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Biology of Cataracts and Opportunities for Treatment

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Abstract

Cataract, the clinical correlate of opacity or light scattering in the eye lens, is usually caused by the presence of high molecular weight protein aggregates or disruption of the lens microarchitecture. In general, genes involved in inherited cataract reflect important processes and pathways in the lens including lens crystallins, connexins, growth factors, membrane proteins, intermediate filament proteins, and chaperones. Usually, mutations causing severe damage to proteins cause congenital cataracts, while milder variants increasing susceptibility to environmental insults are associated with age-related cataracts. These might have different pathogenic mechanisms, with congenital cataracts inducing the UPR and apoptosis, while in age-related cataract denatured crystallins are bound by α-crystallin and form light scattering high molecular weight aggregates. New therapeutic approaches to age related cataracts involve using chemical chaperones to solubilize high molecular weight aggregates, while attempts are being made to regenerate lenses using endogenous stem cells to treat congenital cataracts.

Keywords

Lens; Cataract; Genetics; Crystallin

Introduction

Overview of the eye lens

The eye lens transmits and focuses light on the retina, where photoreceptors detect it and along with the other retinal cell types convert it into visual signals which then undergo initial processing before being transmitted through the optic nerve to the optic cortex. This function is facilitated by the lens structure, which consists of a single layer of anterior epithelial cells that migrate laterally during development towards the lens equator where they invert, elongate, synthesize large amounts of proteins specific to the lens including the lens crystallins, and finally degrade their organelles so as to increase their transparency. They are then overlayed by succeeding lens epithelial cells so that they eventually form an onion like structure of mature fiber cells called the lens nucleus. While this process begins during

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embryogenesis and is most active during development, it continues more gradually throughout life, so that older fiber cells reside in the lens nucleus, around which younger cortical fiber cells continue to be layered at the equator.

The mechanisms through which lens epithelial cells are transformed to elongated fiber cells lacking organelles is an area of active investigation. There is strong evidence that as the epithelial cells reach the equator they are exposed to increased levels of FGF (Dawes et al. 2018) and possibly oxidative stress (Brennan et al. 2018) to induce lens fiber differentiation. Mechanistically, the loss of organelles has been shown to involve the ubiquitin-proteasome pathway (Wride 2011), although there is increasing evidence that autophagy has an essential role in this process (Costello et al. 2013), However, both the organelle-free nature of lens fiber cells and their precise organization within the lens are critical to lens transparency and vision, as deviations from either can scatter light.

Since lens fiber cells lack ribosomes and other organelles, they cannot repair or replace damaged or modified proteins. This requires that lens crystallins be extremely stable so that they can last the lifetime of the organism, and also requires that the lens maintain strong homeostatic metabolic systems, especially those that contribute to maintenance of a reducing environment, to minimize damage to crystallins and other lens components (Ganea & Harding 2006) or reduce oxidative damage once it occurs (Kantorow et al. 2004), and avoid glycation and osmotic damage to the lens (Linetsky et al. 2008). The central nuclear fiber cells, are mostly dependent on glycolysis as an intrinsic energy source, which limits the energy available to them for these homeostatic activities. However, they receive considerable metabolic support from the anterior epithelia through an intrinsic circulation of fluid that appears to be critical for maintenance of lens homeostasis and transparency (Gao et al. 2018). Thus, the lens represents a delicately balanced anatomical and biochemical system, disruption of any part of which can result in loss of lens transparency or cataracts.

Overview of lens opacity

Opacity or cloudiness of the eye lens, the optical basis of cataract result when the refractive index within the lens varies significantly over distances approximating the wavelength of the transmitted light (Benedek 1971, Delaye & Tardieu 1983). Lens transparency requires both the orderly arrangement of lens cells and the high density and close packing of their protein constituents, primarily the lens crystallins. Variation in the refractive index and hence light scattering can result from changes in lens microarchitecture, the protein constituents, or both (Shiels & Hejtmancik 2017). Breakdown of the lens microarchitecture, including vacuole formation and disarray and degeneration of the lens fiber cells, results in large fluctuations in optical density, causing light scattering and hence cataract. Similarly, light scattering and opacity also can result from increased concentrations of high molecular weight protein aggregates (HMW) larger than 1000 Å in size. As lens crystallins make up over 90% of soluble lens proteins, their short-range ordered packing in a homogeneous phase is critical for lens transparency.

For patients, cataracts become important when they begin to interfere with vision, and they can be categorized by the age at which this occurs, even though some lens opacity probably precedes the clinical recognition. Congenital cataracts are diagnosed in the first year of life,

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while juvenile cataracts declare themselves between one and ten years of life. Presenile cataracts come to clinical attention before the age of 45–55 years, and cataracts diagnosed after that time are classified as senile or age-related cataract. These definitions are approximate and somewhat arbitrary, so that different studies might shift the limits by 5–10 years. Also, as mentioned, asymptomatic mild cataracts might not be diagnosed for years after they occur. The age of onset of a cataract does not necessarily imply a specific cause. Congenital cataracts might be inherited or secondary to an intrauterine insult (e.g. viral or parasitic disease). Cataracts associated with a systemic metabolic disease such as diabetes or an ophthalmic genetic disease such as retinitis pigmentosa may not occur until the later in life. Age-related cataracts are almost always associated with both a variety of environmental insults accumulated over many years, and the susceptibility to these insults may be modulated directly or indirectly by genetic risk factors (1994, Hammond et al. 2001, Hammond et al. 2000, Heiba et al. 1993, Heiba et al. 1995, Leske et al. 1998, Yonova-Doing et al. 2016).

The genetic origin of an inherited cataract can be suggested by the time it first appears and the specific region of the lens in which it occurs. Opacity should present in lens cells synthesizing large amounts of a mutant protein at the time at which it is being synthesized. One example of this principle is the γ-crystallins, which are synthesized at high levels early in development in fiber cells which are destined to populate the embryonic or central nucleus. For this reason, mutations in γ-crystallins often tend to cause nuclear cataracts, with ~49% of mutations in γ-crystallins listed in CAT-MAP (Shiels et al. 2010) being nuclear and ~15% nuclear lamellar. In spite of these general tendencies, mutations in a variety of genes can cause clinically indistinguishable cataracts and identical mutations in the same gene can cause varying cataract phenotypes. However, one general principle seems to be that mutations in crystallins or other lens proteins are sufficiently severe to cause protein aggregation or directly damage lens cells by themselves, thereby resulting 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.(Hejtmancik & Smaoui 2003) Thus, hereditary congenital cataracts tend to be inherited in a Mendelian fashion with high penetrance, while age-related cataracts tend to be multifactorial, with both multiple genes and environmental factors influencing the phenotype, making them significantly less amenable to classical genetic and biochemical analysis.

Congenital cataract

Estimates of the incidence of congenital cataracts vary from 12 to 136 per 100,000 births, with most countries showing about 72 per 100,000 children. The incidence tends to be higher in less developed countries, probably because of a higher risk of infectious disease and other environmental causes (Gilbert & Foster 2001, Haargaard et al. 2004, Stoll et al. 1992). Overall, between 8.3 and 25 percent of congenital or infantile cataracts are inherited (Francois 1982, Haargaard et al. 2005, Merin 1991). They may be isolated cataracts or may be accompanied by anterior chamber developmental anomalies including microphthalmia, microcornea, or aniridia. Cataracts may also occur as part of multisystem genetic problems including chromosome disorders, developmental defects, or metabolic disorders. There can

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be overlap between isolated and syndromic cataracts, as in the case of cataracts occurring because of defects in many growth factors. In some patients these may cause cataracts associated with defects in the anterior segment or optic disc in some family members while resulting in isolated cataracts in other members of the same family.

Hereditary Mendelian cataracts are most frequently inherited as an autosomal dominant trait, ~85% in CAT-MAP (Shiels et al. 2010) but can also show autosomal recessive, or X-linked inheritance. As mentioned above clinically similar cataracts can result from mutations in different genes and also may show different inheritance patterns, while phenotypically variable cataracts can result from the same mutation in a single gene, and even be found in a single family (Scott et al. 1994). Several classification systems have been developed based on the clinical presentation and anatomic location of the opacity, with the one proposed by Merin being the most commonly used. In this system cataracts are classified as polar (anterior or posterior), zonular (nuclear, lamellar, sutural, etc.), total (mature or complete), and capsular or membranous (Merin & Crawford 1971). A revision of this system taking anterior segment characteristics into account has recently been proposed (Lin et al. 2016a).

Age-related cataract

Age-related or senile cataracts present after the age of 45–55 years, with the lens clear before that time. They tend to be progressive in nature and are extremely common. Age related cataracts usually represent the effects of various combinations and cumulative damage of environmental effects acting in concert with the genetic predisposition encoded in genes for lens proteins (1994, Hammond et al. 2001, Hammond et al. 2000, Heiba et al. 1993, Heiba et al. 1995, Leske et al. 1998, Yonova-Doing et al. 2016).

Lens crystallins show multiple types of modifications with aging of the lens. Most of the changes are caused or accelerated by oxidative, UV, osmotic, or other types of damage, and these environmental risks are independently associated with cataractogenesis in epidemiological studies (Sharma & Santhoshkumar 2009). Alterations of lens crystallins include proteolysis, an increase in disulfide bridges, phosphorylation, nonenzymatic glycosylation, carbamylation, deamidation of asparagine and glutamine residues, and racemization of aspartic acid residues among others (Sharma & Santhoshkumar 2009). Just as the environmental stresses that cause these changes have been linked epidemiologically to age related cataracts in human populations, the chemical modifications themselves are increased in lenses with cataracts as well as in *in vitro* or in model systems in which the model animals are subjected to similar environmental insults as seen in human age related cataract (Ottonello et al. 2000).

Crystallins comprise over 90% of the soluble proteins in the eye lens and are the most studied proteins in the aging lens. In humans there are three major classis of lens, α-, β- and γ-crystallins, each of which consist of gene families, the latter two of which share a very stable structure composed of two domains, each comprising two very stable Greek key motifs (Jaenicke & Slingsby 2001). As individuals age, the β- and γ-crystallins are modified, especially under the influence of environmental stress, and start to lose their normally stable protein fold and form irreversible aggregates. The slowly denaturing β- and γ-crystallins are bound by α-crystallins, which have a chaperone-like activity (Rao et al.

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1995). However, complexing of the denatured βγ-crystallins by α-crystallins maintains their solubility and thus reduces light scattering, it does not result in their being recycled into the cytoplasm as would happen with true chaperones. Instead, the denatured crystallins are held in complexes with α-crystallins that increase in size over time as increasing amounts of damaged protein are bound until they become high molecular weight aggregates that are large enough to scatter light (Datiles et al. 2008, Rao et al. 1995). With sufficient time and insults, even the high level of α-crystallin in the lens is exhausted and the high molecular weight aggregates precipitate, joining the insoluble protein that increases with age and in cataractous lenses. Whether this process involves complete or partial denaturation or the modified crystallins simply have decreased solubility but intact protein folds is not known currently, and might vary for each crystallin and mutation. However, both mouse models and cell culture studies of mutant proteins associated with human cataracts strongly suggest that the presence of large amounts of denatured protein damages the lens cell, and contributes to cataracts not only through light scattering by protein aggregates, but eventually also through toxicity to lens fiber cells and resultant disruption of cellular architecture (Ma et al. 2011, Wang et al. 2007). Similarly mutations in proteins that maintain intracellular homeostasis can disrupt the intracellular environment of lens cells and eventually cause damage to their constituents, contributing to age related cataract.

Age-related cataracts, while not having as severe an impact on each affected individual as congenital cataracts, have a much greater overall burden on the population because they are extremely common. They are responsible for blinding 17 million persons worldwide, causing just under half of all blindness (Congdon et al. 2003), and are the leading cause of low vision in the United States (Congdon et al. 2003). Cataract surgery is required by about 5% of the American population over 40 years old, making it the most frequently performed surgical procedure. It has been pointed out that due to the advanced age at which age related cataracts are found, delaying their age of onset by only ten years would decrease cataract surgery in the United States by about 45% (Kupfer 1984).

The risk of age-related nuclear cataract is increased by exposure to certain environmental factors such as elevated blood glucose levels, cigarette smoking or chronic exposure to wood smoke, or obesity (Chang et al. 2011, Foster et al. 2003, Leske et al. 1991, Lu et al. 2012, Ye et al. 2012). Similarly, the risk of age related cortical cataracts is increased by ultraviolet light and elevated glucose levels (Brown & Hill 1987, Foster et al. 2003, Group 1991, Hennis et al. 2004, Machan et al. 2012), and the risk of age related PSC is increased by smoking, diabetes, radiation, corticosteroids, and some other drugs (Abe et al. 2012). Alcohol consumption has been suggested to be associated with age-related cataract, but the relationship appears to be complicated and results are somewhat inconsistent (1991, Kanthan et al. 2010). Conversely, exercise, vitamin D, and antioxidant vitamins might have a protective effect, although this has not been borne out by all studies (Chang et al. 2011, West & Valmadrid 1995, Williams 2012) (Park & Choi 2017). One interesting aspect of these studies is that not only have they identified a number of potentially correctable environmental risk factors for age related cataract, but the different risk factors for nuclear, cortical and posterior subcapsular cataracts suggest that they might have distinct pathogenic mechanisms that begin to converge in the final steps of cataractogenesis.

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Many epidemiological studies also support a role for genetic factors in age-related cataract (Group 1991, McCarty & Taylor 2001). The Italian American cataract study group (1991) and the Lens Opacity Case Control Study (Leske et al. 1991) both suggest that family history is a risk factor for cortical, combined nuclear and cortical, and posterior subcapsular cataracts. The Framingham Offspring Eye Study (1994) found a threefold increased risk for cataract in individuals with a sibling having a cataract. Results from the Beaver Dam Eye Study (Klein et al. 2001) and Twin Eye Study (Hammond et al. 2001) both suggest that genetic factors could account for as much as 35–48% of the risk for nuclear and 53–75% of the risk for nuclear and cortical cataract, respectively. Finally, a recent twin study suggests that genetic factors might account for 20–39% of intraocular light scattering that didn't reach the stage of cataract (Benito et al. 2016).

Genes Associated with Congenital or Mendelian Cataracts

While most Mendelian cataracts (whether autosomal dominant, recessive, or X-linked) occur as isolated traits diagnosed at birth or early childhood, some of them can present as late as adulthood, and those will also be covered in this section (Hejtmancik et al. 2001). The most common inheritance pattern is autosomal dominant, although this might be influenced by the tendency for dominant inheritance to result in larger pedigrees with multiple affected individuals. While new cataract loci are being mapped and their genes are being identified at a rapid rate, at this time there are about 60 mapped of which the causative gene has been identified in about 40 (Table 1). Those listed present as isolated cataracts in at least some individuals, although in some cases they can be associated with additional abnormalities in other family members, mostly as part of developmental syndromes affecting the optic disc area. A larger number of inherited cataracts occur as part of syndromes affecting multiple organ systems (Hejtmancik et al. 2001), often caused by mutations in transcription factors or metabolic enzymes. In addition some examples result from genes expressed at high levels in the lens as well as other tissues, such as αB-crystallin mutations which can cause myopathy as well as isolated cataracts, and ferritin, which causes the hyperferritinemia-cataract syndrome (Table 1). Finally, mutations in some genes can lead to extralenticular effects as the result of a developmental sequence, such as crystallin mutations that cause early and severe damage to the lens preventing its normal role in development of the anterior chamber and leading to microcornea and even microphthalmia. Also, if the cataract is early and severe, the resulting visual deprivation during this early critical period inhibits formation of the normal pathways from the retina to the optic cortex with resultant nystagmus or even blindness.

From Table 1 it can be seen that causative genes have not been identified for about a third of mapped cataract loci. The genes that have been identified can be grouped functionally by the processes and pathways to which they belong suggesting that these are critical for the development and homeostasis of the lens, although this analysis is imperfect because it also reflects the predispositions of investigators in their mapping and sequencing efforts. At this time, about 37% of the independent families for whom the causative gene is known show mutations in lens crystallins, about 22% show mutations in connexins, about 14% show mutations in growth or transcription factors, and 3–7% each in intermediate filaments or aquaporin 0, membrane proteins, chaperones or components of the protein degradation

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apparatus and a mix of other genes, while about 5% are unknown. As mentioned above, 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. This suggests that additional genetic or environmental factors might modify the expression of the primary mutation associated with the cataracts. 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.

Genes encoding crystallins

The importance of lens crystallins in lens biology and especially in transparency is indicated by their accounting for the largest fraction of cataract mutations. α-Crystallins have a dual role in the lens, both as highly expressed lens proteins and as chaperones important to protect the lens from toxicity of denatured βγ-crystallins (Horwitz 2003). Severe mutations in the αA- and αB-crystallin genes that result in a complete loss of the proteins or their chaperone-like activity can cause autosomal recessive cataracts, which suggests that decreased levels of functional α-crystallin are sufficient to maintain lens transparency. A prime example of this is a p.W9X chain termination mutation near the beginning of the protein (Pras et al. 2000), which would be expected to result in nonsense mediated decay and complete absence of the mutant allele without affecting protein synthesized from the normal gene. A p.R54C mutation causes total congenital cataracts in homozygotes, but the effects in carriers are limited to punctate opacities in carriers (Khan et al. 2007), and three families have been identified with autosomal recessive cataracts caused by CRYAB mutations.(Jiao et al. 2015, Safieh et al. 2009) These suggest that even decreased levels of α-crystallin can provide sufficient chaperone-like activity and structural crystallin packing to establish and maintain lens transparency during childhood, consistent with results from αA-crystallin knock-out mice (Brady et al. 1997). In contrast autosomal dominant cataracts, which tend to be associated with nonconservative missense mutations resulting in a change in the amino acid sequence, probably produce a deleterious mutant α-crystallin protein that actively damages the lens cell or inhibits function of the remaining normal α-crystallin in a dominant negative mechanism rather than simply acting through loss of chaperone function as the recessive cataract appears to do (2005). Many CRYAA mutations are also associated with microcornea, possibly due to this gene’s early and abundant expression in the lens causing severe effects during lens formation that might interfere with possible developmental interactions between the lens and the rest of the anterior chamber.

The similar biochemical properties and function of αA- and αB-crystallin and their association into large multimeric complexes might suggest that mutations in CRYAB would have a similar effect to those in CRYAA, at least in the lens. However, the family harboring the first human mutation reported in CRYAB, a missense mutation that reduced αB-crystallin chaperone activity resulting in aggregation and precipitation of the protein under stress, had myofibrillar myopathy but only “discrete” cataracts (Vicart et al. 1998), consistent with the αB-crystallin knockout mouse, which shows myopathy without cataracts (Brady et al. 2001). The myopathy is probably related to high level expression of CRYAB but not CRYAA in muscle cells, where it binds and stabilizes desmin.(Brady et al. 2001) However, multiple missense and frame-shift mutations in CRYAB have been shown to cause

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autosomal dominant cataracts without myopathy, probably through a similar toxic effect as the dominant CRYAA associated cataracts (Berry et al. 2001).

While mutations in the α-crystallins could cause cataract either by loss of chaperone-like activity or synthesis of a deleterious mutant protein, most mutations in the βγ-crystallins appear to cause cataract through producing an unstable protein that aggregates and then precipitates from the cytosol (Ma et al. 2016c), being bound by α-crystallin or possibly serving as a nidus for additional protein denaturation and precipitation, with resultant toxicity to lens cells and cataract. The exceptions to this are a p.N58TfsX106 CRYBB1 mutation in 3 families (Aldahmesh et al. 2012, Cohen et al. 2007, Khan et al. 2012) and a p.(G65R) CRYBB3 mutation in a two families (Riazuddin et al. 2005), suggesting that these two basic β-crystallins might have a lenticular function beyond being structural crystallins. Consistent with their early expression and high levels in the lens nucleus, γ-crystallin mutations tend to result in nuclear (49%) or zonular (15%) cataracts, although their phenotypes may vary (Shiels et al. 2010). Mutations in the β-crystallins produce phenotypes ranging from dense nuclear (49%) to zonular (16%) pulverulent cataract with or without involvement of the sutures, to cerulean cataracts (Shiels et al. 2010). Zonular or lamellar cataracts might reflect synthesis of the crystallin later in development than the γ-crystallins and for a limited period of time, resulting in a shell of opaque cells surrounded internally by a clear central lens nucleus and externally by relatively clear cortical lens fiber cells (Amaya et al. 2003). However, the occurrence of a variety of cataract phenotypes in a large family with autosomal dominant cataracts resulting from a c.119_123dup mutation emphasizes the importance of modifying genes in the phenotypic expression of these mutations, a point that is supported by variable severity of cataracts resulting from expression of this mutant CRYGC in transgenic mice (Ma et al. 2011).

While most βγ-crystallin mutations appear to cause cataract by destabilizing the structure of the protein, eventually resulting in denaturation, there are exceptions to this general rule. At least 3 separate mutations leave the protein fold intact, but modify the γD-crystallin's surface characteristics, thus lowering their solubility or enhancing their protein to protein interaction strength so that they come out of solution (Pande et al. 2001). A p.(P23T) mutation of CRYGD increases inter-protein hydrophobic interactions causing protein precipitation, a p.R36S mutation actually results in crystallization of the protein within the lens (Kmoch et al. 2000), and a third p.(R14C), makes the protein susceptible to thiol-mediated aggregation (Pande et al. 2000). These results emphasize that crystallins need not undergo denaturation or other major changes in their protein folds in all cases to cause cataracts.

Genes encoding membrane proteins

As lens epithelia cells elongate dramatically during their transition to fiber cells in a process requiring rapid synthesis of large quantities of membrane lipids and proteins, it is not surprising that membrane-related proteins comprise a large share of cataract genes. One set of genes in this group encode enzymes required for the synthesis of specific membrane lipids including lanosterol synthase, although this might also have a role through its chaperone-like action on denatured crystallins (Zhao et al. 2015). Mutations in acylglycerol

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kinase (AGK), a lipid kinase that catalyzes synthesis of phosphatidic and lysophosphatidic acids and CYP51A1, an enzyme in the cholesterol synthesis pathway, have been implicated in autosomal recessive cataracts in Saudi Arabia (Aldhamesh et al. 2012).

Mutations in *GCNT2*, the I-branching enzyme for poly-N-acetyllactosaminoglycans responsible for the adult I blood type, also cause autosomal recessive cataract (Yu et al. 2003). Interestingly, these cataracts are only associated with adult persistence of the childhood i (rather than change to the adult I) phenotype in Japanese rather than Caucasians because of differential splicing of the GCNT2 mRNA in erythrocytes and lens cells and the population specific location of the causative mutations in the two populations. Mutations in CHMP4B, part of the endosomal sorting complex required for transport-III (ESCRT-III) assembly cause posterior polar or subcapsular cataract (Shiels et al. 2007), and mutations in LIM2, a lens-specific membrane protein important for cell junctions cause nuclear cataract (Pras et al. 2002).

Membrane proteins with specialized function in transport of ions or solutes also contribute to this group. Mutations in SLC16A12, a transmembrane transporter active in monocarboxylic acid transport can cause dominant cataracts as well as microcornea and renal glycosuria in some cases (Kloeckener-Gruissem et al. 2008), perhaps by interfering with the circulation of water and small molecules necessary for lens homeostasis and function. Similarly, mutations in aquaporin 0 (also known as AQP0 or MIP), a member of the aquaporin water-channel family, are a common cause of cataract. Two mutations, p.(E134G) and p.(T138R) appear to act by interfering with normal trafficking of AQP0 to the plasma membrane and also with water channel activity by normal AQP0, consistent with a dominant negative mechanism and with dominant inheritance of the cataracts (Francis et al. 2000). Mutations in the ATP-binding cassette transporter ABCA3, a lipid transporter also implicated in respiratory disease (Chen et al. 2014), and the transmembrane protein TMEM114 can also cause cataract (Jamieson et al. 2007), as can DNMBP, a guanine nucleotide exchange factor that regulates the configurations of cell junctions (Ansar et al. 2018).

Gap junctions are critical for nutrition and intercellular communication in the lens, and mutations in the two major gap junction proteins GJA3 and GJA8 (connexins 46 and 50) are responsible for about 22% of cataract families (Shiels et al. 2010). The p.(P88S) mutation in GJA8 modifies the second transmembrane domain so that it fails to form functional gap junction channels (Berthoud et al. 2003). In Xenopus oocytes, incorporation of just one mutant protein molecule into a gap junction inhibits channel function, consistent with a dominant negative effect similar to AQP0 (Minogue et al. 2005). Other mutant connexin proteins, such as an N63S missense mutation also fail to form intercellular channels in paired Xenopus oocytes (Pal et al. 2000), but are unable to participate in gap junction formation at all, and thus do not inhibit channel function by products of the normal gene. The cataracts caused by both *GJA3 and GJA8* mutations are phenotypically similar, and predominantly nuclear or zonular pulverulent cataracts (Gong et al. 2007).

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Genes encoding cytoskeletal proteins

BFSP1 (filensin, CP115) and BFSP2 (phakinin, CP49) are intermediate filament proteins that are similar to each other but show only low levels of sequence similarity to other members of the intermediate filament family. They too form beaded filaments, only with the chaperone-like assistance of the α-crystallins. Like BFSP1 and BFSP2 themselves, beaded filaments are unique to lens fiber cells. Missense or in-frame deletion mutations in BFSP2 tend to cause nuclear or nuclear lamellar dominant cataracts with some involvement of the sutures, consistent with fiber cell specific expression of the beaded filament proteins (Conley et al. 2000, Jakobs et al. 2000). In contrast, frameshift and nonsense mutations cause recessive cortical cataracts (Aldahmesh et al. 2011, Aldahmesh et al. 2012). Similarly, a missense mutation in BFSP1 causes nuclear cataracts while a frameshift mutation that is probably null has been associated with cystic cortical cataracts (Kumar et al. 2013, Li et al. 2016, Ma et al. 2016a, Ramachandran et al. 2007, Zhai et al. 2017).

Genes encoding transcription or developmental factors

PAX6, a paired box and homeobox domain protein expressed in the developing nervous system and eye, is one of the earliest transcription factors active in eye development (Kamachi et al. 2001). Most PAX6 mutations cause generalized eye developmental defects such as anophthalmia, aniridia or Peter's anomaly. However, one mild mutation affecting only the C-terminal PST domain has been associated with lamellar cataract and later onset corneal dystrophy (Glaser et al. 1994). Mutations in other transcription factors occurring further down the control pathways for lens development also cause cataract, including VSX2, MAF, FOXE3, EYA1, and PITX3 (Shiels et al. 2010). As these transcription factors influence gene expression in the entire eye field, they can all contribute to a variety of developmental defects in the anterior segment, ranging from microcornea to anterior segment mesenchymal dystrophy (ASMD). NHS has a broader field of activity, and beyond isolated cataracts, mutations in NHS cause the Nance Horan syndrome, characterized by cataracts, dental abnormalities, dysmorphic facies and in some cases mental retardation (Burdon et al. 2003).

In contrast, mutations in HSF4, a member of the heat-shock transcription factor family, appear to cause isolated cataracts not associated with extralenticular effects even though HSF4 is broadly expressed in most eye tissues (Shiels et al. 2010). HSF4 regulates transcription of αB-crystallin in the lens, among other heat shock proteins (Somasundaram & Bhat 2004). HSF4 mutations can cause both autosomal dominant and recessive cataracts. The dominant cataracts are most often lamellar or zonular and most often result from missense mutations in the α-helical DNA-binding domain (Eiberg et al. 1988). In contrast, the recessive cataracts tend to result from homozygous null mutations outside the highly conserved DNA-binding domain and have a congenital onset, ranging in severity from nuclear with some cortical involvement (Forshew et al. 2005) to total lens opacities with secondary nystagmus (Smaoui et al. 2004).

EPHA2, a member of the ephrin receptor subfamily (EPH) of protein-tyrosine kinases, is not itself a transcription factor but is heavily involved in developmental processes in both the eye and the nervous system. Not only can mutations in EPHA2 cause both dominant and

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recessive congenital cataracts, but have also been shown to contribute to age-related cataract. (Jun et al. 2009, Kaul et al. 2010, Shiels et al. 2008, Sundaresan et al. 2012, Tan et al. 2011, Zhang et al. 2009)

Genes encoding chaperones or protein degradation apparatus

Lens development requires extensive restructuring of the lens itself, and differentiation of lens epithelia cells into cortical and nuclear fiber cells requires elimination of cellular organelles, both of which require high levels of protein degradation. Mutations in FYCO1, a scaffolding protein active in microtubule transport of autophagic vesicles cause autosomal recessive cataracts (Chen et al. 2011), suggesting that autophagic vesicles are important in organelle degradation in developing lens fiber cells among other roles (Brennan et al. 2012). Consistent with this concept, mutations in RRAGA, a GTPase active in the TORC1 pathway are associated with congenital nuclear cataracts (Chen et al. 2016), and mutations in CHMP4B, a member of the endosomal sorting complex that interacts with programmed cell death 6 interacting protein PDCD6IP can cause progressive posterior polar and subcapsular cataracts (Shiels et al. 2007). As the lens fiber cells lack organelles and have no way of turning over damaged proteins, it is not surprising that UNC45B, a co-chaperone with HSP90, can cause juvenile cataracts (Hansen et al. 2014).

Additional genes encoding proteins in biological processes highly active in the lens

Differentiation of lens epithelia and fiber cells requires an extremely high level of protein synthesis, perhaps explaining the role of mutations in TDRD7, a widely expressed component of RNA granules active in RNA processing, in hereditary cataract (Lachke et al. 2011). Finally, the hyperferritinemia-cataract syndrome, characterized by hyperferritinemia in the absence of iron overload and cataracts is the result of inadvertent expression of a non-crystallin protein at crystallin-like levels (Beaumont et al. 1995). Ferritin is widely expressed in the body as well as eye tissues and serves to sequester iron in a soluble and nontoxic state The mutations in the hyperferritinemia-cataract syndrome are in the iron responsive element, a stem loop structure in the 5’ untranslated region of the FTL mRNA, which in the absence of excess iron binds the cytoplasmic iron regulatory protein which inhibit its translation. Overexpression of FTL to levels approaching that of a crystallin occur through loss of this translational control, resulting in crystallization of ferritin in the lens with resultant breadcrumb like opacities in the lens cortex and nucleus (Girelli et al. 1995). This cataract shows that crystallins must be exceptionally soluble to be expressed at high levels in the lens without causing dysfunction.

Genes Associated with Age-Related Cataract

Linkage and family studies

A subset of Mendelian cataract loci and genes identified using classical linkage analysis have a childhood to presenile age of onset or show progression throughout life, including some resulting from mutations in genes that are also implicated in congenital cataract (Shiels et al. 2010). These include BFSP2, in particular 3 families with a p.(E233del) mutation, the a p.(R119C) mutation in HSF4 (Marner, a childhood cataract), p.(890C) and p.(G948W) mutations in EPHA2 (childhood progressive cataracts), p.(T138R) and p.(T138T) mutations

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in AQP0 (progressive cataracts), the p.(D129V) mutation in CHMP4B (childhood progressive cataracts), the p.(I247M) mutation of GJA8, the p.(Q215X) mutation in SLC16A12, the p.(R37S) mutation in CRYGD, a p.(N115D) mutation in CRYBA2, the p.(I33_A119del) mutation in CRYBA3 (childhood progressive cataracts), the p.(G217AfsX91) and p.(G220PfsX95) mutations in PITX3, the progressive Volkmann cataract, and the CAAR locus are linked to familial adult onset pulverulent cataracts. Only 2 of 7 families with a p.(Q155X) mutation in CRYBB2 have a progressive cataract, the remaining families showing congenital cataract, which suggests the effect of modifying genes or a stochastic biological process. A p.(F104V) mutation in LIM2 causes a presenile cataract as does a p.(G98R) mutation in CRYAA, the remainder of mutations in these genes causing congenital cataracts. Other than the nonsense mutations in CRYBB2 and SLC16A12 and the frameshift mutations in PITX3, mutations associated with late onset or progressive cataracts are missense mutations that might retain some level of function or stability of the original protein.

This concept is exemplified by the p.(G18V) and p.(G18D) mutations in CRYGS, which cause progressive childhood cataracts (Sun et al. 2005, Zhai et al. 2017). The p.(G18V) mutation has been shown to cause minimal perturbation of the CRYGS protein fold under physiological conditions, but to destabilize the crystallin when it is subjected to thermal or chemical stress (Ma et al. 2009), and this is associated with preferential binding of the p.G18V mutant by CRYAB even under relatively benign conditions (Kingsley et al. 2013). Thus, these examples seem consistent with the hypothesis that a mutation that causes major structural damage to the protein or completely disrupts its function might cause highly penetrant Mendelian congenital cataracts, while a mutation resulting in somewhat less severe damage to the same protein or its function might contribute to Mendelian age-related or progressive cataracts. Furthermore, changes causing even milder damage might show reduced penetrance or even require multiple mutant genes and environmental insults for a phenotype, thus showing a complex or multifactorial inheritance pattern. Similarly, mutations causing severe damage to cell architecture or environment seem likely to result in congenital cataracts, while mutations resulting in only mild disruption of lens cell systems might contribute to age-related cataract, especially when combined with environmental stresses.

The reduced penetrance of age-related cataract mutations, especially when combined with their frequent requirement for contributions from multiple genes and environmental factors, as well as their late onset, makes carrying out linkage analysis for this form of inherited cataract much more difficult than for Mendelian congenital cataracts. A genome-wide linkage scan of age-related cortical cataract (Iyengar et al. 2004) identified a locus on chromosome 6p12 that may coincide with a susceptibility locus for type 2 diabetes with retinopathy (OMIM #125853), and a second locus on chromosome 1p near the EPHA2 gene (see below). Other than this, most genes implicated in age related cataract have been identified by association studies, often guided by epidemiological or animal data.

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Association studies

Several genes implicated in age-related cataracts support the concept that severe mutations might cause congenital cataracts with Mendelian inheritance while less damaging changes might contribute to age related cataracts along with other genes and environmental stresses (Skalka & Prchal 1980). Deficiency of galactokinase (GALK1), galactose-1-phosphate uridyl transferase (GALT), or deficiencies of galactose epimerase (GALE) cause galactitol accumulation and subsequent osmotic swelling of lens cells resulting in autosomal recessive congenital cataracts (Kinoshita 1965). In 2001 a p. A198V mutation in GALK1, called the "Osaka" variant, was shown to cause instability of the mutant GALK1 protein with resulting low levels of functional galactokinase and an increase in bilateral cataracts in Japanese adults.(Okano et al. 2001) The mutant allele is present in 4.1% of the Japanese population but increases to 7.1% of Japanese with age related cataracts. It appears to be largely confined to the Japanese population with a lower presence (2.8%) in Koreans and much lower in Chinese, but was absent from other ethnic groups tested. In addition, parents of children with galactosemia from GALK1 and GALT deficiency have an increased risk of age related cataract (Stevens et al. 1989). These findings are consistent with the known increased risk of age-related cataract from hyperglycemia, and also with animal data and the finding that susceptibility to cataracts as a diabetic complication in humans is associated with specific allele Z of the microsatellite polymorphism at the 5'-end of the aldose reductase gene (Lee et al. 1995, Lee et al. 2001).

Another gene with a variety of severity and types of mutations resulting in a spectrum of cataract severity is SLC16A12, a creatine transporter also implicated in renal glycosuria. A p.(Q215X) mutation causes juvenile cataracts, microcornea, and glycosuria and appears to act by impairing protein trafficking to the plasma membrane (Castorino et al. 2011, Kloeckener-Gruissem et al. 2008). In contrast, 4 missense mutations in SLC16A12 that decrease creatine have been identified in patients with age related cataract (Staubli et al. 2017). EPHA2, the Eph-receptor type-A2 (EPHA2), functions in the ephrin cell signaling and guidance pathway and lies in the candidate region on chromosome 1p identified by linkage analysis (Iyengar et al. 2004). It is a third gene with strong support for both congenital and age related cataracts, mutations in the coding region being able to cause both dominant and recessive congenital cataracts (Kaul et al. 2010, Shiels et al. 2008, Zhang et al. 2009). In addition, 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 inherited and age-related forms of cataract.(Jun et al. 2009, Shiels et al. 2008, Sundaresan et al. 2012, Tan et al. 2011) and the association is consistent with demonstrations that the risk allele of SNP, rs6603883, which is located in in a PAX2 binding-site of the EPHA2 promoter region, decreases EPHA2 expression (Jun et al. 2009, Ma et al. 2017).

Sequence variations in the αA-crystallin gene (CRYAA) have also been associated with age related cataract in a number of studies, and a p.(F71L) amino acid change identified in patients with age-related cataract has been shown to reduce CRYAA chaperone activity (Bhagyalaxmi et al. 2010, Bhagyalaxmi et al. 2009, Liao et al. 2014). In addition, CRYAA was one of two genes identified as associated in a meta-analysis of Asian patients with age

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related cataracts, the other being KCNAB1 (Liao et al. 2014). Finally, in addition to the mutation analysis described above, there is some functional support for sequence variations decreasing CRYAA expression increasing the risk of age related cataracts. Age related cataract associated SNP rs7278468 lies in a binding site for both KLF10 and Sp1 and the risk T allele increases binding of the former and decreases binding of the latter, which decreases CRYAA expression and provides a possible reason for the increased risk of cataract (Ma et al. 2016b, Zhao et al. 2017).

A number of additional loci and genes have been reported to be associated with age related cataract, although these have not been reproduced in multiple studies and populations. Evidence for one of the first loci associated with age related cataract, the null allele of the GSTM1 locus, has proved to be inconsistent (Sun et al. 2010), as has that for GSTT1 (Zuercher et al. 2010). Polymorphisms in a number of additional genes including MTHFR, PARP1,RNF149, OGG1, EFNA5, NAT2, WRN, P2RY2, ATM, MIP, B3GNT4, GJA3, OSGEP, BMP4, CYP46A1, KLC1, FTO, HSF4, TP53, ACE, MUC16, XRCC1, APOE, and ERCC2, have all been suggested to be associated with age-related cataract (Shiels et al. 2010). While it is highly likely that some of these genes do contribute to age-related cataract, additional work is required to confirm their role.

Thus, the genetic architecture of both inherited congenital and age-related cataracts reflects the developmental and cell biology of the lens. Not only does each novel mutation yield additional insight into the structural or functional biology of the affected protein, each newly identified gene provides similar insight into the lens development, function, and homeostasis. The genes currently associated with cataract are incomplete, with most estimates in the range of 40–50% even for the best characterized populations (Chen et al. 2017), and less for age related cataract, so that much additional information remains to be discovered through further genetic studies.

Hypothesis: Congenital vs. Age Related Cataract Mechanisms

Mechanisms of congenital cataract

It has been shown that alpha-crystallin interacts only with the aggregation prone molten globule state of partially denatured proteins (Rajaraman et al. 1998, Sathish et al. 2004). Thus, while denatured or partially denatured crystallins might normally be bound by α-crystallin, since mutations causing congenital cataract are expected to be particularly severe, it is possible that many or most of are not bound and solubilized by α-crystallin (Moreau & King 2012a). Alternatively, the rapidity and completeness with which the mutant crystallins denature might overwhelm the capability of α-crystallin to buffer the lens from these damaged proteins. Not only would this lead to the presence of high molecular weight aggregates that would scatter light but would also result in free potentially toxic denatured proteins that might damage the systems responsible for lens cell homeostasis and even survival.

The disarray and destruction of lens microarchitecture seen in many experimental cataracts studied by expressing mutant crystallins in model systems supports the concept that lens cells themselves might be damaged in congenital cataracts. This is demonstrated by cataracts

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caused by a 5-base insertion (c.119_123dup, c.238insGCGGC, p.C42Afs*63) in the CRYGC gene.(Ma et al. 2011, Ren et al. 2000, Scott et al. 1994) Unlike the p.Gly18Val CRYGS mutation, this mutation caused a variable cataract morphology extending from total to lamellar to nuclear pulverulent. The basis of this cataract is expression of an unstable hybrid protein of which the first 41 amino acids are those of CRYGC and the last 62 are random amino acids resulting from the frameshift. Expression of the mutant CRYGC in transgenic mice causes degeneration of lens fiber cells with resultant disruption of lens microarchitecture. Although the lenses initially appear normal, by about 3 weeks of age vacuolization of equatorial epithelial and superficial cortical fiber cells becomes apparent (Ma et al. 2011). This progresses to degeneration of the fiber cells resulting in large intracellular vacuoles and eventually lacunae filled with proteinaceous debris. The mutant protein is found in both the soluble and insoluble fractions of lens cells, consistent with the observation that α-crystallin binds to a molten globule like intermediate in protein unfolding (Rajaraman et al. 1998) and some severe mutations in lens crystallins escape binding by the α-crystallins (Moreau & King 2012a). Taken together histology showing death of lens fiber cells and disruption of lens architecture and biochemical characterization of mutant proteins are most consistent with a direct toxic effect of the mutant protein on the lens cells, either by escaping α-crystallin chaperone action or after saturating it.

Induction of the unfolded protein response and apoptosis

One pathway through which the mutant crystallins might directly damage lens cells is through induction of the unfolded protein response (UPR) followed by apoptosis (Ikesugi et al. 2006). The UPR is a set of adaptive intracellular signaling pathways that reduce stress on the endoplasmic reticulum (ER stress) secondary to large amounts of denatured, protein accumulation in the ER lumen. Under benign conditions, the 70kDa heat shock protein 5, HSPA5 (BiP, GRP78), binds to at least three major sensors in the endoplasmic reticulum, IRE1, ATF6, and EIF2AK3, maintaining them in an inactive state. In the presence of large amounts of unfolded protein HSPA5 dissociates from these three sensors, activating them and initiating the UPR (Schroder & Kaufman 2005). Initially, the UPR attempts to reduce ER stress by decreasing protein synthesis, upregulating levels of endoplasmic reticulum associated degradation proteins (ERAD), and increasing chaperone levels (Sovolyova et al. 2014). In the face of severe ER stress the UPR can fail to achieve homeostasis at which point it can induce apoptosis (Lai et al. 2007, Rasheva & Domingos 2009) through both the intrinsic and mitochondrial-mediated pathways (Gupta et al. 2010, Szegezdi et al. 2008) as well as EIF2AK3 regulation of gene expression. This includes activation of specific gene transcription by ATF6 (Gupta et al. 2012), including induction of XBP1 and IRE1, which cleaves XBP1 activating it and inducing transcription of a broad array of downstream mediators including P58 (Gorman et al. 2012) and DNA-damage-inducible transcript 3 (DDIT3). All of these downstream mediators tend to induce apoptosis, which could easily result in the toxic picture of lens histology seen in many types of congenital cataract.

In fact, there is increasing evidence for a potential role for both the UPR and apoptosis in congenital cataract, especially in lens epithelial cells, which have a higher level of metabolic activity than fiber cells. An early example of the UPR in an animal model of cataract was its in lens epithelial cells from galactosemic rats, and cultured transformed lens epithelial cells

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deprived of glucose (Mulhern et al. 2006). The histologic picture in galactosemic cataracts is similar to that seen in the early stages of the p.C42Afs*63 mutant CRYGC transgenic mouse cataracts mentioned above (Ma et al. 2011) with debris filled vacuoles and cell death. In addition, the UPR also contributes to the selenite induced cataract in rats (Palsamy et al. 2014) as well as cataracts resulting from expression of abnormal collagens in transgenic mice (Firtina et al. 2009). Relating to inherited congenital cataract more directly, apoptosis and elements of the UPR are implicated in cataracts in the knock-in p.Arg49Cys CRYAA mouse (Andley & Goldman 2015) and in cataractous mice expressing p.Ser50Pro and p.Gly22Arg GJA8 mutations (Alapure et al. 2012), although the UPR was only modestly induced in the latter. The UPR and apoptosis were also shown to be induced in cultured lens cells expressing p.V114L CRYBB2 and p.116_118del CRYAA, implicated in autosomal dominant congenital cataracts (Li et al. 2017). Finally, the UPR and all pathways of apoptosis with destruction of the lens microarchitecture were shown to result from expression of a human cataract associated p.Ile33_Ala119del mutant βA3/A1-crystallin protein in transgenic mice (Ma et al. 2016c). Thus, induction of the UPR followed by apoptosis of epithelial and cortical fiber cells appears to be an excellent candidate for the mechanism of severe mutations in lens crystallins or proteins supporting homeostasis of lens cells in causing congenital cataracts. The best evidence supports a different pathogenic mechanism for age-related cataract, although in some cases they might share a final common pathway (Fig. 1).

Most age-related cataracts are the end point of an extended process in which crystallins undergo slow denaturation by a combination of environmental stress, sequence variants causing decreased stability, or disruption of cellular homeostasis (Hejtmancik & Kantorow 2004). Because they are highly expressed in the lens and act like chaperones, α-crystallins, are important in delaying light scattering resulting from this process (Haslbeck et al. 2015). By binding partially denatured βγ-crystallins and holding them in a soluble state in the lens fiber cells, α-crystallins provide protection from the toxic effects of denatured and precipitated proteins (Horwitz 2003). This has been confirmed in human lenses by using dynamic light scattering, which allows measurement of the fraction of free α-crystallin and that complexed with denatured βγ-crystallins in high molecular weight complexes (Datiles et al. 2008). As individuals age, the fraction of unbound α-crystallin decreases about 6-fold in clear lenses. Even when controlled for age, free α-crystallin decreases approximately 10-fold in cataractous lenses as the AREDS nuclear opacity grade increases from 0 to 2 or more. Eventually the α-crystallin is completely consumed so that lenses with nuclear cataracts having AREDS scores greater than 2 have both HMW complexes large enough to scatter light and no remaining free α-crystallin to buffer additional damaged proteins. Thus, it seems likely that most age-related cataracts result from accumulation of HMW protein aggregates large enough to scatter light, with the lens cell architecture largely preserved. In some cases of age-related cataract, after depletion of free α-crystallin and saturation of the HMW complexes, the UPR might be activated by unbound denatured protein. This is also suggested by reports that expression of various parts of the UPR are elevated in age related cataract (Yang et al. 2015). This also would be compatible with a slow increase in opacity over years followed by an accelerated phase over weeks described clinically in some individuals.

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Thus, although cataract represents a final common pathway for mutations in a variety of genes in different cellular processes, the molecular mechanisms of many inherited cataracts seem to fall into two general groups. Congenital and age-related cataracts appear to occur by distinct mechanisms, between which there is possibly some overlap. At least some congenital cataracts result from mutations causing severe insults to crystallin stability or dramatic loss of lens cell homeostasis, often with resulting activation of the UPR followed by apoptosis. In contrast, progressive or age-related cataracts proceed through a gradual but progressive denaturation of βγ-crystallins that complex with α-crystallin until this 'buffer' is exhausted. The aggregates increase in size until they become HMW aggregates and scatter light or actually precipitate, both resulting in cataract. Although there are exceptions such as amyloid-like fibrils that might contribute to some cataracts (Meehan et al. 2004, Xi et al. 2015), given our current state of knowledge the dual pathway concept is a reasonable hypothesis at this time.

Therapy

Despite the wide availability of highly efficacious surgical treatment, age-related cataract is still a leading cause of low vision and blindness worldwide (Pascolini & Mariotti 2012). With continued aging of populations across the world the resultant increase in age-related cataract is projected to pose a major stress on surgical intraocular lens delivery (Rao et al. 2011, Taylor 2000), and this has prompted the search for non-surgical means to delay, prevent, or reverse cataract formation (Moreau & King 2012b, Toh et al. 2007). Classically, dietary adjustment coupled with avoidance of environmental stress such as UV light, smoking, and hyperglycemia have been suggested to be helpful in preventing or delaying age related cataract, and an inverse association between plasma vitamin C and age-related cataract was shown in India, a population with low vitamin C levels (Ravindran et al. 2011). However, the results of dietary vitamin supplementation in humans have been mixed (Toh et al. 2007), as have oral aspirin, aldose reductase inhibitors and topical N-acetylcarnosine therapy (Abdelkader et al. 2015).

Implication of mutations in *LSS*, encoding lanosterol synthase, an enzyme in the cholesterol biosynthesis pathway in recessive congenital cataract prompted examination of its role in stabilizing mutant crystallins and suggested a possible topical eye-drop therapy for cataract (Zhao et al. 2015). Because it is soluble in both aqueous and lipids (amphiphatic) and present at high levels in the lens, lanosterol was tested for its ability to solubilize aggregates of mutant and wild-type crystallins associated with inherited and age-related forms of cataract. Not only did lanosterol treatment reverse crystallin aggregation and solubilize amyloid-like fibril formed by denatured crystallins *in vitro* and in transfected cells but it also improved transparency of rabbit and dog lenses with naturally occurring cataract. Physico-chemical analysis has shown that lanosterol disrupts aggregation of γD-crystallin by binding to the hydrophobic regions? (Kang et al. 2018). However, lanosterol failed to reverse opacities in human lenses removed for age-related cataracts (Shanmugam et al. 2015), although this might relate to the length of time the human cataracts had been present before surgery. Another promising development is the demonstration that a group of pharmacological chaperones can reverse aggregation of mutant αA- and αB-crystallins in vitro as well as in isolated mouse and human lenses (Makley et al. 2015). While these

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preliminary results with lanosterol and other chaperone-like therapies are promising, much work remains to be done before they are proven clinically, although lanosterol eye drops are currently available for treatment of canine cataracts.

While small molecules that act as chaperones to inhibit protein misfolding and aggregation might show promise for cataract resulting from the accumulation of HMW aggregates that scatter light in intact lens cells, they would not be expected to treat congenital cataracts in which the lens microarchitecture itself is damaged or destroyed. These would require surgical intervention with placement of an intraocular lens within the first few months of life, which fortunately is highly efficacious and widely available. In addition, promising results have been reported using lens regeneration approaches in rabbits, macaques, and human infants (Lin et al. 2016b). While this approach is highly experimental, if proved reliable it promises to preserve refractive and accommodative abilities and greater visual axis transparency than current approaches. Taken together with the small molecule chaperone approach, this progress provides new paradigms in the prevention and therapy of both congenital and age-related cataract.

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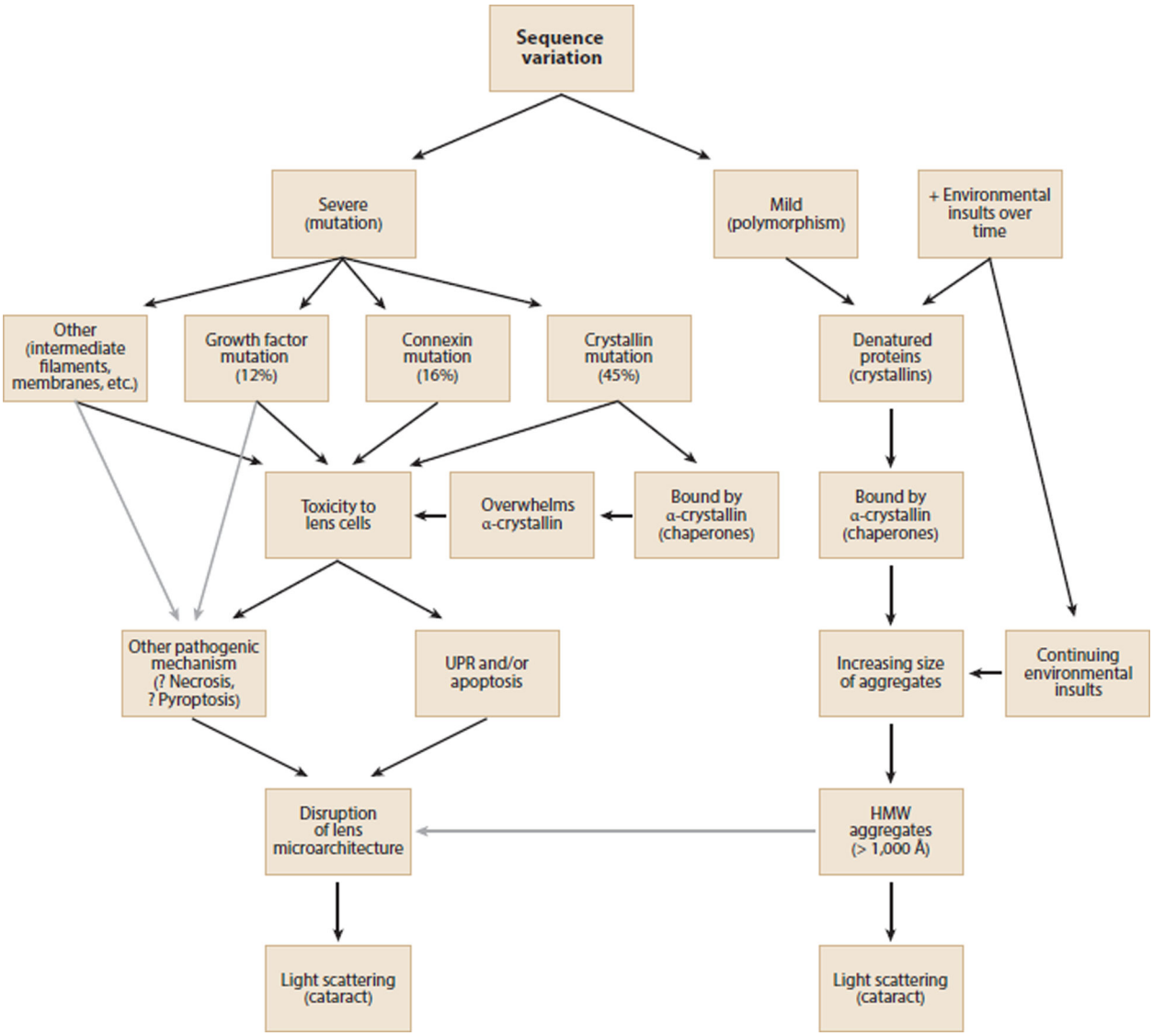

Figure 1.

Possible pathways for inherited cataracts. Severe mutations would be more likely to cause highly penetrant Mendelian congenital cataracts, while mild changes would be likely to increase susceptibility to environmental insults and lead to multifactorial age-related cataracts. Black arrows show demonstrated pathways and gray arrows show likely pathways.

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Table 1

Loci, genes, and phenotypes for nonsyndromic cataract (CTRCT)

Locus	Gene	Cataract phenotype	Inheritance	Associated phenotypes	Phenotype MIM number	
1pter-p36.13	?	CTRCT8; multiple types	AD		115665	
1p36.13	EPHA2	CTRCT6; multiple types	AD/AR	Age-related cortical cataract, susceptibility to	116600	
1p34.3-p32.2	?	CTRCT34; multiple types	AR	With or without microcornea	612968	
1q21.1	GJA8	CTRCT1; multiple types	AD/AR	With or without microcornea	116200	
2pter-p24	?	CTRCT29; coralliform	AD		115800	
2p12	?	CTRCT27; nuclear progressive	AD		607304	
2q34	CRYGB	CTRCT39; multiple types	AD		615188	
2q34	CRYBA2	CTRCT42	AD		115900	
2q33.3	CRYGC	CTRCT2; multiple types	AD	With or without microcornea	604307	
2q33.3	CRYGD	CTRCT4; multiple types	AD	With or without microcornea	115700	
3p21.31	FYCO1	CTRCT18	AR		610019	
3q22.1	BFSP2	CTRCT12; multiple types	AD	Myopia?	611597	
3q27.3	CRYGS	CTRCT20; multiple types	AD		116100	
4p16.1	WFS1	CTRCT41	AD	Wolfram syndrome (DIDMOAD)	116400	
6p12-q12	?	CTRCT28	?	Age-related cortical cataract, susceptibility to	609026	
6p24	GCNT2	CTRCT13	AR	Adult i (blood group) phenotype	110800	
6p21.31	LEMD2	CTRCT46, juvenile onset	AR		212500	
7q34	AGK	CTRCT38	AR	Senger's syndrome	614691	
9q13-q22	?	CTRCT26; multiple types	AR		605749	
9q22.33	TDRD7	CTRCT36	AR		613887	
10p13	VIM	CTRCT30; pulverulent	AD		116300	
10q24.32	PITX3	CTRCT11; multiple types	AD	Anterior segment mesenchymal dysgenesis, microphthalmia, neurodevelopmental abnormalities	610623	
11q22.3	CRYAB	CTRCT16; multiple types	AD/AR	Myopathy, multiple types	613763	123590
12q13.3	MIP	CTRCT15; multiple types	AD		615274	154050
12q24.2-q24.3	?	CTRCT37; cerulean	AD		614422	?
13q12.1	GJA3	CTRCT14; multiple types	AD		601885	121015
14q22-q23	?	CTRCT32; multiple types	AD		115650%	?
15q21-q22	?	CTRCT25	AD		605728	?
16q21	HSF4	CTRCT5; multiple types	AD/AR		116800	602438
16q22-q23	MAF	CTRCT21; multiple types	AD	With or without microcornea	610202	177075
17p13	?	CTRCT24; anterior polar	AD		601202	?

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Locus	Gene	Cataract phenotype	Inheritance	Associated phenotypes	Phenotype MIM number	
17q11.2	CRYBA1	CTRCT10; multiple types	AD		600881	123610
17q12	UNC45B	CTRCT43	AD		616279	611220
17q24	?	CTRCT7	AD		115660	?
19q13	?	CTRCT35; congenital nuclear	AR		609376	?
19q13.1–13.2	SIPAIL3	CTRCT45	AR		616851	616655
19q13.41	LIM2	CTRCT19	AR		615277	154045
20p12.1	BFSP1	CTRCT33; cortical	AR		611391	603307
20q11.21	CHMP4B	CTRCT31; multiple types	AD		605387	610897
21q22.3	CRYAA	CTRCT9; multiple types	AD/AR	With or without microcornea, age-related nuclear cataract, susceptibility to	604219	123580
21q22.3	LSS	CTRCT44	AR		616509	600909
22q11.23	CRYBB2	CTRCT3; multiple types	AD	With or without microcornea	601547	123620
22q11.23	CRYBB3	CTRCT22; multiple types	AD/AR		609741	123630
22q12.1	CRYBB1	CTRCT17; multiple types	AD/AR		611544	6009291
22q12.1	CRYBA4	CTRCT23	AD		610425	123631
Xp22.13	NHS	CTRCT40	X-linked	Nance-Horan (cataract dental) syndrome	302200	300457

For further information, readers are referred to CAT-MAP (https://cat-map.wustl.edu/). Abbreviations: AD, autosomal dominant; AR, autosomal recessive.