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Mutations and mechanisms in congenital and age-related cataracts

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Abstract

The crystalline lens plays an important role in the refractive vision of vertebrates by facilitating variable fine focusing of light onto the retina. Loss of lens transparency, or cataract, is a frequently acquired cause of visual impairment in adults and may also present during childhood. Genetic studies have identified mutations in over 30 causative genes for congenital or other early-onset forms of cataract as well as several gene variants associated with age-related cataract. However, the pathogenic mechanisms resulting from genetic determinants of cataract are only just beginning to be understood. Here, we briefly summarize current concepts pointing to differences in the molecular mechanisms underlying congenital and age-related forms of cataract.

Keywords

Cataract; Lens; Genetic; Crystallin; UPR

1. Introduction

Cataract can be defined broadly as any opacity of the crystalline lens. This has been shown to happen whenever the refractive index of the lens varies significantly over distances approximating the wavelength of the transmitted light (Benedek, 1971; Delaye and Tardieu, 1983). This variation in the refractive index can occur as a result of a variety of changes, including alterations of lens cell structure, lens proteins or a combination of both (Hejtmancik et al., 2001). Alterations to the geometric order of the lens and its membranes can amplify these effects and this can increase light scattering. Congenital cataracts are often associated with breakdown of the lens micro-architecture. Vacuoles can form and cause large fluctuations in optical density with concomitant light scattering. In contrast, age related cataracts are often characterized by light scattering and opacity resulting from the buildup of high molecular weight protein aggregates (HMW), generally 1000 Å or more in size. This can also disrupt the short-range ordered packing of lens crystallins, which is critical for maintaining the crystallins in a homogeneous phase, with disastrous consequences for lens

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transparency as they compose over 90% of soluble lens proteins. However, while formation of large protein complexes might be a common end point in many cataracts, it is important to remember that reduced and disrupted refractive properties in the lens do not result from protein aggregation and precipitation in all cases. Mutations in BFSP2 were first identified in myopic patients in whom opacification of the lens sutures was only found upon closer examination (Zhang et al., 2004). In addition, age related cataract might not be a simple function of protein precipitation, as shown by the existence of multilamellar bodies in age related cataract (Costello et al., 2012). Finally, the two mechanisms of crystallin aggregation and micro-architectural disruption are not exclusive, as the proper lens cell environment is important for the maintenance of lens crystallin structure and existence in a homogeneous phase.

Cataracts can be defined by age at onset, although the boundaries between different types of cataract are approximate. A cataract is termed congenital or infantile if it is observed within the first year of life. If onset occurs within the first decade of life cataract is termed juvenile and a cataract with an onset later but before the age of 45 years is called presenile, with senile or age-related cataracts generally occurring after 50 or perhaps 60 years of age. The situation is complicated because subtle cataracts, which can easily be asymptomatic, might not be brought to clinical attention for years after their onset. In addition, a cataract's age of onset does not imply a particular etiology. About 8.3–25% of congenital cataracts are hereditary (Francois, 1982; Haargaard et al., 2005; Merin, 1991) with the remainder generally caused by an intrauterine infection (e.g. rubella) or other prenatal insult. Secondary cataracts such as those occurring as part of a systemic disease life (e.g., retinitis pigmentosa) may be delayed as late as the second or third decade of life. However, the age of onset of a cataract serves as a useful metric with which to group cataracts, and it would seem logical that, while cataracts within each group will certainly have a variety of mutations in different genes affecting specific cellular processes they might share some similarities in their general pathogenic mechanisms, as detailed in the following paragraph.

We and others have suggested that when mutations in crystallins or other lens proteins are sufficient in and of themselves to cause protein aggregation rapidly and directly, they usually result in congenital cataract. In contrast, if they are benign enough merely to increase susceptibility to environmental insults, including hyperglycemic and dietary (Weikel et al., 2014), ultraviolet light (Taylor et al., 1988), or oxidative (Brennan et al., 2012; Truscott, 2005) damage, they would tend to contribute to age related cataract (Hejtmancik and Smaoui, 2003; Shiels and Hejtmancik, 2007) by exacerbating the accumulation of damage seen to long lived lens proteins with aging (Truscott and Friedrich, 2016). Consistent with these proposed mechanisms, hereditary congenital cataracts are most often transmitted in a highly penetrant Mendelian fashion, and cataracts with a later origin, including progressive and age-related cataracts, are often multifactorial, with contributions from multiple genes providing from 35% to as much as 58% of the risk (McCarty and Taylor, 2001) as well as environmental insults. Although this makes them significantly less amenable to genetic and biochemical study than congenital cataracts, inroads are beginning to be made into their genetic etiologies and in some cases their molecular mechanisms.

2. Congenital cataract

2.1. Inherited congenital cataract mutations

Isolated or primary congenital cataracts currently have been mapped to at least 44 genetic loci (Table 1), exhibiting a wide variety of lens opacity morphologies including, nuclear, lamellar, sutural, polar and total (Merin, 1991). While the causative genes have not been identified at 11 of these loci the genes that have been discovered tend to fall into a number of functional groups that identify critical biological processes in the eye lens. Of the cataract families for whom the mutant gene is known, about 45% show mutations in lens crystallins, about 12% have mutations in various growth or transcription factors; 16% show mutations in connexins, about 5% each show mutations in intermediate filament proteins, membrane proteins, or the protein degradation apparatus, and about 8% show mutations in a variety of other functionally divergent genes including those for lipid metabolism (Shiels et al., 2010). Inheritance of the same mutation in different families or in different individuals within the same family can result in radically different cataract phenotypes (phenotypic heterogeneity), which suggests additional genetic or environmental factors might modify expression of the mutant protein that is the primary cause of the cataracts. Conversely, mutations in different genes active in apparently unrelated biological processes can cause cataracts having similar or identical morphologies (genotypic heterogeneity), suggesting that the cataract observed clinically might be a final common pathway for a varied spectrum of initial insults.

In addition to occurring as an isolated defect, congenital cataracts may be associated with other anterior chamber developmental anomalies such as microphthalmia, aniridia or microcornea. Lens opacities may also be part of multisystem genetic disorders such as chromosome abnormalities, DNA repair deficiencies, Lowe syndrome, or Nance Horan Syndrome. Cataracts resulting from mutations in *CRYAB* are often associated with myofibrillar myopathy and cardiomyopathy (Selcen and Engel, 2003). In some cases the distinction between syndromic and isolated cataract becomes somewhat arbitrary, such as in anterior segment mesenchymal dysgenesis resulting from mutations in the *PITX3* gene (Semina et al., 1998). Here, inherited cataracts may be isolated in some family members and associated with additional findings in others. Some of the more common syndromic cataract mutations that also occur as isolated cataracts are shown in Table 1, while a more complete list is provided in the Molecular and Metabolic Basis of Inherited Diseases (Hejtmancik et al., 2001) and in Cat-Map (Shiels et al., 2010; Zhang et al., 2004).

2.2. Congenital cataract mechanisms

As stated above, congenital cataracts tend to result from mutations with severe functional consequences for the mutant protein structure and function. For transcription factors such as *PITX3* and *MAF* this might mean absence of a transcriptional activator at a critical point in lens development resulting in failure of appropriate lens structures and protein components (Burdon et al., 2003; Ferda et al., 2000; Jamieson et al., 2002; Semina et al., 1998, 2001). For membrane and channel proteins this might mean absent or dramatically inappropriate ion or solute transport (Pal et al., 2000; Shiels et al., 1998). For $\beta\gamma$ -crystallins, this usually implies gross disruption of the protein fold, resulting in rapid denaturation of the protein, often accompanied by precipitation from the soluble phase of the lens cytoplasm. A number

of these mutations have been studied in detail, providing some insight into the pathogenic mechanisms of congenital cataract, and their common aspects. While there are too many of these to explore them all here, it is instructive to examine a few that have been studied in detail.

One crystallin that has been studied extensively is γ S-crystallin, which combines some properties of both the β - and γ -crystallins (Hejtmancik and Piatigorsky, 2000). Mutations in γ S-crystallin have been implicated in both congenital cataract and progressive juvenile cataracts (Sun et al., 2005; Vanita et al., 2009). One congenital cataract that has been well studied is that resulting from the c.124G > A (p.Val42Met) mutation, which causes a congenital nuclear cataract in which the central nuclear opacity is denser than that in the periphery (Vanita et al., 2009), as might be expected from the expression patterns of the γ -crystallins. This mutation has been shown to distort the compact packing of the molecule, opening up the tertiary structure and exposing hydrophobic residues normally buried in the internal protein to the surface (Bharat et al., 2014; Vendra et al., 2012). Similar increases of surface hydrophobicity with corresponding decreases in solubility have been shown for other γ -crystallin mutations associated with cataract (Pande et al., 2005, 2010). This then causes both self-aggregation of the crystallin under mild (approximately physiological) conditions as well as an increased sensitivity to both chemical and thermal denaturation. Overall, the mutant precipitates and scatters light more readily than the wild type γ S-crystallin.

While the denatured γ S-crystallin might normally be expected to be bound up by α -crystallin, which acts as a chaperone, binding of destabilized proteins is also dependent on the dynamic population of folding intermediates, so that it is possible that many or most of the mutant crystallins implicated in congenital cataracts escape binding by α -crystallin (Sathish et al., 2004). Alternatively, the mass of denatured protein and the rapidity with which denaturation occurs might overwhelm the capability of α -crystallin to buffer the lens from partially denatured or damaged proteins. Not only would this lead to the presence of large particles capable of scattering light in the lens, but would also expose the lens to potentially toxic denatured proteins that might then disturb the homeostasis of the lens cells.

That the lens cells themselves might be damaged in congenital cataracts is supported by the disarray in lens microarchitecture seen in many cataracts that have been studied in model systems. One example of this is seen in cataracts 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.Val42Met CRYGS mutation, this one caused a variable phenotype ranging from total to lamellar to nuclear pulverulent. The basis of this cataract is expression of an unstable hybrid protein comprising the first 41 amino acids of γ C-crystallin followed by 62 novel amino acids. While this protein is found in both the soluble and insoluble fractions of lens cells, its transgenic expression in the mouse lens leads to degeneration of the lens fiber cells with concomitant destruction of the lens microarchitecture. Initially, the lenses appear normal, but there is vacuolization of the equatorial epithelial and superficial cortical fiber cells by about 21 days after birth, followed by degeneration of the fiber cells with large vacuoles filled with proteinaceous debris. These findings, and especially the lens histology, are most consistent with a direct toxic effect of the mutant protein on the lens cells.

2.3. The unfolded protein response in congenital cataracts

One possible mechanism through which the mutant protein might exert this effect is induction of the unfolded protein response (UPR) and eventually apoptosis (Ikesugi et al., 2006). The UPR consists of an evolutionarily conserved group of adaptive intracellular signaling pathways that serve to reduce stress on the endoplasmic reticulum (ER stress) that occurs when large amounts of denatured, misfolded, or unfolded proteins accumulate within the ER lumen. The UPR is induced by heat shock 70 kDa protein 5, HSPA5 (also called BiP or GRP78) that binds to at least three major ER-resident sensors, IRE1, ATF6, and EIF2AK3, maintaining them in inactive states. When large amounts of unfolded proteins accumulate HSPA5 dissociates from these three sensors, activating them and initiating the UPR. Initially, the UPR attempts to reduce ER stress by decreasing protein synthesis through induction of eukaryotic translation initiation factor 2-alpha kinase 3 (EIF2AK3), which phosphorylates the alpha subunit of eukaryotic translation-initiation factor 2, inactivating it and thus inhibiting initiation of translation. It also upregulates levels of endoplasmic reticulum associated degradation proteins (ERAD), and increasing chaperone levels (Sovolyova et al., 2014). If stress on the ER is severe, the UPR might fail to achieve homeostasis and then it induces apoptosis (Lai et al., 2007; Rasheva and Domingos, 2009), through both the intrinsic and mitochondrial-mediated pathways (Gupta et al., 2010; Szegezdi et al., 2008) and also EIF2AK3 regulation of gene expression. This regulation includes decreased synthesis of microRNAs (Gupta et al., 2012), activation of specific gene transcription by ATF6, including induction of XBP1 and IRE1, which cleaves XBP1 activating it and inducing transcription of a broad array of mediators including P58 (Gorman et al., 2012) and DNA-damage-inducible transcript 3 (DDIT3). DDIT3 belongs to the CCAAT/ enhancer-binding protein (C/EBP) family of transcription factor and inhibits transcription of a number of genes when activated by ER stress, thus promoting apoptosis. Although fiber cells within the lens core lack nuclei and other organelles such as endoplasmic reticulum or Golgi, the lens epithelium and cortical fiber cells still retain their organelles and could participate in the UPR.

While previously, support for the UPR having a major role in cataract was mixed, there is increasing evidence for a potential role, especially in lens epithelial cells, which have a higher level of metabolic activity. One of the first examples of the UPR in a cataract model was its demonstration in lens epithelial cells from galactosemic rats, as well as cultured transformed lens epithelial cells deprived of glucose (Mulhern et al., 2006). Interestingly, the vacuolization seen in the galactosemic cataracts appears similar to that seen in the early stages of the p.C42Afs*63 mutant CRYGC transgenic mouse cataracts mentioned above (Ma et al., 2011). The UPR also has been shown to contribute to a selenite induced cataract model in rats (Palsamy et al., 2014). The UPR was activated in another model in which expression of two abnormal collagens was used to induce cataracts in transgenic mice, although only one of the abnormal collagens could be shown to cause cell death (Firtina et al., 2009). Perhaps more directly apropos of inherited congenital cataract, variable activation of the UPR has been reported in lenses from mice expressing mutant forms of GJA8/Cx50 (p.Ser50Pro, p.Gly22Arg) that arose spontaneously, or transgenic mutant forms of CRYAA (p.Arg49Cys), and CRYBA1 (c.215 + 1G > A splice-site) shown to underlie human congenital cataracts (Alapure et al., 2012; Andley and Goldman, 2015; Ma et al., 2016b).

Such induction of the UPR with subsequent apoptosis of at least lens epithelial cells appears to be an excellent candidate for having a role in those congenital cataracts resulting from severe mutations in lens crystallins or proteins vital to lens cell homeostasis.

3. Age related cataract

3.1. Age-related cataract variants and loci

Age-related cataracts (ARC) also have a genetic component, although the sequence variations contributing to ARC tend to increase the risk of disease against a background of environmental insults to which all individuals are exposed presumably by making individuals having the variation more vulnerable to a variety environmental insults accumulated over many years (McCarty and Taylor, 2001; Shiels and Hejtmancik, 2010). Although often occurring in a mixed pattern when advanced, age-related cataracts may be divided into three sub-types based on their location within the lens: nuclear, cortical, and posterior subcapsular (Merin, 1991). Each of these forms of cataract has its own multifactorial epidemiology involving contributions from multiple environmental and genetic risk factors. In contrast to inherited congenital cataracts, relatively few genes or loci have been unambiguously associated with the risk for age-related cataract, perhaps because their complex inheritance pattern and late age of onset makes them more difficult to study.

Sequence changes in or near a number of genes have been associated with ARC. The first of these was the “Osaka” variant (Ala198Val) of the gene for galactokinase-1 (GALK1) (Okano et al., 2001). GALK1 catalyzes phosphorylation of galactose, the first step in metabolism of galactose to glucose. The Osaka variant has been detected at an increased frequency, about 7.8% in a Japanese cohort with age-related cataract while being present in 4.1% of the general population. In heterozygotes this protein variation results in reduced stability of the variant enzyme and mild galactokinase deficiency equivalent to about 20% of normal levels, presumably sufficient to result in cataract as an individual ages. Among others, SNPs in and near the EPH receptor A2 (EPA2) have been associated with ARC, especially cortical (Shiels et al., 2008; Sundaresan et al., 2012), as have sequence variations in the α A-crystallin gene (CRYAA) (Bhagyalaxmi et al., 2009, 2010; Liao et al., 2014).

Association of the null allele of the GSTM1 locus with ARC, has proved to be inconsistent, as has that for GSTT1 (Liao et al., 2015; Sun et al., 2010). Alterations in the monocarboxylate (creatine) transporter SLC16A12 are also implicated in juvenile cortical and nuclear cataract and have been associated with age-related cataract (Abplanalp et al., 2013). 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 *KCL1* have been reported with age-related cataract (Jiang et al., 2013a, 2013b; Padma et al., 2011; Su et al., 2013).

In addition, there are mutations resulting in progressive or presenile Mendelian cataracts (Shiels et al., 2010). While the overall spectrum of these mutations is similar to those of congenital cataracts, with the respective frequencies of missense (63% vs. 65%), splice-site (8% vs. 12%), and insertion/deletion resulting in a frameshift (15% vs. 12%) of congenital and progressive cataracts are relatively similar, congenital cataracts might be somewhat

enriched for nonsense (12% vs. 6%), and progressive cataracts for insertion/ deletions with no frameshift (18% vs. 3%), consistent with the concept of less severe mutations resulting in later onset cataracts that develop over the course of a prolonged period of time. Also of interest is the high frequency of BFSP2 mutations causing progressive cataracts (44%, with most being insertions or deletions not resulting in a shift in the reading frame) relative to those in other genes.

3.2. Mechanisms of progressive or age-related cataracts

Among mutations implicated in progressive cataract is the p.Gly18Val mutation in CRYGS (Ma et al., 2009; Sun et al., 2005). In contrast to the p.Val42Met mutant γ S-crystallin protein, which results in congenital cataract, the p.Gly18Val mutant has a normal protein fold and overall structure under normal physiological conditions. Only under chemical or thermal stress does the protein show distortion of the protein fold. The p.Val42Met mutant γ S-crystallin protein is destabilized at lower temperatures and in lower concentrations of chemical denaturants. In an exactly analogous fashion, the protein functions normally in the lens, but under the continued impact of time and environmental insults denatures over a period of years or decades. These two superficially similar mutations in γ S-crystallin appear to result in congenital or age related cataract based on their differential effects on the structure and stability of the protein. A similar example is seen in the p.Phe71Leu mutation in CRYAA associated with age related cataract (Bhagyalaxmi et al., 2009). This mutation results in a protein that does not differ significantly from wild-type α A-crystallin under benign conditions with regard to secondary and tertiary structure, hydrophobicity and the apparent molecular mass of the oligomer, however in the mutant, each of these properties is more easily disturbed by heat treatment. In addition, wild-type α A-crystallin showed increased chaperone like activity following heat treatment, but the p.Phe71Leu mutant protein lost a significant amount of its chaperone activity after heat treatment. These are just two examples of relatively mild mutations that result in age-related or progressive cataract. Additional insight is provided by association of SNP rs7278468 in the CRYAA promoter region, which contributes to age-related cataracts by increasing binding of the inhibitory transcription factor KLF10, resulting in decreased α -crystallin expression (Ma et al., 2016a). One might hypothesize that similarly, mutations that severely disrupt homeostatic functions, for example in ion channels, or glycemic control, might cause congenital cataract, but those that simply stress the system might result in ARC.

3.3. Role of α -crystallin

While there are probably a number of pathways through which age related cataracts occur, and components of the UPR have been reported to be increased in age related cataract (Yang et al., 2015), most age related cataracts appear to occur through a prolonged process in which crystallins are slowly denatured, either by environmental insults, intrinsically lower stability of the crystallins themselves, or degradation of lens cell homeostasis (Hejtmancik and Kantorow, 2004). α -Crystallins, with their chaperone like activity and high concentration in the lens, appear to play a central role in delaying this process (Haslbeck et al., 2015). It has long been appreciated that α -crystallin, acting as a molecular chaperone, would bind partially denatured proteins and maintain them in a soluble state *in vitro*, providing a type of 'buffer' against the untoward effects of denatured and precipitated

protein (Horwitz, 2003). Using dynamic light scattering, it has been possible to confirm this in the lens cell cytoplasm, and to measure the fraction of free α -crystallin in human lenses (Datiles et al., 2008). The fraction of unbound α -crystallin decreases about 6 fold in clear lenses as individuals age. Moreover, the fraction of unbound α -crystallin in cataractous lenses decreases approximately 10 fold as the AREDS nuclear opacity grade increases from 0 to 2 and greater, even when this is controlled for age. This process continues until there is little or no free α -crystallin remaining in lenses with nuclear cataracts having AREDS scores greater than 2. Overall, for age related cataract, these findings support the classical view that lens opacities result from accumulation of protein aggregates large enough to scatter light about 1000 Å, (Benedek, 1971), even in cases in which the lens cell architecture remains largely intact. It is possible that after saturation of the α -crystallin buffer, the UPR might be activated by unbound denatured protein in ARC. This would be compatible with a slow increase in opacity over years followed by an accelerated phase over weeks to months seen clinically in some individuals.

Thus, while cataract can be considered a final common pathway for a number of pathological processes, the molecular mechanisms of many inherited cataracts are beginning to be elucidated and appear to fall into two general groups (Fig. 1). Although there is probably some overlap in the processes, at least many congenital and age-related cataracts appear to occur by distinct mechanisms. Those congenital cataracts whose mechanisms have been delineated appear to occur through mutations causing severe insults to crystallin stability or dramatic loss of lens cell homeostasis, often with resulting activation of the UPR and accompanying apoptosis. In contrast, progressive or age related cataracts often appear to follow a relatively gradual process consisting of denaturation of increasing amounts of $\beta\gamma$ -crystallins that are then bound by α -crystallin until this 'buffer' is completely consumed. At that point the aggregates grow in size until they become large enough to scatter light, with resulting opacity. There will certainly be exceptions to this general process, e.g., amyloid-like fibrils appear to be involved in some cataracts (Meehan et al., 2004; Sandilands et al., 2002; Xi et al., 2015), although these mechanisms are not mutually exclusive and can overlap (Xi et al., 2015). However, based on the present state of knowledge regarding inherited cataracts, this appears to be a reasonable working hypothesis at the present time.

3.4. Anti-cataract therapeutics and future directions

Despite advances in its surgical treatment, age-related cataract remains a leading cause of low vision and blindness worldwide (Pascolini and Mariotti, 2012). With continued aging of global populations the socioeconomic burden of cataract is projected to increase and this has prompted the search for non-surgical means to reverse, delay or prevent cataract formation (Moreau and King, 2012; Toh et al., 2007). However, recent progress in therapy for both congenital and age-related cataracts provides some hope. Lin et al. claim to have developed a modification of conventional surgery for congenital cataracts that enables lens regeneration from endogenous stem cells thereby avoiding the need to implant an artificial intraocular lens (Lin et al., 2016). While this would presumably not be applicable to genetic cataracts, which would regenerate with the causative mutation, these might possibly be amenable to a combined approach incorporating correction of the mutation with a CRISPER/Cas9 technology in order to correct the genetic mutation in the regenerated lens. Also, in the case

of cataracts occurring as part of systemic disease, early conventional or genetic therapy of the underlying metabolic disease should mitigate the associated cataracts.

For age related cataracts, the recent identification of two families with recessive forms of congenital cataract caused by mutations in the gene coding for lanosterol synthase (LSS), a key enzyme in the cholesterol biosynthesis pathway, has suggested a possible topical eye-drop therapy for cataract (Zhao et al., 2015). Because of its amphipathic (water-lipid solubility) properties and enrichment in the lens, lanosterol was tested for its ability to solubilize the amyloid-like fibril aggregates of mutant and wild-type crystallins associated with inherited and age-related forms of cataract. Not only did lanosterol treatment reverse crystallin aggregation *in vitro* and in transfected cells but it also improved transparency of rabbit and dog lenses with naturally occurring cataract. Comparable results have been obtained with a variety of structurally similar steroids acting on α -crystallin aggregates (Makley et al., 2015). These anti-aggregation or chaperone approaches might be combined with inhibitors of the UPR to help mitigate the effects of any unstable protein resistant to small molecule chaperones. In addition, it has been demonstrated that topical administration of an aldose reductase inhibitor (Kinostat) delays onset and progression of cataracts in dogs with naturally occurring diabetes mellitus (Kador et al., 2010). While these preliminary results with small molecules are promising, it is noteworthy that several other animal-model studies of small molecules with anti-oxidant and/or anti-aggregation (chaperone) properties including; plant-flavonoids, aspirin, N-acetyl carnosine, curcumin, caffeine, and multivitamins have not resulted in universal clinical approval for use as anti-cataract drugs in humans. Nevertheless, continued investigation of small-molecule strategies that combat protein misfolding and aggregation and/or oxidative stress in the lens are anticipated to aid in the discovery of efficacious medical treatments for cataract and may have broader treatment implications for other protein-aggregation diseases including neurodegenerative conditions and diabetes.

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Fig. 1. Possible genetic pathways leading to 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.

Table 1

Loci and genes for cataract (CTRCT).

Cataract phenotype	Locus	Inheritance	Associated phenotypes	Gene	Phenotype MIM no.	Gene/locus MIM no.
CTRCT1; multiple types	1q21.1	AD/AR	±microcornea	<i>GJA8</i>	116200	600897
CTRCT2; multiple types	2q33.3	AD	±microcornea	<i>CRYGC</i>	604307	123680
CTRCT3; multiple types	22q11.23	AD	±microcornea	<i>CRYBB2</i>	601547	123620
CTRCT4; multiple types	2q33.3	AD	±microcornea	<i>CRYGD</i>	115700	123690
CTRCT5; multiple types	16q21	AD/AR		<i>HSF4</i>	116800	602438
CTRCT6; multiple types	1p36.13	AD/AR	Age-related cortical	<i>EPHA2</i>	116600	176946
CTRCT7	17q24	AD		?	115660	?
CTRCT8; multiple types	1pter-p36.13	AD		?	115665	?
CTRCT9; multiple types	21q22.3	AD/AR	±microcornea	<i>CRYAA</i>	604219	123580
CTRCT10; multiple types	17q11.2	AD		<i>CRYBA1</i>	600881	123610
CTRCT11; multiple types	10q24.32	AD	Anterior segment mesenchymal dysgenesis, microphthalmia, neurodevelopmental abnormalities	<i>PITX3</i>	610623	602669
CTRCT12; multiple types	3q22.1	AD	Myopia?	<i>BFSF2</i>	611597	603212
CTRCT13	6p24	AR	Adult i (blood group) phenotype	<i>GCNT2</i>	110800	600429
CTRCT14; multiple types	13q12.1	AD		<i>GJA3</i>	601885	121015
CTRCT15; multiple types	12q13.3	AD		<i>MIP</i>	615274	154050
CTRCT16; multiple types	11q22.3	AD/AR	Myopathy, cardiomyopathy	<i>CRYAB</i>	613763	123590
CTRCT17; multiple types	22q12.1	AD/AR		<i>CRYBB1</i>	611544	6009291
CTRCT18	3p21.31	AR		<i>FYCO1</i>	610019	607182
CTRCT19	19q13.41	AR		<i>LIM2</i>	615277	154045
CTRCT20; multiple types	3q27.3	AD		<i>CRYGS</i>	116100	123730
CTRCT21; multiple types	16q22-q23	AD	±microcornea	<i>MAF</i>	610202	177075
CTRCT22; multiple types	22q11.23	AD/AR		<i>CRYBB3</i>	609741	123630
CTRCT23	22q12.1	AD		<i>CRYBA4</i>	610425	123631
CTRCT24; anterior polar	17p13	AD		?	601202	?
CTRCT25	15q21-q22	AD		?	605728	?
CTRCT26; multiple types	9q13-q22	AR		?	605749	?
CTRCT27; nuclear progressive	2p12	AD		?	607304	?

Cataract phenotype	Locus	Inheritance	Associated phenotypes	Gene	Phenotype MIM no.	Gene/locus MIM no.
CTRCT28	6p12-q12	Complex	Age-related cortical, susceptibility to	?	609026	?
CTRCT29; coralliform	2pter-p24	AD		?	115800	?
CTRCT30; pulverulent	10p13	AD		<i>VIM</i>	116300	193060
CTRCT31; multiple types	20q11.21	AD		<i>CHMP4B</i>	605387	610897
CTRCT32; multiple types	14q22-q23	AD		?	%115650	?
CTRCT33; cortical	20p12.1	AR		<i>BFSPI</i>	611391	603307
CTRCT34; multiple types	1p34.3-p32.2	AR	±microcornea	?	612968	?
CTRCT35; congenital nuclear	19q13	AR		?	609376	?
CTRCT36	9q22.33	AR		<i>TDRD7</i>	613887	611258
CTRCT37; cerulean	12q24.2-q24.3	AD		?	614422	?
CTRCT38	7q34	AR	Senger's syndrome	<i>AGK</i>	614691	610345
CTRCT39; multiple types	2q34	AD		<i>CRYGB</i>	615188	123670
CTRCT40	Xp22.13	X-linked	Nance-Horan (cataract dental) syndrome	<i>NHS</i>	302200	300457
CTRCT41	4p16.1	AD	Wolfram syndrome, (DIDMOAD)	<i>WFS1</i>	116400	606201
CTRCT42	2q34	AD		<i>CRYBA2</i>	115900	600836
CTRCT43	17q12	AD		<i>UNC45B</i>	616279	611220
CTRCT44	21q22.3	AR		<i>LSS</i>	616509	600909