Published in final edited form as:

Clin Genet. 2013 August ; 84(2): 120–127. doi:10.1111/cge.12182.

Genetics of human cataract

A Shiels^a and JF Hejtmancik^b

^aDepartment of Ophthalmology and Visual Sciences, Washington University School of Medicine, St. Louis, MO, USA

^bOphthalmic Genetics and Visual Function Branch, National Eye Institute, National Institutes of Health, Bethesda, MD, USA

Abstract

The pathogenesis of inherited cataracts of all kinds recapitulates the developmental and cell biology of the lens. Just as each novel mutation provides additional information about the structural or functional biology of the affected gene, each newly identified gene provides insight into the developmental and cellular biology of the lens. The set of genes currently known to be associated with cataract is far from complete, especially for age-related cataract, and there is much additional information to be discovered through further genetic studies.

Keywords

cataract; genetics; lens; mutations

The eye lens and its function

The function of the eye lens is to transmit and focus light onto the retina, where it is detected by the photoreceptors and converted into visual signals. This is accomplished structurally by the lens architecture, consisting of a single layer of anterior epithelial cells that migrate during development toward the lens equator where they elongate, synthesize large amounts of lens crystallins, and finally degrade their organelles to form the central lens nucleus. While this process begins during embryo-genesis, it continues at a slower pace throughout life, resulting in older fibers in the lens center, or nucleus, and younger cortical fiber cells constantly being layered at the equator (1). As lens fiber cells lack organelles, it has been assumed that they cannot replace or turn over damaged proteins, so both the structure and stability of the lens crystallins and maintenance of strong cellular homeostatic systems are necessary to maintain normal lens function. However, recent evidence suggests that newly

© 2013 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

Corresponding author: James F. Hejtmancik, Ophthalmic Genetics and Visual Function Branch, National Eye Institute, National Institutes of Health, Bethesda, MD 20892-1860, USA. Tel.: +1 301 496 8300; f3h@helix.nih.gov.

Conflict of interest

None.

Supporting Information

The following Supporting information is available for this article:

Appendix S1. Supporting information references.

Additional Supporting information may be found in the online version of this article.

synthesized proteins might be present in the lens nucleus (2), and that central nuclear fiber cells, largely restricted to glycolysis as an intrinsic energy source, receive metabolic support from the anterior epithelium through circulation of fluid, although this remains controversial (3, 4). Disruption of any part of this delicately balanced system can result in cataract.

Cataract can be defined as any opacity or cloudiness of the crystalline lens (5, 6). Opacity and light scattering result when the refractive index of the lens varies significantly over distances, approximating the wavelength of the transmitted light (7, 8). Lens transparency is critically dependent on both the orderly arrangement of lens cells and the high density and close packing of their protein constituents (5). Breakdown of the lens microarchitecture, including cellular disarray and vacuole formation, can cause large fluctuations in optical density, resulting in light scattering and cataract. Light scattering and opacity can also result from significant concentrations of high-molecular-weight protein aggregates of 1000Å or more in size. As lens crystallins make up over 90% of soluble lens proteins, their short-range ordered packing in a homogeneous phase is important for the maintenance of lens transparency.

Clinically, cataracts become important when they interfere with vision. They can be categorized by their age-at-onset: congenital or infantile cataracts within the first year of life; juvenile cataracts within the first decade of life; presenile cataracts before the age of 45 years; and senile or age-related cataract thereafter, although these boundaries are approximate and somewhat arbitrary. In addition, mild cataracts might not be seen for years after they occur, especially if they are asymptomatic. While the age-at-onset might provide some suggestions as to the etiology of a cataract, it does not necessarily imply a specific cause. Congenital cataracts might be inherited or secondary to an intrauterine insult, and cataracts associated with a systemic or ophthalmic genetic disease may not occur until the second or third decade of life.

The timing or intralenticular location of an inherited cataract can provide clues regarding its genetic origin. Lens opacities generally tend to occur in cells and at times when high levels of a mutant protein are being synthesized. For example, γ -crystallins are relatively fiber cell-specific and are expressed early in development. Thus, they are a major component of primary fiber cells in the embryonic nucleus and mutations in them tend to be associated with nuclear cataract. While general tendencies such as this can be identified, mutations in different genes can cause clinically indistinguishable cataracts and identical mutations in the same gene can cause different cataract phenotypes. It appears likely that when mutations in crystallins or other lens proteins are sufficiently severe to cause protein aggregation or directly damage lens cells by themselves, they usually result in congenital cataract. In contrast, if mutations merely increase susceptibility to damage from light, hyperglycemia, oxidative stress or other environmental insults they might contribute to age-related cataract (9). Thus, hereditary congenital cataracts tend to be inherited in a Mendelian fashion with high penetrance, whereas age-related cataracts tend to be multifactorial, with both multiple genes and environmental factors influencing the phenotype. Both the late onset and incomplete penetrance of age-related cataracts make them significantly less amenable to genetic and biochemical study.

Congenital cataract

The incidence of congenital or infantile cataracts has been estimated to be about 72 per 100,000 children, with estimates varying from 12 to 136 and being generally higher in less-developed countries (10). Hereditary cataracts usually account for between 8.3% and 25% of congenital cataracts (11–13). Congenital cataracts may occur as isolated defects or may be associated with other anterior chamber developmental anomalies such as microphthalmia or aniridia. Lens opacities may also be part of multisystem genetic disorders such as chromosome abnormalities, Lowe syndrome, or Nance Horan Syndrome. In some cases, this distinction becomes somewhat arbitrary. For example, as part of the anterior segment mesenchymal dysgenesis (ASMD) resulting from abnormalities in the *PITX3* gene (14) inherited cataracts may be isolated in some family members and associated with additional findings in others.

Hereditary Mendelian cataracts are most frequently autosomal dominant, but can also be autosomal recessive or X-linked. Phenotypically identical cataracts can result from mutations at different genetic loci and may have different inheritance patterns, while phenotypically variable cataracts can be found in a single large family (15). There are several classification systems that have been developed based on the anatomic location of the opacity, of which one is proposed by Merin (16), in which cataracts are classified as total (mature or complete), polar (anterior or posterior), zonular (nuclear, lamellar, sutural, etc.), and capsular or membranous (Fig. 1).

Age-related cataract

In age-related cataracts, the lens is clear during infancy and remains clear until sometime after 45 or 50 years of age, when progressive lens opacities begin to form. Age-related cataracts almost certainly result from varying combinations of genetic predisposition and the cumulative damage of environmental insults on lens proteins and cells. Lens proteins are known to undergo a wide variety of alterations with age, and many of these are accelerated in the presence of oxidative, osmotic, or other stresses, which are themselves known to be associated with cataractogenesis (17–19). Alterations of lens crystallins include proteolysis, an increase in disulfide bridges, phosphorylation, non-enzymatic glycosylation, carbamylation, deamidation of asparagine and glutamine residues, and racemization of aspartic acid residues among others (20). These chemical modifications have been shown to be increased in cataractous lenses and to occur in animal models or *in vitro* under the same stresses epidemiologically associated with cataracts (21).

As crystallins are the major soluble structural proteins in the lens, they have been the subject of most studies of the aging lens. In humans, crystallins comprise three major classes encoded by multiple genes: the α -, β - and γ -crystallins, of which the latter two are part of a large gene family (22). As the β - and γ -crystallins are subjected to environmental insults and accumulate damage over the lifetime of an individual, they begin to form irreversible aggregates rather than participating in normal intermolecular interactions, and eventually come out of solution. Usually, this slow denaturation of the crystallins results in their being bound by the α -crystallins, which have a chaperone-like activity (23). However, while

binding by α -crystallins maintains solubility of $\beta\gamma$ -crystallins and reduces light scattering, it does not result in their renaturation and release into the cytoplasm. Rather, a plausible sequence of events that may lead to aggregation and cataractogenesis is that the aggregated crystallins are held in complexes that, while soluble, increase in size as additional damaged protein is bound over time until they themselves become large enough to scatter light (23, 24). Eventually, the available α -crystallin is overwhelmed by increasing amounts of modified $\beta\gamma$ -crystallins and the complexes precipitate within the lens cell, forming the insoluble protein fraction that is known to increase with age and in cataractous lenses.

Age-related cataract is associated with a number of environmental risk factors (25), and some lifestyles seem to show a protective effect, although this has not been borne out by all studies (26, 27) (Table 1). Overall, these studies have not only identified a number of potentially correctable risk factors for age-related cataract, but also suggest that nuclear, cortical and posterior subcapsular cataracts might have distinct but overlapping pathogenic mechanisms. Epidemiological evidence also suggests that genetic factors are important risk factors for age-related cataract (Table 2) (28).

Overview of cataract genetics

Mendelian or familial cataract

Most isolated cataracts inherited as Mendelian traits occur at birth or childhood and conversely most congenital cataracts are inherited as Mendelian traits (5). There are currently about 45 genetic loci to which isolated cataracts have been mapped with specific genes identified in 38, although the number is constantly increasing (Table 3). Some are also associated with additional abnormalities in some affected individuals, including mutations in genes encoding transcriptional activators, CRYAB (myopathy) and ferritin light chain (FTL) hyperferritinemia-cataract syndrome (Table 1). In addition, mutations in some genes, e.g. some crystallin mutations, can cause early and severe damage to the lens, often associated with microcornea and even microphakia.

About 10% of mapped cataract loci have not had causative genes identified, with the remainder reflecting critical processes in lens biology. About half show mutations in lens crystallins, 10% have mutations in transcription factors, 15% in connexins, 5% each in intermediate filaments or aquaporin 0, and 10% in a variety of other genes. Inheritance of the same mutation in different families or even the same mutation within the same family can result in radically different cataract morphologies and severities, suggesting that additional genetic or environmental factors might modify the phenotype. Conversely, cataracts with similar or identical morphologies can result from mutations in quite different genes, perhaps relating to clinical cataract being a final common pathway for a variety of different initial insults.

Mendelian cataracts reflect lens biology

Developmental or transcription factors

Perhaps the primary factor in eye development is PAX6, a paired box and homeo box domain protein, critical for eye development. While most mutations in *PAX6* cause aniridia

or Peter's anomaly, they can also cause isolated cataract. Mutations in other transcription factors including *FOXE3*, *EYA1*, *PITX3*, *VSX2*, *MAF*, and *NHS* can also cause cataract. Mutations in these genes also can be associated with broader defects including microcornea, colobomas of the irides, microphthalmia, corneal defects, and ASMD. An apparent exception to this general rule is *HSF4*, which regulates transcription of heat-shock proteins, including lens α B-crystallin (29). *HSF4* mutations are associated with both autosomal-dominant and recessive cataracts. Interestingly, the dominant mutations in *HSF4* lie within the α -helical DNA-binding domain, whereas the recessive mutations lie outside this highly conserved functional domain.

Additional genes implicated in developmental processes but not themselves transcription factors can also cause cataracts when mutated, including *EPHA2*, a member of the ephrin receptor subfamily of protein-tyrosine kinases. Mutations in *EPHA2* can cause not only both dominant and recessive congenital cataracts, but surprisingly are also implicated in age-related cataract. Mutations in *TDRD7*, a Tudor domain RNA-binding protein component of RNA granules that interact with STAU-1 ribonucleoproteins, also cause cataract (30).

Cataracts identify biological processes unique to or highly active in the lens

Genes required at high levels for specific processes in lens development have been implicated in cataract. Mutations in *FYCO1*, a scaffolding protein active in microtubule transport of autophagic vesicles, are responsible for autosomal-recessive cataracts, suggesting that autophagic vesicles are important in organelle degradation in developing lens fiber cells. Mutations in *GCNT2*, the I-branching enzyme for poly-N-acetyllactosaminoglycans responsible for converting the juvenile 'i' to the adult 'I' blood type, also cause autosomal-recessive cataract. Mutations in *CHMP4B*, part of the endosomal sorting complex required for transport, cause posterior polar or subcapsular cataract. Synthesis of large amounts of membrane components is required for fiber cell differentiation, and mutations in acylglycerol kinase (*AGK*), a lipid kinase catalyzing synthesis of phosphatidic and lysophosphatidic acids, and *LIM2*, a lens-specific cell junction membrane protein, cause cataract.

Circulation of water and small molecules is important for lens homeostasis, and mutations in *SLC16A12*, a transmembrane transporter active in monocarboxylic acid transport, can cause dominant cataracts. More directly, mutations in aquaporin 0 (*AQP0* or *MIP*) are a common cause of Mendelian cataract of various morphologies. Two of the mutations, E134G and T138R appear to act by interfering with normal trafficking of AQP0 to the plasma membrane and thus with water channel activity. Both interfere with water channel activity by normal AQP0, consistent with a dominant negative mechanism for the autosomal-dominant inheritance of the cataracts. A chromosomal translocation affecting *TMEM114*, a transmembrane glycoprotein related to calcium channel gamma subunits, causes cataract. *GJA3* and *GJA8* (encoding connexins 46 and 50) are constituents of gap junctions, also critical for nutrition and intercellular communication in the lens, together account for about 15% of cataract families. Mutations in both *GJA3* and *GJA8* tend to produce phenotypically similar autosomal-dominant nuclear and especially zonular pulverulent cataracts.

BFSP1 (CP115 or filensin) and BFSP2 (CP49, phakinin) are highly divergent intermediate filament proteins that combine in the presence of α -crystallin to form beaded filaments, a type of intermediate filament unique to lens fiber cells. Both dominant and recessive cataracts have been associated with mutations in *BFSP2*, with the dominant cataracts caused by missense or in-frame deletion mutations and the recessive by a frameshift nonsense mutation. The dominant cataracts are nuclear or nuclear lamellar, consistent with fiber cell-specific expression of the beaded filament proteins while the recessive cataracts are cortical.

Lens crystallins are a rich target for cataract mutations

If examination of the genes implicated in congenital cataracts provides insight into those biological pathways important for lens transparency, the frequency of crystallin mutations as a cause of inherited cataracts assigns them a major role in this process. Mutations in the α A-crystallin gene *CRYAA* can cause both autosomal-recessive cataracts, associated with a chain termination mutation near the beginning of the protein predicted to undergo nonsense mediated decay, and autosomal-dominant cataracts, which tend to be associated with non-conservative missense mutations predicted to have a deleterious effect on lens cells.

Because α A- and α B-crystallin are found in the lens associated with large multimeric complexes and function similarly *in vitro*, one might expect that mutations in α B-crystallin would have an effect similar to those in α A-crystallin, at least in the lens. However, the first human mutation reported in α B-crystallin, a missense mutation that reduced α B-crystallin chaperone activity dramatically and caused aggregation and precipitation of the protein under stress, was associated with myofibrillar myopathy but only 'discrete' cataracts. The associated myopathy is probably due to the expression of α B-crystallin, but not α A-crystallin, in muscle cells, where it binds and stabilizes desmin. These results have been recapitulated in *CRYAB* knock-out and knock-in mice.

While α -crystallin mutations could contribute to cataract by reducing their chaperone activity, most mutations in the β γ -crystallins appear to result in abnormal protein structure, with consequent instability and a protein that aggregates and then precipitates from solution, possibly serving as a nidus for additional protein denaturation and precipitation and cataract. Mutations of γ -crystallins tend to produce nuclear cataracts, consistent with their early expression and high levels in the lens nucleus. Association of identical mutations in β B2-crystallin in different families with nuclear lamellar Coppock-like and cerulean cataracts emphasizes the importance of modifying genes in the phenotypic expression of these mutations.

Some mutations in γ D-crystallin have been shown not to damage the protein fold, but to change the surface characteristics of the mutant protein, lowering the solubility and enhancing their crystal nucleation rate (31). This causes them to precipitate out of solution through hydrophobic interactions for the R36S mutation and by actually forming crystals in the lens for the R58H mutation. In a third mutation in γ D-crystallin, R14C, the protein also maintains a normal protein fold, but is susceptible to thiol-mediated aggregation (32). These results emphasize that crystallins need not undergo denaturation or other major changes in their protein folds to cause cataracts.

Finally, the hyperferritinemia-cataract syndrome, in which cataracts are associated with hyperferritinemia without iron overload, provides an example of the consequences of inadvertent expression of an extraneous protein at crystallin-like levels. Mutations in the ferritin L (light chain) iron responsive element release the mRNA from translational control by the iron regulatory protein resulting in overexpression of ferritin with crystallization of ferritin in the lens and the consequent appearance of breadcrumb-like opacities in the cortex and nucleus. This emphasizes the requirement that crystallins must be exceptionally soluble and pack closely to avoid causing dysfunction.

Age-related cataract and lens homeostasis

Linkage studies and adult-onset Mendelian cataracts

A number of inherited cataracts with delayed age-at-onset or progression of the opacity throughout life have been described, including juvenile cataracts from mutations in *BFSP2*, *SLC16A12*, *TMEM114*, *MAF*, aquaporin-0 (MIP), γ C-crystallin, and the CAAR locus. These examples seem to imply that a mutation that severely disrupts the protein or inhibits its function might result in congenital cataracts inherited in a highly penetrant Mendelian fashion, whereas a mutation that causes less severe damage to the same protein or impairs its function only mildly might contribute to age-related or progressive cataracts, with either reduced penetrance or even a more complex multifactorial inheritance pattern. Similarly, mutations that severely disrupt the lens cell architecture or environment might produce congenital cataracts, whereas others that cause relatively mild disruption of lens cell homeostasis might contribute to age-related cataract.

Because of their reduced penetrance, multifactorial origin, and late onset, identification of genes contributing to age-related cataract has proceeded much more slowly than that for congenital and childhood cataract. The only genome-wide linkage scan carried out to date suggested a number of major and minor susceptibility loci for age-related cortical cataract in Caucasians (33). The most statistically significant locus, on chromosome 6p12, maps close to a susceptibility locus for type 2 diabetes and retinopathy [OMIM #125853; OMIM (<http://www.ncbi.nlm.nih.gov/omim/>) and Cat-Map (<http://cat-map.wustl.edu/>) online databases], a known risk factor for age-related cortical cataract. A second locus was identified on chromosome 1p near the *EPHA2* gene (see below).

Association studies

Galactosemic cataracts provide an interesting example of mutations severely affecting a gene causing early-onset cataracts whereas milder mutations simply decreasing its activity contribute to age-related cataracts (34). Deficiencies of galactokinase (GALK1), galactose-1-phosphate uridyl transferase, and severe deficiencies of uridine diphosphate 1–4 epimerase cause autosomal-recessive cataracts as a result of galactitol accumulation and subsequent osmotic swelling. The ‘Osaka’ variant of galactokinase (A198V), resulting in instability of the mutant protein and responsible for mild galactokinase deficiency, is associated with a significant increase in bilateral cataracts in Japanese adults (35). The Osaka variant allele frequency is 4.1% in Japanese overall and 7.1% of Japanese with cataracts. It has a lower incidence in Koreans and Chinese and is absent in blacks or whites

from the United States or Northern Italians (36). Similarly, heterozygous deficiency of GALK1 and galactose-1-phosphate uridyl transferase activity has been associated with increased risk of age-related cataract (37). The GALK1 results fit in well with the known influence of hyperglycemia on age-related cataract, probably with an oxidative component or osmotic damage resulting from polyol accumulation. Consistent with this are animal data and association of susceptibility to cataracts as a diabetic complication in humans is with specific alleles of the aldose reductase gene (38).

A second candidate gene for age-related cataract with strong support is *EPHA2* in the chromosome 1 region identified by non-parametric linkage analysis (33). This region overlaps loci for inherited forms of childhood cataract associated with mutations in the gene coding for Eph-receptor type-A2 (*EPHA2*), which functions in the ephrin cell signaling and axon guidance pathway (39–41). Single-nucleotide polymorphisms (SNPs) in the *EPHA2* region of chromosome 1 are associated with age-related cortical cataract, further suggesting that *EPHA2* variants may underlie both Mendelian and age-related forms of cataract (39, 42–44).

In addition to *GALK1* and *EPHA2*, a number of loci and genes have been reported to be associated with age-related cataract. Association of one of the first identified loci with age-related cataract, the null allele of the *GSTM1* locus, has proved to be inconsistent (45), as has that for *GSTT1*. Alterations in the monocarboxylate transporter *SLC16A12* are also implicated in juvenile cortical and nuclear cataract and have been associated with age-related cataract. In addition, inconsistent or unconfirmed association of the DNA repair genes *WRN*, *XPD* and *XRCC1*, as well as *HSF4* and the kinesin light chain 1 gene *KLC1* have been reported with age-related cataract.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Wride MA. Lens fibre cell differentiation and organelle loss: many paths lead to clarity. *Philos Trans R Soc Lond B Biol Sci*. 2011; 366(1568):1219–1233. [PubMed: 21402582]
2. Stewart DN, Lango J, Nambiar KP, et al. Carbon turnover in the water-soluble protein of the adult human lens. *Mol Vis*. 2013; 19:463–475. [PubMed: 23441119]
3. Donaldson, PJ.; Musil, LS.; Mathias, RT. Invest Ophthalmol Vis Sci. Vol. 51. 2303–2306: 2010. Point: a critical appraisal of the lens circulation model – an experimental paradigm for understanding the maintenance of lens transparency?.
4. Beebe DC, Truscott RJ. Counterpoint: the lens fluid circulation model – a critical appraisal. *Invest Ophthalmol Vis Sci*. 2010; 51(5):2306–2310. discussion 10–2. [PubMed: 20435605]
5. Hejtmancik, JF.; Kaiser-Kupfer, MI.; Piatigorsky, J. Molecular biology and inherited disorders of the eye lens.. In: Scriver, CR.; Beaudet, AL.; Valle, D.; Sly, WS.; Childs, B.; Kinzler, KW.; Vogelstein, B., editors. The metabolic and molecular basis of inherited disease. Vol. 8. McGraw Hill; New York: 2001. p. 6033-6062.
6. Graw J. Genetics of crystallins: cataract and beyond. *Exp Eye Res*. 2009; 88(2):173–189. [PubMed: 19007775]
7. Delaye M, Tardieu A. Short-range order of crystallin proteins accounts for eye lens transparency. *Nature*. 1983; 302:415–417. [PubMed: 6835373]

8. Benedek GB. Theory of transparency of the eye. *Appl Opt.* 1971; 10:459–473. [PubMed: 20094474]
9. Hejtmancik, JF.; Smaoui, N. Molecular genetics of cataract.. In: Wissinger, B.; Kohl, S.; Langenbeck, U., editors. *Genetics in ophthalmology*. S.Karger; Basel: 2003. p. 67-82.
10. Haargaard B, Wohlfahrt J, Fledelius HC, Rosenberg T, Melbye M. Incidence and cumulative risk of childhood cataract in a cohort of 2.6 million Danish children. *Invest Ophthalmol Vis Sci.* 2004; 45(5):1316–1320. [PubMed: 15111583]
11. Francois J. Genetics of cataract. *Ophthalmologica.* 1982; 184:61–71. [PubMed: 7063172]
12. Merin, S. Inherited Cataracts.. In: Merin, S., editor. *Inherited eye diseases*. Marcel Dekker, Inc.; New York: 1991. p. 86-120.
13. Haargaard B, Wohlfahrt J, Rosenberg T, Fledelius HC, Melbye M. Risk factors for idiopathic congenital/infantile cataract. *Invest Ophthalmol Vis Sci.* 2005; 46(9):3067–3073. [PubMed: 16123403]
14. Semina EV, Ferrell RE, Mintz-Hittner HA, et al. A novel homeobox gene PITX3 is mutated in families with autosomal-dominant cataracts and ASMD. *Nat Genet.* 1998; 19(2):167–170. [PubMed: 9620774]
15. Hejtmancik, JF.; Shiels, A. Genetics of congenital cataract.. In: Dartt, DA.; Besharse, J.; Dana, R., editors. *Encyclopedia of the eye*. Elsevier; New York: 2010.
16. Merin S, Crawford JS. The etiology of congenital cataracts. A survey of 386 cases. *Can J Ophthalmol.* 1971; 6:178–182. [PubMed: 4254831]
17. Truscott RJ. Age-related nuclear cataract-oxidation is the key. *Exp Eye Res.* 2005; 80(5):709–725. [PubMed: 15862178]
18. Machan CM, Hrynychak PK, Irving EL. Age-related cataract is associated with type 2 diabetes and statin use. *Optom Vis Sci.* 2012; 89(8):1165–1171. [PubMed: 22797512]
19. Bunce GE, Kinoshita J, Horwitz J. Nutritional factors in cataract. *Annu Rev Nutr.* 1990; 10:233–254. [PubMed: 2200464]
20. Sharma KK, Santhoshkumar P. Lens aging: effects of crystallins. *Biochim Biophys Acta.* 2009; 1790(10):1095–1108. [PubMed: 19463898]
21. Ottonello S, Foroni C, Carta A, Petrucco S, Maraini G. Oxidative stress and age-related cataract. *Ophthalmologica.* 2000; 214(1):78–85. [PubMed: 10657746]
22. Wistow G. Lens crystallins: gene recruitment and evolutionary dynamism. *Trends Biochem Sci.* 1993; 18:301–306. [PubMed: 8236445]
23. Rao PV, Huang QL, Horwitz J, Zigler JS Jr. Evidence that alpha-crystallin prevents non-specific protein aggregation in the intact eye lens. *Biochim Biophys Acta.* 1995; 1245(3):439–447. [PubMed: 8541324]
24. Datiles MB III, Ansari RR, Suh KI, et al. Clinical detection of precatactous lens protein changes using dynamic light scattering. *Arch Ophthalmol.* 2008; 126(12):1687–1693. [PubMed: 19064850]
25. Foster PJ, Wong TY, Machin D, Johnson GJ, Seah SK. Risk factors for nuclear, cortical and posterior subcapsular cataracts in the Chinese population of Singapore: the Tanjong Pagar Survey. *Br J Ophthalmol.* 2003; 87(9):1112–1120. [PubMed: 12928278]
26. West SK, Valmadrid CT. Epidemiology of risk factors for age-related cataract. *Surv Ophthalmol.* 1995; 39(4):323–334. [PubMed: 7725232]
27. Williams PT. Walking and running are associated with similar reductions in cataract risk. *Med Sci Sports Exerc.* 2012 Epub ahead of print.
28. McCarty CA, Taylor HR. The genetics of cataract. *Invest Ophthalmol Vis Sci.* 2001; 42(8):1677–1678. [PubMed: 11431427]
29. Somasundaram T, Bhat SP. Developmentally dictated expression of heat shock factors: exclusive expression of HSF4 in the postnatal lens and its specific interaction with alphaB-crystallin heat shock promoter. *J Biol Chem.* 2004; 279(43):44497–44503. [PubMed: 15308659]
30. Lachke SA, Alkuraya FS, Kneeland SC, et al. Mutations in the RNA granule component TDRD7 cause cataract and glaucoma. *Science.* 2011; 331(6024):1571–1576. [PubMed: 21436445]
31. Pande A, Pande J, Asherie N, et al. Crystal cataracts: human genetic cataract caused by protein crystallization. *Proc Natl Acad Sci USA.* 2001; 98(11):6116–6120. [PubMed: 11371638]

32. Pande A, Pande J, Asherie N, et al. Molecular basis of a progressive juvenile-onset hereditary cataract. *Proc Natl Acad Sci USA*. 2000;97(5):1993–1998. [PubMed: 10688888]
33. Iyengar SK, Klein BE, Klein R, et al. Identification of a major locus for age-related cortical cataract on chromosome 6p12-q12 in the Beaver Dam Eye Study. *Proc Natl Acad Sci USA*. 2004; 101(40):14485–14490. [PubMed: 15452352]
34. Skalka HW, Prchal JT. Presenile cataract formation and decreased activity of galactosemic enzymes. *Arch Ophthalmol*. 1980; 98(2):269–273. [PubMed: 7352874]
35. Okano Y, Asada M, Fujimoto A, et al. A genetic factor for age-related cataract: identification and characterization of a novel galactokinase variant, “Osaka,” in Asians. *Am J Hum Genet*. 2001; 68(4):1036–1042. [PubMed: 11231902]
36. Maraini G, Hejtmancik JF, Shiels A, et al. Galactokinase gene mutations and age-related cataract. Lack of association in an Italian population. *Mol Vis*. 2003; 9:397–400. [PubMed: 12942049]
37. Stevens RE, Datiles MB, Srivastava SK, Ansari NH, Maumenee AE, Stark WJ. Idiopathic presenile cataract formation and galactosaemia. *Br J Ophthalmol*. 1989; 73(1):48–51. [PubMed: 2537652]
38. Lee SC, Wang Y, Ko GT, et al. Risk factors for cataract in Chinese patients with type 2 diabetes: evidence for the influence of the aldose reductase gene. *Clin Genet*. 2001; 59(5):356–359. [PubMed: 11359468]
39. Shiels A, Bennett TM, Knopf HL, et al. The EPHA2 gene is associated with cataracts linked to chromosome 1p. *Mol Vis*. 2008; 14:2042–2055. [PubMed: 19005574]
40. Zhang T, Hua R, Xiao W, et al. Mutations of the EPHA2 receptor tyrosine kinase gene cause autosomal dominant congenital cataract. *Hum Mutat*. 2009; 30(5):E603–E611. [PubMed: 19306328]
41. Kaul H, Riazuddin SA, Shahid M, et al. Autosomal recessive congenital cataract linked to EPHA2 in a consanguineous Pakistani family. *Mol Vis*. 2010; 16:511–517. [PubMed: 20361013]
42. Jun G, Guo H, Klein BE, et al. EPHA2 is associated with age-related cortical cataract in mice and humans. *PLoS Genet*. 2009; 5(7):e1000584. [PubMed: 19649315]
43. Sundaresan P, Ravindran RD, Vashist P, et al. EPHA2 polymorphisms and age-related cataract in India. *PLoS One*. 2012; 7(3):e33001. [PubMed: 22412971]
44. Tan W, Hou S, Jiang Z, Hu Z, Yang P, Ye J. Association of EPHA2 polymorphisms and age-related cortical cataract in a Han Chinese population. *Mol Vis*. 2011; 17:1553–1558. [PubMed: 21686326]
45. Sun L, Xi B, Yu L, et al. Association of glutathione S-transferases polymorphisms (GSTM1 and GSTT1) with senile cataract: a meta-analysis. *Invest Ophthalmol Vis Sci*. 2010; 51(12):6381–6386. [PubMed: 20574021]

Fig. 1. Morphological types of cataract. (a) Dense nuclear. (b) Posterior polar (slit lamp). (c) Anterior polar (slit lamp). (d) Pulverulent lamellar cataract with a cortical rider. (e). Pulverulent nuclear. (f). Posterior subcapsular. (g) Sutural cataract with a cerulean or blue dot component.

Table 1

Environmental variables affecting age-related cataract

Environmental variable	Nuclear	Cortical	PSC
Cigarette smoking/wood smoke	+		+
Obesity	+		
Hyperglycemia	+	+	+
UV light exposure		+	
Radiation			+
Corticosteroids/other drugs			+
Alcohol consumption	?		
Exercise	-?	-?	-?
Antioxidant vitamins	-?	-?	-?

+, increased risk; ?, conflicting results; -?, inconsistent suggestions of decreased risk. PSC, posterior subcapsular cataract.

Table 2

Genetic contributions to age-related cataract

Study ^a	Nuclear	Mixed nuclear and cortical	Cortical	PSC
Lens Opacity Case Control Study		+	+	+
Italian American Cataract Study Group		+	+	+
Framingham Offspring Eye Study ^b	3.4			3.8
Beaver Dam Eye Study (2001) ^c	35%		74%	
Twin Eye Study (2001) ^c	48%		53–58%	

+, increased risk.

^aRefer to Appendix S1 for supplementary references for the respective locus/gene.^bOdds ratio for siblings.^cPercentage of total risk from genetic factors.

Table 3

Genes causing non-syndromic Mendelian cataract

Chromosome	Locus/gene MIM No. ^b	Inh ^a	Cataract phenotype	Associated phenotype
1p36	CCV 115665	AD	Progressive lamellar	
1p36.1	EPHA2 176946	AD AR	Posterior polar, PSC Nuclear	Also associated with age-related cataract Possibly includes CTPP1
1p32	FOXE3 601094	AD	Anterior polar?	Anterior segment ocular dysgenesis
1q21.1	GJA8 600897	AD	Nuclear, zonular pulverulent, PSC	Microcornea, mild myopia
1q25-q31		AD	Nuclear	Nystagmus
2p24-pter	115800	AD	Coralliform	
2p12	CCNP 607304	AD	Nuclear	
2q33-q35	CRYGC 123680	AD	Variable zonular pulverulent	
2q33-q35	CRYGD 123690	AD	Nuclear, punctate, nuclear coralliform, lamellar, cerulean,	High myopia Includes CCP
3p21.3-p22.3	FYCO1 (CATC2) 607182	AR	?	
3q22.3-q25.2	ADCCC	AD	Congenital coronary	
3q21-q22	BFSP2 603212	AD	Nuclear, sutural, stellate, lamellar	Myopia in some
3q25-qter	CRYGS 123730	AD	Cortical progressive, lamellar, sutural	
6p24	GCNT2 600429	AR	?	Adult i blood group
7q34	AGK 610345	AR	?	Some with Senger syndrome
8q13.3	EYA1 601653	AD	Nuclear-type	Central corneal opacity, Peters' anomaly, branchio-oto-renal syndrome
9q13-q22	CAAR 605749	AR	Adult-onset cortical pulverulent, progressive nuclear and posterior subcapsular	
9q22.33	TDRD7 611258	?		
10p13	VIM 193060	AD	Pulverulent	
10q23.31	SLC16A12 605749	AD	Juvenile cortical and nuclear	Also associated with age-related cataract
10q25	PITX3	AD	Posterior polar	ASMD

Chromosome	Locus/gene MIM No. ^b	Inh ^a	Cataract phenotype	Associated phenotype
11p13	<u>602669</u> <i>PAX6</i>	AD?	Lamellar anterior capsular, posterior subcapsular	Corneal dystrophy, most patients have aniridia
11q22.1-q23.2	<u>607108</u> <i>CRYAB</i>	AD	'Discrete', posterior polar, lamellar, nuclear	Myopathy
12q13	<u>123590</u> <i>AQP0</i>	AD	Lamellar Sutural, polymorphic, nuclear, punctate	
12q24	<u>154050</u> <i>CCA5</i>	AD	Cerulean	
13q11-q12	<u>614422</u> <i>GJA3</i>	AD	Variable zonular pulverulent, nuclear, cortical, and punctate	
14q22-q23	<u>121015</u> <i>CTPP5</i>	AD	Posterior polar	
14q24.3	<u>610634</u> <i>VSX2</i>	AR	?	Microphthalmia, iris coloboma, dislocated lens
15q21-q22	<u>142993</u> <i>CCSSO</i>	AD	Central saccular sutural	Includes CHX10
16p13.2	<u>605728</u> <i>TMEM114</i>	AD	?	
16q22.12	<u>611579</u> <i>HSF4</i>	AD	Lamellar, nuclear, sutural, cortical extensions	
16q22-q23	<u>602438</u> <i>MAF</i>	AR		
17p13-p12	<u>177075</u> <i>CTAA2</i>	AD	Anterior polar	
17q11.2-q12	<u>601202</u> <i>CRYBA3/A1</i>	AD	Nuclear zonular, sutural, cortical, lamellar	
17q24	<u>123610</u> <i>GALK1</i>	AR	Age-related (Asian)	Also age-related (Asian)
17q24	<u>604313</u> <i>CCA1</i>	AD	Cerulean	
19q13	<u>609376</u> <i>CATCN1</i>	AR	Nuclear	
19q13.4	<u>115660</u> <i>FTL</i>	AD	Nuclear cortical breadcrumb-like	Hyperferritinemia-cataract syndrome
19q13.4	<u>134790</u> <i>LIM2</i>	AR	Pulverulent cortical, sutural, nuclear, lamellar	One family is presenile
20p11.23	<u>154045</u> <i>BFSP1</i>	AR	Nuclear zonular	

Chromosome	Locus/gene MIM No. ^b	Inh ^a	Cataract phenotype	Associated phenotype
20p12-q12	<u>603307</u>			
	CHMP4B	AD	Posterior polar, posterior subcapsular	
21q22.3	<u>605387</u>			
	CRYAA	AR	?	
22q11.2	<u>123580</u>	AD	Central nuclear, zonular, PSC, cortical	
	CRYBB1	AD	Central sutural pulverulent	
	<u>600929</u>	AD	Nuclear cortical riders	Microcornea
	CRYBB2	AD	Cerulean, zonular pulverulent, sutural, progressive, nuclear	
	<u>123620</u>	AD	Central zonular pulverulent	
	CRYBB3	AR	Nuclear cortical riders	
	<u>123630</u>			
Xp22	CRYBA4	AD	Congenital lamellar	Microphthalmia
	<u>123631</u>			
	CXN (NHS?)	XL	Fan-shaped nuclear	Cardiac anomalies
Xq24	<u>300457</u>			
	X-linked congenital	XL	Nuclear lamellar with sutural component and white dots	Dental and palate anomalies

ASMD, anterior segment mesenchymal dysgenesis, AD, autosomal dominant, AR, autosomal recessive, XL, X-linked.

^a Mutations located in the 5' iron response element.

^b Refer to Appendix S1 for supplementary references for the respective locus/gene.