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Molecular Genetics of Cataract

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Abstract

Lens opacities or cataract(s) represent a universally important cause of visual impairment and blindness. Typically, cataract is acquired with aging as a complex disorder involving environmental and genetic risk factors. Cataract may also be inherited with an early onset either in association with other ocular and/or systemic abnormalities or as an isolated lens phenotype. Here we briefly review recent advances in gene discovery for inherited and age-related forms of cataract that are providing new insights into lens development and aging.

1. INTRODUCTION

The crystalline lens plays a central role in vertebrate eye development and refractive vision.¹ Loss of lens transparency, or cataract, is a frequently acquired cause of visual impairment in those over 40 years of age.² Despite advances in surgical treatment, age-related cataract remains a clinically important cause of visual impairment in economically developed countries (www.preventblindness.org) and of blindness (51%) worldwide.³ Clinical examination of age-related cataract by slit-lamp imaging reveals three classical types of opacities, namely, nuclear cataract, cortical cataract, and posterior subcapsular cataract. Each can occur in isolation or in combination (mixed cataract) and may progress to total opacification of the lens. Several grading systems have been devised that measure cataract severity and progression rate (e.g., Lens Opacities Classification System III).⁴ Epidemiological studies have established that age-related cataract is a multifactorial disorder involving complex interactions between environmental risk factors (e.g., UV exposure, tobacco smoking) and genetic susceptibility loci.⁵ Heritability estimates for age-related cataract range from 35% to 48% for nuclear opacities and 24% to 58% for cortical opacities.⁶ However, the identities of the underlying genetic factors remain poorly characterized.

In addition to being acquired with aging, cataract may present in one or both eyes with an early onset starting at birth (congenital), during infancy, during childhood, or adolescence, and represents a significant cause of visual disability in the pediatric age-group worldwide.⁷ Under slit-lamp examination, pediatric cataract exhibits considerable phenotypic variability

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with respect to location, size, shape, density, age at onset, rate of progression, and even color of opacities within the lens. There is no universally accepted classification system for pediatric cataract. However, several main types of pediatric opacities can be distinguished based on their lens location including nuclear, lamellar, sutural, polar or subcapsular, and total.⁸ Congenital and infantile forms of cataract, especially when unilateral, represent a clinically important cause of impaired visual development as a result of deprivation amblyopia. Surgical treatment of pediatric cataract poses a long-term risk of postoperative complications including secondary glaucoma, nystagmus, and retinal detachment.^{9–11} Etiological studies of pediatric cataract have estimated that genetic causes account for 10–39% of pediatric cataract/cases. However, this may be an underestimate since approximately 50–60% of cases are deemed idiopathic.^{12–14}

Mendelian inheritance of cataract has been documented since the late 1800s and in the 1960s an inherited form of cataract (CAE1) that was closely linked with the Duffy blood-group locus (Fy) became the first monogenic disease assigned to an autosome (chromosome 1) in humans.¹⁵ Since then, considerable progress has been made in mapping, identifying, and characterizing genes underlying inherited forms of cataract mostly as a result of linkage analysis in extended families.^{16–19} Currently, if the keyword “cataract(s)” is used to search the Online Mendelian Inheritance in Man database (www.omim.org), over 600 entries are retrieved revealing a wide spectrum of cataract phenotypes along with many animal—particularly mouse—models. In addition to featuring as a secondary or variably associated symptom of many genetic syndromes and/or metabolic disorders,²⁰ inherited cataract can present as an isolated or primary lens phenotype—the latter accompanied by relatively mild ocular signs including microcornea, refractive error (e.g., myopia), and/or eye movement disorders (nystagmus, strabismus, amblyopia).^{16–19}

Typically, inherited cataract presents bilaterally with an early onset (birth—40 years), and most cases are diagnosed as congenital, infantile, or juvenile and display considerable inter- and intrafamilial variation in clinical appearance. All three classical modes of Mendelian inheritance are represented; however, most families segregating isolated or primary cataract with few other ocular signs exhibit autosomal dominant transmission with high penetrance. In this chapter, we review recent advances in gene discovery for Mendelian forms of isolated or primary cataract and highlight the implications of these findings for identifying genetic determinants of the much more common forms of age-related cataract.

2. GENES UNDERLYING ISOLATED OR PRIMARY INHERITED CATARACT

According to OMIM, at least 42 loci have been identified for inherited forms of isolated or primary cataract (Table 1) with minimal other ocular signs (e.g., microcornea). Currently, 12 of these are “orphan” loci with no identified genes. For convenience, the 30 known genes may be arbitrarily divided into four groups based on subcellular localization and/or protein function, namely, cytoplasmic crystallins, membrane proteins, cytoskeletal proteins, and DNA/RNA-binding proteins.

2.1 Genes Encoding Crystallins

Crystallin (*CRY*) genes encode >90% of the lens cytoplasmic proteins and these highly abundant, long-lived, soluble proteins play a key role in establishing the gradient refractive index of the lens.²¹ Around 100 different mutations in 12 crystallin genes segregating in over 100 families have been identified that account for about 40–50% of all autosomal dominant cataract reported so far. *CRYAA* and *CRYAB* encode the α -crystallins, two members of the small heat-shock protein (sHSP) family, that form large multimeric complexes (Mr ~500 kDa) with chaperone-like properties.²² Mutations in *CRYAA* are variably associated with nuclear-type opacities and microcornea. By contrast, mutations in *CRYAB* are also associated with several myopathies consistent with its abundant expression in muscle where it binds and stabilizes desmin. Mutations in the genes for β -crystallins (*CRYBB1*, *BB2*, *BB3*, *BA1*, *BA2*, and *BA4*) and γ -crystallins (*CRYGB*, *GC*, *GD*, and *GS*) tend to disrupt folding of the structurally conserved Greek-key domains and/or alter the protein's surface properties resulting in reduced solubility and increased precipitation.²³

2.2 Genes Encoding Membrane Proteins

An increasing number of transmembrane and membrane-associated proteins that mostly facilitate diverse transport, junctional, or kinase functions have been associated with inherited forms of cataract.^{16–19} *GJA3* and *GJA8* encode the gap-junction proteins connexin-46 and connexin-50, respectively, that oligomerize to form hexameric gap-junction channels involved in lens intercellular communication (e.g., ions, electrolytes). Mutations in *GJA3* and *GJA8* are typically associated with nuclear and zonular-pulverulent opacities and account for about 20% of families with autosomal dominant cataract. Functional expression studies reveal that mutant connexins exhibit failed targeting to the cell surface and/or altered channel properties that compromise intercellular communication.²⁴ *MIP* encodes the aquaporin-0 water channel that, in addition to water transport, plays an important cell–cell adhesion role critical for lens integrity and transparency. Mutations in *MIP* underlie autosomal dominant cataract with variable morphologies and most are believed to cause abnormal retention of the mutant protein within the endoplasmic reticulum (ER).^{25,26} *LIM2* encodes a member (MP20) of the peripheral myelin protein-22 (PMP22)-claudin family of transmembrane proteins that share functions in cell adhesion and junction formation, and is required for formation of the lens core syncytium. Despite its relative abundance and likely structural role in the lens, mutations in *LIM2* have so far been found to underlie autosomal recessive cataract suggesting loss-of-function effects.^{27,28}

EPHA2 encodes a member of the ephrin receptor subfamily of protein-tyrosine kinases and through its interaction with src kinase has been implicated in lens cell migration. Mutations in *EPHA2* have been associated with autosomal dominant and recessive forms of cataract consistent with deleterious gain-of-function and loss-of-function mechanisms, respectively. Mutations clustered in the cytoplasmic sterile-alpha-motif domain underlying autosomal dominant cataract have been shown to destabilize the receptor and impair Akt-activated cell migration *in vitro*.^{29–31} *AGK* encodes the mitochondrial membrane protein acylglycerol kinase a key enzyme in membrane-lipid metabolism, and a truncation mutation has been associated with autosomal recessive cataract in a Saudi family. Similar mutations in *AGK* have also been associated with “syndromic” cataract including Sengers syndrome and

infantile mitochondrial disease.³² *CHMP4B* encodes charged multivesicular body protein 4B (CHMP4B)—a core component of the endosome sorting complex required for transport-III. *CHMP4B* mutations are associated with posterior-polar cataract consistent with a role for endosome–lysosome pathway in lens homeostasis.³³ *WFS1* encodes the transmembrane protein, wolframin, that is located primarily in the ER, and is believed to play an important role in regulating ER stress and calcium homeostasis. Typically, homozygous mutations in *WFS1* underlie autosomal recessive Wolfram syndrome 1, which is characterized by diabetes insipidus, diabetes mellitus, optic atrophy, and deafness (DIDMOAD). However, a heterozygous missense mutation in *WFS1* has been associated with autosomal dominant congenital nuclear cataract without ocular or systemic abnormalities in an Irish family.³⁴

2.3 Genes Encoding Cytoskeletal Proteins

Genes encoding key components of the lens cytoskeleton or proteins with functional ties to the cytoskeleton have been found to underlie inherited cataract. *BFSP1* (CP115 or filensin) and *BFSP2* (CP49 or phakanin) encode intermediate filament-like proteins that combine with α -crystallin to form beaded-filament structures found only in lens fiber cells.³⁵ Both autosomal dominant and recessive cataracts have been associated with mutations in *BFSP1* and *BFSP2*. The dominant opacities tend to appear as nuclear or lamellar with sutural involvement, whereas the recessive opacities tend to be cortical. A single mutation in the gene coding for the ubiquitous intermediate filament, vimentin (*VIM*) has also been linked with autosomal dominant pulverulent cataract.³⁶ *FYCO1* encodes a scaffolding protein that is active in microtubule transport of autophagic vesicles. Multiple *FYCO1* mutations underlie autosomal recessive cataract consistent with an important role for autophagy in lens transparency.³⁷ *NHS* encodes a regulator of actin remodeling and cell shape. Copy number variations (CNVs) in *NHS* cause X-linked cataract (CXN). However, nonsense and frameshift mutations in *NHS* cause Nance–Horan (cataract-dental) syndrome in males and mild sutural opacities in female carriers.^{38,39}

2.4 Genes Encoding DNA- or RNA-Binding Proteins

Mutations in several transcription factor genes involved in eye development can present primarily as a cataract phenotype. *HSF4* regulates transcription of sHSPs including lens CRYAB.⁴⁰ Mutations in *HSF4* that underlie autosomal dominant cataract lie within the alpha-helical DNA-binding domain, whereas *HSF4* mutations underlying autosomal recessive cataract lie outside this functionally conserved domain. Three *HSF4* truncation mutations linked with recessive cataract have been shown to result in the loss of regulatory domains at the C-terminal end of the protein consistent with loss-of-function mechanisms.⁴¹ *PITX3* encodes a paired-like homeodomain transcription factor that plays a key role in the regulation of genes involved in lens development including *MIP/AQP0*.⁴² Mutations in *PITX3* underlie both dominant and recessive forms of cataract with or without anterior segment dysgenesis and microphthalmia. All known coding mutations are located outside the functionally conserved DNA-binding homeodomain. However, several frameshift mutations, including a recurrent 17 bp duplication, have been shown to disrupt the C-terminal *otp/aristaless/rax* (OAR) domain resulting in an altered DNA-binding profile and reduced transactivation activity.⁴³ *MAF* encodes a bZIP transcription factor that binds to MAF-responsive elements located in the promoter regions of target genes, including those

for crystallins and MIP, with varying transactivation properties. *MAF* mutations, located within the conserved DNA-binding domain, underlie autosomal dominant cataract with or without microcornea and disease severity has been correlated with differential transactivation effects on several of the beta/gamma crystallin genes.⁴⁴

Beyond DNA-binding transcription factors, mutations in the gene coding for an RNA-binding protein, tudor domain containing-7 (*TDRD7*), have been associated with autosomal recessive cataract.⁴⁵ *TDRD7* localizes to a distinct subset of cytoplasmic RNA granules that interact with processing (P) bodies and Staufen-1 (STAU-1) ribonucleoproteins. These findings point to an important role for posttranscriptional regulation of mRNA processing and subcellular localization in lens homeostasis.

3. GENES ASSOCIATED WITH AGE-RELATED CATARACT

Case-control association studies have sought to find genetic susceptibility factors for age-related cataract. Several such studies using a candidate gene approach have found coding and noncoding variations in some of the same genes underlying inherited cataract that are also associated with age-related cataract. These genes include *EPHA2* (1p), *GJA3* (13q), *GJA8* (1q), *MIP* (12q), *HSF4* (16q), *LIM2* (19q), and *CRYAA* (21q).^{46–50} However, only the *EPHA2* association has been replicated in different populations including with cortical cataract in Caucasians and Han Chinese, with cortical cataract and PSC in Indians, and with any cataract in Caucasians and Asians from China and India.^{46,51–54} There was no association of *EPHA2* variants with nuclear cataract in any population.

Candidate genes underlying syndromic or systemic forms of cataract have also been associated with age-related cataract. *GALK1* (17q) encodes the first enzyme in galactose metabolism and causative mutations in this gene underlie autosomal recessive galactokinase 1-deficiency with cataract—the latter as a result of galactitol accumulation and subsequent osmotic stress. The “Osaka” coding variation in *GALK1* (p.A198V) results in enzyme instability and has been associated with increased risk of age-related cataract in the Japanese population.⁵⁵ *SLC16A12* (10q) encodes a creatine transporter and mutations in this gene underlie autosomal dominant juvenile cataract plus microcornea and renal glucosuria.⁵⁶ Variations in the 5′-untranslated region of *SLC16A12* have been associated with age-related cataract in Caucasians.⁵⁷ Mutations in *WRN* (8p), which encodes a genomic DNA helicase, cause autosomal recessive Werner syndrome—a premature aging (progeroid) disorder with early-onset cataract. Both CNVs and single nucleotide variants in *WRN* have been associated with age-related cortical cataract in Han Chinese.^{58–60}

In addition to genes involved in hereditary cataract, variations in other candidate genes not directly associated with inherited forms of cataract have been tentatively implicated in age-related cataract. These include genes that function in antioxidant metabolism (*GSTM1*, *GSTT1*), lactose metabolism (*LCT*), drug metabolism (*NAT2*), folate metabolism (*MTHFR*), DNA repair (*XPD*), lipid/cholesterol transport (*APOE*), kinesin/microtubule motor transport (*KLC1*), actin-cytoskeleton regulation (*EZR*), chaperone activity (*HSP70*), and ephrin signaling (*EFNA5*).^{61–70}

A limitation of candidate gene case-control studies is that they may be statistically underpowered to find genome-wide association and are often not replicated in different populations. A previous genome-wide linkage scan has reported several statistically significant susceptibility loci for age-related cortical cataract in Caucasians, including a locus on chromosome 6p12-q12 (CTRCT28); however, no specific genes were identified.⁷¹ So far, only one of the above genes underlying inherited cataract has met genome-wide statistical significance for association with age-related cataract. A recent meta-analysis of genome-wide association studies (GWAS) in multiethnic Asians has identified variants near the 3'-end of *CRYAA* (21q) strongly associated with age-related nuclear cataract.⁷² This study also identified intronic variations in *KCNAB1* (3q), which encodes a member of the potassium voltage-gated channel, shaker-related subfamily, that were significantly associated with age-related nuclear cataract along with 14 other loci showing suggestive association. Mutations in two of the latter genes, *SLC4A4* (4q) and *COL4A1* (13q), underlie syndromic forms of congenital cataract associated with renal disease. Finally, another GWAS based on electronic medical records linked to DNA biobanks from individuals of mostly European descent identified a novel range of potential susceptibility loci for age-related cataract including those harboring aldolase B (*ALDOB*), mitogen-activated protein kinase kinase 1 (*MAP3K1*), and monocyte-specific enhancer factor 2C (*MEF2C*).⁷³ However, none of these susceptibility loci met genome-wide significance.

4. SUMMARY AND OUTLOOK

In addition to the plethora of genetic syndromes and metabolic disorders that are variably associated with cataract, at least 42 genes and loci have been found to underlie inherited forms of isolated or primary cataract. A review of the known causative genes suggests that they may be arbitrarily divided into two broad groups. The first group recapitulates important structure-function aspects of lens biology involving α - and β/γ -crystallins (e.g., *CRYAA*, *CRYBB2*, *CRYGD*), α -connexins (*GJA3*, *GJA8*), and other lens abundant membrane or cytoskeleton proteins (e.g., *MIP/AQP0*, *BFSP2*). The second group highlights developmental and/or regulatory processes or pathways in the lens involving several transcription factors (e.g., *HSF4*, *PITX3*) and an expanding cohort of functionally diverse genes (e.g., *EPHA2*, *TDRD7*, *FYCO1*).

Despite the increasing genetic heterogeneity of inherited cataract, gene discovery studies remain both scientifically and clinically important for several reasons. First, they provide a rational, "gene-centric" basis for clinical classification and molecular diagnosis of Mendelian forms of cataract. While morphological descriptions of lens opacities may assist in the diagnosis of certain genetic syndromes (e.g., sutural opacities in female NHS carriers), in most cases phenotype-genotype correlations are challenging as morphologically similar opacities may be caused by different genes and vice versa. Genetic studies employing next-generation (massively parallel) exome sequencing now facilitate concurrent profiling of the known candidate genes for underlying mutations and may also enable the identification of novel genes for cataract. As exome sequencing becomes more cost effective, such studies of inherited cataract will provide personalized diagnosis and enhanced genetic counseling for affected families and sporadic cases. Second, they identify plausible candidate genes for genome-wide association (or linkage) studies seeking to discover genetic determinants of

age-related cataract. Currently, there is increasing evidence that several genes underlying rare forms of inherited cataract can also influence susceptibility to the much more prevalent forms of age-related cataract (e.g., *EPHA2*, *CRYAA*). These observations raise the possibility of molecular genetic links between lens development and aging. Finally, they provide new insights into lens biology. Notably, the recent discovery of mutations in genes coding for *EPHA2*, *TDRD7*, and *FYCO1* has provided the first evidence for the functional importance of ephrin signaling, posttranscriptional mRNA regulation, and the autophagy pathway, respectively, in human lens transparency. In the longer term, such discoveries may translate into novel therapeutic strategies that can delay or even prevent cataract onset.

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Table 1

Loci and Genes for Cataract (CTRCT)

Cataract Phenotype	Locus	Inheritance	Associated Phenotypes	Gene	Phenotype MIM No.	Gene/Locus MIM No.
CTRCT1; multiple types	1q21.1	AD/AR	± Microcornea	<i>GJA8</i>	116200	600897
CTRCT2; multiple types	2q33.3	AD	± Microcornea	<i>CRYGC</i>	604307	123680
CTRCT3; multiple types	22q11.23	AD	± Microcornea	<i>CRYBB2</i>	601547	123620
CTRCT4; multiple types	2q33.3	AD	± Microcornea	<i>CRYGD</i>	115700	123690
CTRCT5; multiple types	16q21	AD/AR		<i>HSE4</i>	116800	602438
CTRCT6; multiple types	1p36.13	AD/AR	Age-related cortical	<i>EPHA2</i>	116600	176946
CTRCT7	17q24	AD		?	115660	?
CTRCT8; multiple types	1pter-p36.13	AD		?	115665	?
CTRCT9; multiple types	21q22.3	AD/AR	± Microcornea	<i>CRYAA</i>		123580
CTRCT10; multiple types	17q11.2	AD		<i>CRYBA1</i>	600881	123610
CTRCT11; multiple types	10q24.32	AD	Anterior segment mesenchymal dysgenesis, microphthalmia, neurodevelopmental abnormalities	<i>PITX3</i>	610623	602669
CTRCT12; multiple types	3q22.1	AD	Myopia?	<i>BFSF2</i>	611597	603212
CTRCT13	6p24	AR	Adult i (blood group) phenotype	<i>GCNT2</i>	110800	600429
CTRCT14; multiple types	13q12.1	AD		<i>GJA3</i>	601885	121015
CTRCT15; multiple types	12q13.3	AD		<i>MIP</i>	615274	154050
CTRCT16; multiple types	11q22.3	AD/AR	Myopathy, cardiomyopathy	<i>CRYAB</i>	613763	123590
CTRCT17; multiple types	22q12.1	AD/AR		<i>CRYBB1</i>	611544	6009291
CTRCT18	3p21.31	AR		<i>FYCO1</i>	610019	607182
CTRCT19	19q13.41	AR		<i>LIM2</i>	615277	154045
CTRCT20; multiple types	3q27.3	AD		<i>CRYGS</i>	116100	123730
CTRCT21; multiple types	16q22-q23	AD	± Microcornea	<i>MAF</i>	610202	177075
CTRCT22; multiple types	22q11.23	AD/AR		<i>CRYBB3</i>	609741	123630
CTRCT23	22q12.1	AD		<i>CRYBA4</i>	610425	123631
CTRCT24; anterior polar	17p13	AD		?	601202	?
CTRCT25	15q21-q22	AD		?	605728	?
CTRCT26; multiple types	9q13-q22	AR		?	605749	?

Cataract Phenotype	Locus	Inheritance	Associated Phenotypes	Gene	Phenotype MIM No.	Gene/Locus MIM No.
CTRCT27; nuclear progressive	2p12	AD		?	607304	?
CTRCT28	6p12-q12	Complex	Age-related cortical, susceptibility to	?	609026	?
CTRCT29; coralliform	2pter-p24	AD		?	115800	?
CTRCT30; pulverulent	10p13	AD		<i>VIM</i>	116300	193060
CTRCT31; multiple types	20q11.21	AD		<i>CHMP4B</i>	605387	610897
CTRCT32; multiple types	14q22-q23	AD		?	%115650	?
CTRCT33; cortical	20p12.1	AR		<i>BFSP1</i>	611391	603307
CTRCT34; multiple types	1p34.3-p32.2	AR	± Microcornea	?	612968	?
CTRCT35; congenital nuclear	19q13	AR		?	609376	?
CTRCT36	9q22.33	AR		<i>TDRD7</i>	613887	611258
CTRCT37; cerulean	12q24.2-q24.3	AD		?	614422	?
CTRCT38	7q34	AR	Sengers syndrome	<i>AGK</i>	614691	610345
CTRCT39; multiple types	2q34	AD		<i>CRYGB</i>	615188	123670
CTRCT40	Xp22.13	X-linked	Nance-Horan (cataract-dental) syndrome	<i>NHS</i>	302200	300457
CTRCT41	4p16.1	AD	Wolfram syndrome (DIDMOAD)	<i>WFS1</i>	116400	606201
CTRCT42	2q34	AD		<i>CRYBA2</i>	115900	600836