featuring autosomal dominant congenital perinuclear cataract. *Genet Mol Res* 14:426–432 (2015).
- Kumar M, Agarwal T, Khokhar S, Kumar M, Kaur P, et al: Mutation screening and genotype phenotype correlation of α -crystallin, γ -crystallin and *GJA8* gene in congenital cataract. *Mol Vis* 17:693–707 (2011).
- Lachke SA, Alkuraya FS, Kneeland SC, Ohn T, Aboukhalil A, et al: Mutations in the RNA granule component TDRD7 cause cataract and glaucoma. *Science* 331:1571–1576 (2011).
- Laurie KJ, Dave A, Straga T, Souzeau E, Chataway T, et al: Identification of a novel oligomerization disrupting mutation in *CRYAA* associated with congenital cataract in a South Australian family. *Hum Mutat* 34:435–438 (2013).
- Li B, Liu Y, Liu Y, Guo H, Hu Z, et al: Identification of a *GJA3* mutation in a large family with bilateral congenital cataract. *DNA Cell Biol* 35:135–139 (2016).
- Li D, Wang S, Ye H, Tang Y, Qiu X, et al: Distribution of gene mutations in sporadic congenital cataract in a Han Chinese population. *Mol Vis* 22:589–598 (2016).
- Li FF, Zhu SQ, Wang SZ, Gao C, Huang SZ, et al: Nonsense mutation in the *CRYBB2* gene causing autosomal dominant progressive polymorphic congenital coronary cataracts. *Mol Vis* 14:750–755 (2008).
- Li FF, Yang M, Ma X, Zhang Q, Zhang M, et al: Autosomal dominant congenital nuclear cataracts caused by a *CRYAA* gene mutation. *Curr Eye Res* 35:492–498 (2010).
- Li J, Wang Q, Fu Q, Zhu Y, Zhai Y, et al: A novel connexin 50 gene (gap junction protein, α 8) mutation associated with congenital nuclear and zonular pulverulent cataract. *Mol Vis* 19:767–774 (2013).
- Li XQ, Cai HC, Zhou SY, Yang JH, Xi YB, et al: A novel mutation impairing the tertiary structure and stability of γ C-crystallin (*CRYGC*) leads to cataract formation in humans and zebrafish lens. *Hum Mutat* 2:391–401 (2012).
- Li Y, Wang J, Dong B, Man H: A novel connexin46 (*GJA3*) mutation in autosomal dominant congenital nuclear pulverulent cataract. *Mol Vis* 10:668–671 (2004).
- Liang C, Liang H, Yang Y, Ping L, Jie Q: Mutation analysis of two families with inherited congenital cataracts. *Mol Med Rep* 12:3469–3475 (2015).
- Lin H, Hejtmancik JF, Qi Y: A substitution of arginine to lysine at the COOH-terminus of MIP caused a different binocular phenotype in a congenital cataract family. *Mol Vis* 13:1822–1827 (2007).
- Lin Y, Liu NN, Lei CT, Fan YC, Liu XQ, et al: A novel *GJA8* mutation in a Chinese family with autosomal dominant congenital cataract (in Chinese). *Zhonghua Yi Xue Yi Chuan Xue Za Zhi* 25:59–62 (2008).
- Litt M, Carrero-Valenzuela R, LaMorticella DM, Schultz DW, Mitchell TN, et al: Autosomal dominant cerulean cataract is associated with a chain termination mutation in the human beta-crystallin gene *CRYBB2*. *Hum Mol Genet* 6:665–668 (1997).
- Litt M, Kramer P, LaMorticella DM, Murphey W, Lovrien EW, Weleber RG: Autosomal dominant congenital cataract associated with a missense mutation in the human alpha crystallin gene *CRYAA*. *Hum Mol Genet* 7:471–474 (1998).
- Liu BF, Liang JJ: Confocal fluorescence microscopy study of interaction between lens MIP26/AQP0 and crystallins in living cells. *J Cell Biochem* 104:51–58 (2008).
- Liu J, Xu J, Gu S, Nicholson BJ, Jiang JX: Aquaporin 0 enhances gap junction coupling via its cell adhesion function and interaction with connexin 50. *J Cell Sci* 124:198–206 (2011).
- Liu L, Zhang Q, Zhou LX, Tang ZH: A novel *HSF4* mutation in a Chinese family with autosomal dominant congenital cataract. *J Huazhong Univ Sci Technolog Med Sci* 35:316–318 (2015).
- Liu Q, Wang KJ, Zhu SQ: A novel p.G112E mutation in *BFSP2* associated with autosomal dominant pulverulent cataract with sutural opacities. *Curr Eye Res* 39:1013–1019 (2014).
- Liu Y, Zhang X, Luo L, Wu M, Zeng R, et al: A novel alphaB-crystallin mutation associated with autosomal dominant congenital lamellar cataract. *Invest Ophthalmol Vis Sci* 47:1069–1075 (2006).
- Lou D, Tong JP, Zhang LY, Chiang SW, Lam DS, Pang CP: A novel mutation in *CRYBB2* responsible for inherited coronary cataract. *Eye (Lond)* 23:1213–1220 (2009).
- Lovicu FJ, Overbeek PA: Overlapping effects of different members of the FGF family on lens fiber differentiation in transgenic mice. *Development* 125:3365–3377 (1998).
- Lu S, Zhao C, Jiao H, Kere J, Tang X, et al: Two Chinese families with pulverulent congenital cataracts and deltaG91 *CRYBA1* mutations. *Mol Vis* 13:1154–1160 (2007).
- Lv H, Huang C, Zhang J, Liu Z, Zhang Z, et al: A novel *HSF4* gene mutation causes autosomal dominant cataracts in a Chinese family. *G3 (Bethesda)* 4:823–828 (2014).
- Ma AS, Grigg JR, Ho G, Prokudin I, Farnsworth E, et al: Sporadic and familial congenital cataracts: mutational spectrum and new diagnoses using next-generation sequencing. *Hum Mutat* 37:371–384 (2016).
- Ma J, Becker C, Reyes C, Underhill DM: Cutting edge: FYCO1 recruitment to dectin-1 phagosomes is accelerated by light chain 3 protein and regulates phagosome maturation and reactive oxygen production. *J Immunol* 192: 1356–1360 (2014).
- Ma MF, Li LB, Pei YQ, Cheng Z: Use of high-throughput targeted exome sequencing in genetic diagnosis of Chinese family with congenital cataract. *Int J Ophthalmol* 9:650–654 (2016).
- Ma X, Li FF, Wang SZ, Gao C, Zhang M, Zhu SQ: A new mutation in *BFSP2* (G1091A) causes autosomal dominant congenital lamellar cataracts. *Mol Vis* 14:1906–1911 (2008).
- Ma ZW, Zheng JQ, Li J, Li XR, Tang X, et al: Two novel mutations of connexin genes in Chinese families with autosomal dominant congenital nuclear cataract. *Br J Ophthalmol* 89:1535–1537 (2005).
- Mackay D, Ionides A, Kibar Z, Rouleau G, Berry V, et al: Connexin46 mutations in autosomal dominant congenital cataract. *Am J Hum Genet* 64:1357–1364 (1999).
- Mackay DS, Andley UP, Shiels A: Cell death triggered by a novel mutation in the alphaA-crystallin gene underlies autosomal dominant cataract linked to chromosome 21q. *Eur J Hum Genet* 11:784–793 (2003).
- Mackay DS, Andley UP, Shiels A: A missense mutation in the gammaD crystallin gene (*CRYGD*) associated with autosomal dominant 'coral-like' cataract linked to chromosome 2q. *Mol Vis* 10:155–162 (2004).
- Mackay DS, Bennett TM, Culican SM, Shiels A: Exome sequencing identifies novel and recurrent mutations in *GJA8* and *CRYGD* associated with inherited cataract. *Hum Genomics* 8:19 (2014).
- Marner E, Rosenberg T, Eiberg H: Autosomal dominant congenital cataract: morphology and genetic mapping. *Acta Ophthalmol (Copenh)* 67:151–158 (1989).
- Martinez-Wittingham FJ, Sellitto C, White TW, Mathias RT, Paul D, Goodenough DA: Lens gap junctional coupling is modulated by connexin identity and the locus of gene expression. *Invest Ophthalmol Vis Sci* 45:3629–3637 (2004).
- McAvoy JW, Chamberlain CG: Fibroblast growth factor (FGF) induces different responses in lens epithelial cells depending on its concentration. *Development* 107:221–228 (1989).
- Messina-Baas OM, Gonzalez-Huerta LM, Cuevas-Covarrubias SA: Two affected siblings with nuclear cataract associated with a novel missense mutation in the *CRYGD* gene. *Mol Vis* 12:995–1000 (2006).
- Messina-Baas OM, Gonzalez-Garay ML, González-Huerta LM, Toral-López J, Cuevas-Covarrubias SA: Whole exome sequencing reveals a mutation in *CRYBB2* in a large Mexican family with autosomal dominant pulverulent cataract. *Mol Syndromol* 7:87–92 (2016).
- Meyer E, Rahman F, Owens J, Pasha S, Morgan NV, et al: Initiation codon mutation in betaB1-crystallin (*CRYBB1*) associated with autosomal recessive nuclear pulverulent cataract. *Mol Vis* 15:1014–1019 (2009).
- Miao H, Wang B: Eph/ephrin signaling in epithelial development and homeostasis. *Int J Biochem Cell Biol* 41:762–770 (2009).

- Min HY, Qiao PP, Asan, Yan ZH, Jiang HF, et al: Targeted genes sequencing identified a novel 15 bp deletion on *GJA8* in a Chinese family with autosomal dominant congenital cataracts. *Chin Med J (Engl)* 129:860–867 (2016).
- Mothobi ME, Guo S, Liu Y, Chen Q, Yussuf AS, et al: Mutation analysis of congenital cataract in a Basotho family identified a new missense allele in *CRYBB2*. *Mol Vis* 15:1470–1475 (2009).
- Müller M, Bhattacharya SS, Moore T, Prescott Q, Wedig T, et al: Dominant cataract formation in association with a vimentin assembly disrupting mutation. *Hum Mol Genet* 18:1052–1057 (2009).
- Nandrot E, Slingsby C, Basak A, Cherif-Chefchaoui M, Benazzouz B, et al: Gamma-D crystallin gene (*CRYGD*) mutation causes autosomal dominant congenital cerulean cataracts. *J Med Genet* 40:262–267 (2003).
- Narumi Y, Nishina S, Tokimitsu M, Aoki Y, Kosaki R, et al: Identification of a novel missense mutation of *MAF* in a Japanese family with congenital cataract by whole exome sequencing: a clinical report and review of literature. *Am J Med Genet A* 164A:1272–1276 (2014).
- Nettleship E, Ogilvie FM: A peculiar form of hereditary congenital cataract. *Trans Ophthalmol Soc UK* 26:191–206 (1906).
- Ormestad M, Blixt A, Churchill A, Martinsson T, Enerbäck S, Carlsson P: *Foxe3* haploinsufficiency in mice: a model for Peters' anomaly. *Invest Ophthalmol Vis Sci* 43:1350–1357 (2002).
- Pankiv S, Alemu EA, Brech A, Bruun JA, Lamark T, et al: FYCO1 is a Rab7 effector that binds to LC3 and PI3P to mediate microtubule plus end-directed vesicle transport. *Cell Biol* 188:253–269 (2010).
- Park JE, Son AI, Zhou R: Roles of EphA2 in development and disease. *Genes (Basel)* 4:334–357 (2013).
- Pasquale EB: Eph receptors and ephrins in cancer: bidirectional signalling and beyond. *Nat Rev Cancer* 10:165–180 (2010).
- Pauli S, Söker T, Klopp N, Illig T, Engel W, Graw J: Mutation analysis in a German family identified a new cataract-causing allele in the *CRYBB2* gene. *Mol Vis* 13:962–967 (2007).
- Plotnikova OV, Kondrashov FA, Vlasov PK, Grigorenko AP, Ginter EK, Rogaev EI: Conversion and compensatory evolution of the gamma-crystallin genes and identification of a cataractogenic mutation that reverses the sequence of the human *CRYGD* gene to an ancestral state. *Am J Hum Genet* 81:32–43 (2007).
- Polyakov AV, Shagina IA, Khlebnikova OV, Evgrafov OV: Mutation in the connexin 50 gene (*GJA8*) in a Russian family with zonular pulverulent cataract. *Clin Genet* 60:476–478 (2001).
- Ponnam SP, Ramesha K, Tejwani S, Ramamurthy B, Kannabiran C: Mutation of the gap junction protein alpha 8 (*GJA8*) gene causes autosomal recessive cataract. *J Med Genet* 44:e85 (2007).
- Ponnam SP, Ramesha K, Tejwani S, Matalia J, Kannabiran C: A missense mutation in *LIM2* causes autosomal recessive congenital cataract. *Mol Vis* 14:1204–1208 (2008).
- Ponnam SP, Ramesha K, Matalia J, Tejwani S, Ramamurthy B, Kannabiran C: Mutational screening of Indian families with hereditary congenital cataract. *Mol Vis* 19:1141–1148 (2013).
- Pras E, Frydman M, Levy-Nissenbaum E, Bakhan T, Raz J, et al: A nonsense mutation (W9X) in *CRYAA* causes autosomal recessive cataract in an inbred Jewish Persian family. *Invest Ophthalmol Vis Sci* 41:3511–3515 (2000).
- Pras E, Raz J, Yahalom V, Frydman M, Garzozzi HJ, et al: A nonsense mutation in the glucosaminyl (N-acetyl) transferase 2 gene (*GCNT2*): association with autosomal recessive congenital cataracts. *Invest Ophthalmol Vis Sci* 45:1940–1945 (2004).
- Prokudin I, Simons C, Grigg JR, Storen R, Kumar V, et al: Exome sequencing in developmental eye disease leads to identification of causal variants in *GJA8*, *CRYGC*, *PAX6* and *CYP11B1*. *Eur J Hum Genet* 22:907–915 (2014).
- Qi Y, Jia H, Huang S, Lin H, Gu J, et al: A deletion mutation in the betaA1/A3 crystallin gene (*CRYBA1/A3*) is associated with autosomal dominant congenital nuclear cataract in a Chinese family. *Hum Genet* 114:192–197 (2004).
- Qin L, Guo L, Wang H, Li T, Lou G, et al: A novel *MIP* mutation in familial congenital nuclear cataracts. *Eur J Med Genet* 59:488–491 (2016).
- Ramachandran RD, Perumalsamy V, Hejtmancik JF: Autosomal recessive juvenile onset cataract associated with mutation in *BFSPI*. *Hum Genet* 121:475–482 (2007).
- Ramprasad VL, Thool A, Murugan S, Nancarrow D, Vyas P, et al: Truncating mutation in the *NHS* gene: phenotypic heterogeneity of Nance-Horan syndrome in an Asian Indian family. *Invest Ophthalmol Vis Sci* 46:17–23 (2005).
- Reddy MA, Bateman OA, Chakarova C, Ferris J, Berry V, et al: Characterization of the G91del *CRYBA1/3*-crystallin protein: a cause of human inherited cataract. *Hum Mol Genet* 13:945–953 (2004).
- Rees MI, Watts P, Fenton I, Clarke A, Snell RG, et al: Further evidence of autosomal dominant congenital zonular pulverulent cataracts linked to 13q11 (*CZP3*) and a novel mutation in connexin 46 (*GJA3*). *Hum Genet* 106:206–209 (2000).
- Reich S, Hennermann J, Vetter B, Neumann LM, Shin YS, et al: An unexpectedly high frequency of hypergalactosemia in an immigrant Bosnian population revealed by newborn screening. *Pediatr Res* 51:598–601 (2002).
- Reis LM, Tyler RC, Schneider A, Bardakjian T, Stoler JM, et al: *FOXE3* plays a significant role in autosomal recessive microphthalmia. *Am J Med Genet A* 152A:582–590 (2010).
- Reis LM, Tyler RC, Muheisen S, Raggio V, Salvati L, et al: Whole exome sequencing in dominant cataract identifies a new causative factor, *CRYBA2*, and a variety of novel alleles in known genes. *Hum Genet* 132:761–770 (2013).
- Reis LM, Tyler RC, Semina EV: Identification of a novel C-terminal extension mutation in *EPHA2* in a family affected with congenital cataract. *Mol Vis* 20:836–842 (2014).
- Ren Z, Li A, Shastry BS, Padma T, Ayyagari R, et al: A 5-base insertion in the gammaC-crystallin gene is associated with autosomal dominant variable zonular pulverulent cataract. *Hum Genet* 106:531–537 (2000).
- Riazuddin SA, Yasmeen A, Yao W, Sergeev YV, Zhang Q, et al: Mutations in betaB3-crystallin associated with autosomal recessive cataract in two Pakistani families. *Invest Ophthalmol Vis Sci* 46:2100–2106 (2005).
- Richardson JS: beta-Sheet topology and the relatedness of proteins. *Nature* 268:495–500 (1977).
- Richter L, Flodman P, Barria F, Burch D, Brown S, et al: Clinical variability of autosomal dominant cataract, microcornea and corneal opacity and novel mutation in the alpha A crystallin gene (*CRYAA*). *Am J Med Genet A* 146A:833–842 (2008).
- Roshan M, Vijaya PH, Lavanya GR, Shama PK, Santhiya ST, et al: A novel human *CRYGD* mutation in a juvenile autosomal dominant cataract. *Mol Vis* 16:887–896 (2010).
- Safieh LA, Khan AO, Alkuraya FS: Identification of a novel *CRYAB* mutation associated with autosomal recessive juvenile cataract in a Saudi family. *Mol Vis* 15:980–984 (2009).
- Sajjad N, Goebel I, Kakar N, Cheema AM, Kubisch C, Ahmad J: A novel *HSF4* gene mutation (p.R405X) causing autosomal recessive congenital cataracts in a large consanguineous family from Pakistan. *BMC Med Genet* 9:99 (2008).
- Santana A, Waiswol M, Arcieri ES, Cabral de Vasconcellos JP, Barbosa de Melo M: Mutation analysis of *CRYAA*, *CRYGC*, and *CRYGD* associated with autosomal dominant congenital cataract in Brazilian families. *Mol Vis* 15:793–800 (2009).
- Santhiya ST, Shyam M, Rawlley D, Vijayalakshmi P, Namperumalsamy P, et al: Novel mutations in the gamma-crystallin genes cause autosomal dominant congenital cataracts. *J Med Genet* 39:352–358 (2002).
- Santhiya ST, Manisastry SM, Rawlley D, Malathi R, Anishetty S, et al: Mutation analysis of congenital cataracts in Indian families: identification of SNPs and a new causative allele in *CRYBB2* gene. *Invest Ophthalmol Vis Sci* 45:3599–3607 (2004).
- Santhiya ST, Soker T, Klopp N, Illig T, Prakash MV, et al: Identification of a novel, putative cataract-causing allele in *CRYAA* (G98R) in an Indian family. *Mol Vis* 12:768–737 (2006).
- Santhiya ST, Kumar GS, Sudhakar P, Gupta N, Klopp N, et al: Molecular analysis of cataract families in India: new mutations in the *CRYBB2* and *GJA3* genes and rare polymorphisms. *Mol Vis* 16:1837–1847 (2010).
- Schmidt W, Klopp N, Illig T, Graw J: A novel *GJA8* mutation causing a recessive triangular cataract. *Mol Vis* 14:851–856 (2008).

- Semina EV, Brownell I, Mintz-Hittner HA, Murray JC, Jamrich M: Mutations in the human forkhead transcription factor *FOXE3* associated with anterior segment ocular dysgenesis and cataracts. *Hum Mol Genet* 10:231–236 (2001).
- Senthil Kumar G, Kyle JW, Minogue PJ, Dinesh Kumar K, Vasantha K, et al: An *MIP/AQP0* mutation with impaired trafficking and function underlies an autosomal dominant congenital lamellar cataract. *Exp Eye Res* 110:136–141 (2013).
- Sharma S, Burdon KP, Dave A, Jamieson RV, Yaron Y, et al: Novel causative mutations in patients with Nance-Horan syndrome and altered localization of the mutant NHS-A protein isoform. *Mol Vis* 14:1856–1864 (2008).
- Shentu X, Yao K, Xu W, Zheng S, Hu S, Gong X: Special fasciculiform cataract caused by a mutation in the gammaD-crystallin gene. *Mol Vis* 10:233–239 (2004).
- Shentu X, Zhao SJ, Zhang L, Miao Q: A novel p.R890C mutation in *EPHA2* gene associated with progressive childhood posterior cataract in a Chinese family. *Int J Ophthalmol* 6:34–38 (2013).
- Shentu X, Miao Q, Tang X, Yin H, Zhao Y: Identification and functional analysis of a novel *MIP* gene mutation associated with congenital cataract in a Chinese family. *PLoS One* 10:e0126679 (2015).
- Shiels A, Mackay D, Ionides A, Berry V, Moore A, Bhattacharya S: A missense mutation in the human connexin50 gene (*GJA8*) underlies autosomal dominant “zonular pulverulent” cataract, on chromosome 1q. *Am J Hum Genet* 62:526–532 (1998).
- Shiels A, Bassnett S, Varadaraj K, Mathias R, Al-Ghoul K, et al: Optical dysfunction of the crystalline lens in aquaporin-0-deficient mice. *Physiol Genomics* 7:179–186 (2001).
- Shiels A, Bennett TM, Knopf HL, Yamada K, Yoshiura K, et al: *CHMP4B*, a novel gene for autosomal dominant cataracts linked to chromosome 20q. *Am J Hum Genet* 81:596–606 (2007).
- Shiels A, Bennett TM, Knopf HL, Maraini G, Li A, et al: The *EPHA2* gene is associated with cataracts linked to chromosome 1p. *Mol Vis* 14:2042–2055 (2008).
- Shiels A, Bennett TM, Hejtmancik JF: Cat-Map: putting cataract on the map. *Mol Vis* 16:2007–2015 (2010).
- Singh R, Ram J, Kaur G, Prasad R: Galactokinase deficiency induced cataracts in Indian infants: identification of 4 novel mutations in *GALK* gene. *Curr Eye Res* 37:949–954 (2012).
- Slingsby C, Wistow GJ, Clark AR: Evolution of crystallins for a role in the vertebrate eye lens. *Protein Sci* 22:367–380 (2013).
- Smaoui N, Beltaief O, BenHamed S, M’Rad R, Maazoul F, et al: A homozygous splice mutation in the *HSF4* gene is associated with an autosomal recessive congenital cataract. *Invest Ophthalmol Vis Sci* 45:2716–2721 (2004).
- Song Z, Wang L, Liu Y, Xiao W: A novel nonsense mutation in the *MIP* gene linked to congenital posterior polar cataracts in a Chinese family. *PLoS One* 10:e0119296 (2015).
- Stambolian D, Ai Y, Sidjanin D, Nesburn K, Sathe G, et al: Cloning of the galactokinase cDNA and identification of mutations in two families with cataracts. *Nat Genet* 10:307–312 (1995).
- Stephan DA, Gillanders E, Vanderveen D, Freas-Lutz D, Wistow G, et al: Progressive juvenile-onset punctate cataracts caused by mutation of the gammaD-crystallin gene. *Proc Natl Acad Sci USA* 96:1008–1012 (1999).
- Su D, Guo Y, Li Q, Guan L, Zhu S, Ma X: A novel mutation in *CRYAA* is associated with autosomal dominant suture cataracts in a Chinese family. *Mol Vis* 18:3057–3063 (2012).
- Su D, Yang Z, Li Q, Guan L, Zhang H, et al: Identification and functional analysis of *GJA8* mutation in a Chinese family with autosomal dominant perinuclear cataracts. *PLoS One* 8:e59926 (2013).
- Sun H, Ma Z, Li Y, Liu B, Li Z, et al: Gamma-S crystallin gene (*CRYGS*) mutation causes dominant progressive cortical cataract in humans. *J Med Genet* 42:706–710 (2005).
- Sun W, Xiao X, Li S, Guo X, Zhang Q: Mutational screening of six genes in Chinese patients with congenital cataract and microcornea. *Mol Vis* 17:1508–1513 (2011a).
- Sun W, Xiao X, Li S, Guo X, Zhang Q: Mutation analysis of 12 genes in Chinese families with congenital cataracts. *Mol Vis* 17:2197–2206 (2011b).
- Sun W, Xiao X, Li S, Guo X, Zhang Q: Exome sequencing of 18 Chinese families with congenital cataracts: a new sight of the *NHS* gene. *PLoS One* 9:e100455 (2014).
- Valleix S, Niel F, Nedelec B, Algrès MP, Schwartz C, et al: Homozygous nonsense mutation in the *FOXE3* gene as a cause of congenital primary aphakia in humans. *Am J Hum Genet* 79:358–364 (2006).
- Vanita V, Singh D: A missense mutation in *CRYGD* linked with autosomal dominant congenital cataract of aculeiform type. *Mol Cell Biochem* 368:167–172 (2012).
- Vanita V, Sarhadi V, Reis A, Jung M, Singh D, et al: A unique form of autosomal dominant cataract explained by gene conversion between beta-crystallin B2 and its pseudogene. *J Med Genet* 38:392–396 (2001).
- Vanita V, Singh D, Robinson PN, Sperling K, Singh JR: A novel mutation in the DNA-binding domain of MAF at 16q23.1 associated with autosomal dominant “cerulean cataract” in an Indian family. *Am J Med Genet A* 140:558–566 (2006).
- Vanita V, Singh JR, Singh D, Varon R, Sperling K: A mutation in *GJA8* (p.P88Q) is associated with “balloon-like” cataract with Y-sutural opacities in a family of Indian origin. *Mol Vis* 14:1171–1175 (2008).
- Vanita V, Singh JR, Singh D, Varon R, Sperling K: Novel mutation in the gamma-S crystallin gene causing autosomal dominant cataract. *Mol Vis* 15:476–481 (2009).
- Wang H, Zhang T, Wu D, Zhang J: A novel beaded filament structural protein 1 (*BFSP1*) gene mutation associated with autosomal dominant congenital cataract in a Chinese family. *Mol Vis* 19:2590–2595 (2013).
- Wang J, Ma X, Gu F, Liu NP, Hao XL, et al: A missense mutation S228P in the *CRYBB1* gene causes autosomal dominant congenital cataract. *Chin Med J (Engl)* 120:820–824 (2007).
- Wang KJ, Zhu SQ: A novel p.F206I mutation in *Cx46* associated with autosomal dominant congenital cataract. *Mol Vis* 18:968–973 (2012).
- Wang KJ, Li SS, Yun B, Ma WX, Jiang TG, Zhu SQ: A novel mutation in *MIP* associated with congenital nuclear cataract in a Chinese family. *Mol Vis* 17:70–77 (2011a).
- Wang KJ, Wang BB, Zhang F, Zhao Y, Ma X, Zhu SQ: Novel beta-crystallin gene mutations in Chinese families with nuclear cataracts. *Arch Ophthalmol* 129:337–343 (2011b).
- Wang L, Lin H, Gu J, Su H, Huang S, Qi Y: Autosomal-dominant cerulean cataract in a Chinese family associated with gene conversion mutation in beta-B2-crystallin. *Ophthalmic Res* 41:148–153 (2009).
- Wang L, Luo Y, Wen W, Zhang S, Lu Y: Another evidence for a D47N mutation in *GJA8* associated with autosomal dominant congenital cataract. *Mol Vis* 17:2380–2385 (2011).
- Wang L, Chen Y, Chen X, Sun X: Further evidence for P59L mutation in *GJA3* associated with autosomal dominant congenital cataract. *Indian J Ophthalmol* 64:508–512 (2016).
- Wang W, Jiang J, Zhu Y, Li J, Jin C, et al: A novel mutation in the major intrinsic protein (*MIP*) associated with autosomal dominant congenital cataracts in a Chinese family. *Mol Vis* 16:534–539 (2010).
- Weisschuh N, Aisenbrey S, Wissinger B, Riess A: Identification of a novel *CRYBB2* missense mutation causing congenital autosomal dominant cataract. *Mol Vis* 18:174–180 (2012).
- Willoughby CE, Arab S, Gandhi R, Zeinali S, Arab S, et al: A novel *GJA8* mutation in an Iranian family with progressive autosomal dominant congenital nuclear cataract. *J Med Genet* 40:e124 (2003).
- Willoughby CE, Shafiq A, Ferrini W, Chan LL, Billingsley G, et al: *CRYBB1* mutation associated with congenital cataract and microcornea. *Mol Vis* 11:587–593 (2005).
- Wu Q, Shi H, Liu N, Lu N, Jiang M, et al: Mutation analysis of *CRYBB1* gene and prenatal diagnosis for a Chinese kindred featuring autosomal dominant congenital nuclear cataract (in Chinese). *Zhonghua Yi Xue Yi Chuan Xue Za Zhi* 30:266–269 (2013).
- Wussuki-Lior O, Abu-Horowitz A, Netzer I, Almer Z, Morad Y, et al: Hematologic biomarkers in childhood cataracts. *Mol Vis* 17:1011–1015 (2011).
- Xia XY, Li N, Cao X, Wu QY, Li TF, et al: A novel *COL4A1* gene mutation results in autosomal dominant non-syndromic congenital cataract in a Chinese family. *BMC Med Genet* 15:97 (2014a).

- Xia XY, Wu QY, An LM, Li WW, Li N, et al: A novel P20R mutation in the alpha-B crystallin gene causes autosomal dominant congenital posterior polar cataracts in a Chinese family. *BMC Ophthalmol* 14:108 (2014b).
- Xiao X, Li W, Wang P, Li L, Li S, et al: Cerulean cataract mapped to 12q13 and associated with a novel initiation codon mutation in *MIP*. *Mol Vis* 17:2049–2055 (2011).
- Xu WZ, Zheng S, Xu SJ, Huang W, Yao K, Zhang SZ: Autosomal dominant coralliform cataract related to a missense mutation of the gammaD-crystallin gene. *Chin Med J (Engl)* 117: 727–732 (2004).
- Yan M, Xiong C, Ye SQ, Chen Y, Ke M, et al: A novel connexin 50 (*GJA8*) mutation in a Chinese family with a dominant congenital pulverulent nuclear cataract. *Mol Vis* 14:418–424 (2008).
- Yang G, Xing B, Liu G, Lu X, Jia X, et al: A novel mutation in the *GJA3* (connexin46) gene is associated with autosomal dominant congenital nuclear cataract in a Chinese family. *Mol Vis* 17:1070–1073 (2011a).
- Yang G, Zhang G, Wu Q, Zhao J: A novel mutation in the *MIP* gene is associated with autosomal dominant congenital nuclear cataract in a Chinese family. *Mol Vis* 17:1320–1323 (2011b).
- Yang G, Chen Z, Zhang W, Liu Z, Zhao J: Novel mutations in *CRYGD* are associated with congenital cataracts in Chinese families. *Sci Rep* 6:18912 (2016).
- Yang J, Zhu Y, Gu F, He X, Cao Z, et al: A novel nonsense mutation in *CRYBB1* associated with autosomal dominant congenital cataract. *Mol Vis* 14:727–731 (2008).
- Yang J, Li D, Fan Q, Cai L, Qiu X, et al: The polymorphisms with cataract susceptibility impair the EPFA2 receptor stability and its cytoprotective function. *J Ophthalmol* 2015: 401894 (2015).
- Yang Z, Li Q, Ma Z, Guo Y, Zhu S, Ma X: A G→T splice site mutation of *CRYBA1/A3* associated with autosomal dominant suture cataracts in a Chinese family. *Mol Vis* 17:2065–2071 (2011).
- Yang Z, Su D, Li Q, Yang F, Ma Z, et al: A novel T→G splice site mutation of *CRYBA1/A3* associated with autosomal dominant nuclear cataracts in a Chinese family. *Mol Vis* 18: 1283–1288 (2012).
- Yang Z, Su D, Li Q, Ma Z, Yang F, et al: A R54L mutation of *CRYAA* associated with autosomal dominant nuclear cataracts in a Chinese family. *Curr Eye Res* 38:1221–1228 (2013).
- Yang Z, Li Q, Ma X, Zhu SQ: Mutation analysis in Chinese families with autosomal dominant hereditary cataracts. *Curr Eye Res* 40:1225–1231 (2015).
- Yao K, Tang X, Shentu X, Wang K, Rao H, Xia K: Progressive polymorphic congenital cataract caused by a *CRYBB2* mutation in a Chinese family. *Mol Vis* 11:758–763 (2005).
- Yao K, Jin C, Zhu N, Wang W, Wu R, et al: A nonsense mutation in *CRYGC* associated with autosomal dominant congenital nuclear cataract in a Chinese family. *Mol Vis* 14:1272–1276 (2008).
- Yao K, Li J, Jin C, Wang W, Zhu Y, et al: Characterization of a novel mutation in the *CRYBB2* gene associated with autosomal dominant congenital posterior subcapsular cataract in a Chinese family. *Mol Vis* 17:144–152 (2011a).
- Yao K, Wang W, Zhu Y, Jin C, Shentu X, et al: A novel *GJA3* mutation associated with congenital nuclear pulverulent and posterior polar cataract in a Chinese family. *Hum Mutat* 32: 1367–1370. (2011b).
- Yasmeen A, Riazuddin SA, Kaul H, Mohsin S, Khan M, et al: Autosomal recessive congenital cataract in consanguineous Pakistani families is associated with mutations in *GALK1*. *Mol Vis* 16:682–688 (2010).
- Yu LC, Twu YC, Chang CY, Lin M: Molecular basis of the adult i phenotype and the gene responsible for the expression of the human blood group I antigen. *Blood* 98:3840–3845 (2001).
- Yu Y, Li J, Xu J, Wang Q, Yu Y, Yao K: Congenital polymorphic cataract associated with a G to A splice site mutation in the human beta-crystallin gene *CRYβA3/A1*. *Mol Vis* 18:2213–2220 (2012).
- Yu Y, Yu Y, Chen P, Li J, Zhu Y, et al: A novel *MIP* gene mutation associated with autosomal dominant congenital cataracts in a Chinese family. *BMC Med Genet* 15:6 (2014).
- Yu Y, Wu M, Chen X, Zhu Y, Gong X, Yao K: Identification and functional analysis of two novel connexin 50 mutations associated with autosomal dominant congenital cataracts. *Sci Rep* 6:26551 (2016).
- Yuan L, Guo Y, Yi J, Xiao J, Yuan J, et al: Identification of a novel *GJA3* mutation in congenital nuclear cataract. *Optom Vis Sci* 92:337–342 (2015).
- Yuan L, Yi J, Lin Q, Xu H, Deng X, et al: Identification of a PRX variant in a Chinese family with congenital cataract by exome sequencing. *QJM* 109:731–735 (2016).
- Zeng L, Liu W, Feng W, Wang X, Dang H, et al: A novel donor splice-site mutation of major intrinsic protein gene associated with congenital cataract in a Chinese family. *Mol Vis* 19:2244–2249 (2013).
- Zenteno JC, Morales ME, Moran-Barroso V, Sanchez-Navarro A: *CRYGD* gene analysis in a family with autosomal dominant congenital cataract: evidence for molecular homogeneity and intrafamilial clinical heterogeneity in aculeiform cataract. *Mol Vis* 11:438–442 (2005).
- Zhai Y, Li J, Zhu Y, Xia Y, Wang W, et al: A nonsense mutation of γ D-crystallin associated with congenital nuclear and posterior polar cataract in a Chinese family. *Int J Med Sci* 11: 158–163 (2014).
- Zhang J, Zhang Y, Fang F, Mu W, Zhang N, et al: Congenital cataracts due to a novel 2-bp deletion in *CRYBA1/A3*. *Mol Med Rep* 10:1614–1618 (2014).
- Zhang L, Gao L, Li Z, Qin W, Gao W, et al: Progressive sutural cataract associated with a *BFSP2* mutation in a Chinese family. *Mol Vis* 12:1626–1631 (2006).
- Zhang L, Qu X, Su S, Guan L, Liu P: A novel mutation in *GJA3* associated with congenital Coppock-like cataract in a large Chinese family. *Mol Vis* 18:2114–2118 (2012).
- Zhang LY, Yam GH, Fan DS, Tam PO, Lam DS, Pang CP: A novel deletion variant of gammaD-crystallin responsible for congenital nuclear cataract. *Mol Vis* 13:2096–2104 (2007).
- Zhang LY, Yam GH, Tam PO, Lai RY, Lam DS, et al: An alphaA-crystallin gene mutation, Arg12Cys, causing inherited cataract-microcornea exhibits an altered heat-shock response. *Mol Vis* 15:1127–1138 (2009a).
- Zhang LY, Gong B, Tong JP, Fan DS, Chiang SW, et al: A novel gammaD-crystallin mutation causes mild changes in protein properties but leads to congenital coralliform cataract. *Mol Vis* 15:1521–1529 (2009b).
- Zhang Q, Guo X, Xiao X, Yi J, Jia X, Hejtmancik JF: Clinical description and genome wide linkage study of Y-sutural cataract and myopia in a Chinese family. *Mol Vis* 10:890–900 (2004).
- Zhao H, Brown PH, Magone MT, Schuck P: The molecular refractive function of lens γ -crystallins. *J Mol Biol* 411:680–699 (2011).
- Zhao L, Chen XJ, Zhu J, Xi YB, Yang X, et al: Lanosterol reverses protein aggregation in cataracts. *Nature* 523:607–611 (2015).
- Zheng JQ, Ma ZW, Sun HM: A heterozygous transversion of connexin 50 in a family with congenital nuclear cataract in the northeast of China (in Chinese). *Zhonghua Yi Xue Yi Chuan Xue Za Zhi* 22:76–78 (2005).
- Zhou D, Ji H, Wei Z, Guo L, Li Y, et al: A novel insertional mutation in the connexin 46 (gap junction alpha 3) gene associated with autosomal dominant congenital cataract in a Chinese family. *Mol Vis* 19:789–795 (2013).
- Zhou G, Zhou N, Hu S, Zhao L, Zhang C, Qi Y: A missense mutation in *CRYBA4* associated with congenital cataract and microcornea. *Mol Vis* 16:1019–1024 (2010).
- Zhou Z, Hu S, Wang B, Zhou N, Zhou S, et al: Mutation analysis of congenital cataract in a Chinese family identified a novel missense mutation in the connexin 46 gene (*GJA3*). *Mol Vis* 16:713–719 (2010).
- Zhu Y, Shentu X, Wang W, Li J, Jin C, Yao K: A Chinese family with progressive childhood cataracts and IVS3+1G>A *CRYBA3/A1* mutations. *Mol Vis* 16:2347–2353 (2010).
- Zhu Y, Yu H, Wang W, Gong X, Yao K: A novel *GJA8* mutation (p.V44A) causing autosomal dominant congenital cataract. *PLoS One* 9: e115406 (2014).
- Zhuang X, Wang L, Song Z, Xiao W: A novel insertion variant of *CRYGD* is associated with congenital nuclear cataract in a Chinese family. *PLoS One* 10:e0131471 (2015).