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Inherited cataracts: molecular genetics, clinical features, disease mechanisms and novel therapeutic approaches

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ABSTRACT

Cataract is the most common cause of blindness in the world; during infancy and early childhood, it frequently results in visual impairment. Congenital cataracts are phenotypically and genotypically heterogeneous and can occur in isolation or in association with other systemic disorders. Significant progress has been made in identifying the molecular genetic basis of cataract; 115 genes to date have been found to be associated with syndromic and non-syndromic cataract and 38 disease-causing genes have been identified to date to be associated with isolated cataract. In this review, we briefly discuss lens development and cataractogenesis, detail the variable cataract phenotypes and molecular mechanisms, including genotype–phenotype correlations, and explore future novel therapeutic avenues including cellular therapies and pharmacological treatments.

INTRODUCTION

Cataract is the most common, but treatable cause of blindness in the world. Recently, during the 70th World Health Assembly (October 2019), WHO estimated that 2.2 billion people are visually impaired around the world, out of which 65.2 million people are affected with cataract (https://www.who.int/publications-detail/world-report-on-vision). Congenital cataracts are detected at birth or during the first decade of life. WHO estimated that >14 million children are bilaterally blind from cataract, representing >50% of all causes of blindness globally.[1] Congenital cataracts are present in 1–6/10 000 live-births in developed countries and 5–15/10 000 births in developing countries. They are a prominent cause of vision loss in infants and children.[2 3] Most vision loss is due to amblyopia, but some are due to postoperative complications such as glaucoma and retinal detachment.

Approximately half of the congenital cataracts are characterised as inherited and are a clinical feature of nearly 200 syndromic genetic diseases,[4] including for instance diabetes and cholesterol metabolism diseases. Congenital cataract was the first autosomal disease to be genetically mapped in humans[5] and has subsequently been shown to be associated with considerable genetic and phenotypic heterogeneity.[6–8] Several distinct phenotypes have been identified in families with autosomal-dominant congenital cataract based mainly on the location and appearance of the opacification in the lens: anterior polar, posterior polar, nuclear, lamellar, coralliform, blue dot (cerulean), cortical, pulverulent and polymorphic.[9–11] The majority of the inherited cataracts are autosomal dominant with complete penetrance, but variable expression, autosomal recessive and X-linked inheritance patterns are less frequent.

Over the last 10 years, enormous progress has been made in elucidating the molecular basis of congenital cataract, with causative mutations identified in genes encoding many different proteins including intracellular lens proteins (crystallins), membrane gap junction proteins (connexins), water channel proteins (aquaporins), cytoskeletal proteins (eg, BFSP1 (filensin), BFSP2 (phakinin) and vimentin) and transcription factors (TFs) (eg, *FOXE3*, *PAX6*, *PITX3* and *MAFA*) (table 1). Recent advances in molecular genetics, particularly next-generation sequencing, has improved molecular diagnosis in the clinic.[12]

LENS EMBRYOLOGY AND MORPHOLOGY

The ocular lens is a unique model to understand the important aspects of embryonic development, signalling, induction, cell differentiation, cell physiology, biochemistry, organelle degradation and cellular longevity. Several reviews can provide a detailed description.[6 13 14]

During gastrulation (day 22, Carnegie stage 9 in human development), a single eye field forms in the middle of the anterior neural plate, which separates into two optic vesicles and further induce the nearby surface ectoderm to form the lens placode (a precursor of the lens) by day 28 (Carnegie stages 12–13) (figure 1A,B). At this stage, a series of inductive interactions begin to shape the eye, orchestrated by signalling molecules such as bone morphogenetic proteins and fibroblastic growth factor 2, as well as TFs such as OTX2, PAX6 and PITX3.[15] This programme can be mimicked in culture conditions to determine the differentiation pathway of pluripotent cells and their derivatives.[16]

The lens placode invaginates to form the lens pit (figure 1C), which makes a complete circle of cells and detaches from the surface ectoderm to develop into the lens vesicle (figure 1D). By the end of week 4 (Carnegie stages 10–13), the cells from the posterior vesicle start elongating towards the anterior epithelial cell layer to become the primary lens fibres that fill the lens vesicle and later become the embryonic nucleus of the mature lens (figure 1E). The portion of the optic vesicle

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Table 1 Genes implicated in inherited cataract

Gene classification	Gene	Gene locus	Inheritance
Crystallins	*CRYAA*	21q22.3	AD/AR
	CRYAB	11q22.1-q23.2	AD/AR
	CRYBA1	17q11.2-q12	AD/AR
	CRYBA2	2q34	AD
	CRYBA4	22q12.1	AD/AR
	CRYBB1	22q12.1	AD/AR
	CRYBB2	22q11.23	AD
	CRYBB3	22q11.23	AD/AR
	CRYGA	2q33q35	AD
	CRYGB	2q33q35	AD
	CRYGC	2q33q35	AD
	CRYGD	2q33q35	AD
	CRYGS	3q25-qter	AD
Lens membrane protein	*GJA3*	13q11-q12	AD/AR
	GJA8	1q21.1	AD/AR
	MIP	12q13	AD/AR
	TMEM114	16p13.2	AD
	EPHA2	1p36	AD/AR
	SLC16A12	10q23.13	COMPLEX
	LIM2	19q13.4	AR
Developmental factors	*PAX6*	11p13	AD
	PITX3	10q25	AD/AR
	FOXE3	1p32	AD/AR
	MAF	16q22-q23	AD
	EYA1	8q13.3	AD
	VSX2	14q24.3	AR
	HSF4	16q21	AD/AR
Cytoskeletal proteins	*BFSP1*	20p11.23-p12.1	AD/AR
	BFSP2	3q21-q22	AD/AR
	VIM	10p13	AD/AR
	NHS	Xp22.13	XL
Genes with special roles in the lens	*TDRD7*	9q22.33	AD
	CHMP4B	20q11.22	AD
	WFS1	4p16.1	AD
	FYCO1	3p21.31	AR
	GCNT2	6p24.2	AR
	FTL	19q13.33	AD
	AGK	7q34	AR

As described in *Cat-Map*; an online chromosome map and reference database for inherited and age-related forms of cataract(s) in humans, mice and other vertebrates (https://cat-map.wustl.edu/).

that faced the lens placode gives rise to the retina. The retina, in turn, provides inductive signals that regulate the growth and apical-posterior axis of the lens. In the early optic cup stage, the lens vesicle releases signals that induce the overlying surface ectoderm to differentiate into the corneal epithelium. Around weeks 6–7 (Carnegie stages 16-19), lens fibres start to develop from the epithelial cells located at the equator where they begin to elongate and differentiate into the secondary lens fibres (fetal nucleus) of the developing lens (figure 1F). Around week 8 (Carnegie stage 20), the Y-shaped suture appears at the anterior and posterior poles of the embryonic nucleus of the lens as a result of the terminal ends of the secondary lens fibres abutting each other. The newly differentiated fibre cells continue to grow throughout life. During this process of terminal differentiation, fibre cells remove their nucleus and other cell organelles to minimise light scattering.

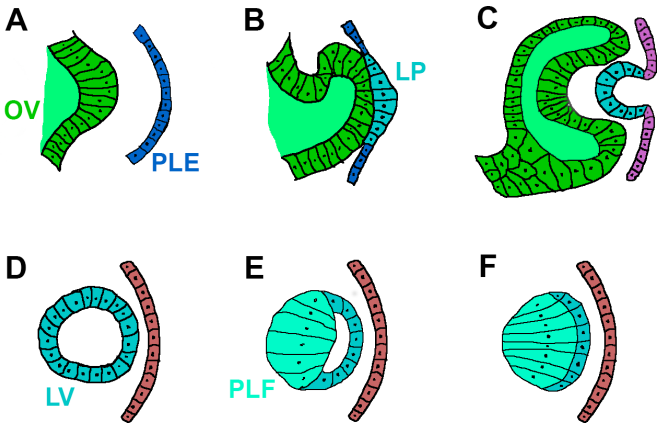

Figure 1 Schematic diagram of the developing lens. (A) The OV approaches the PLE at human age 4 weeks, embryo length 3–5 mm, carnegie stage 12. (B) Contact between OV and PLE results in the LP formation at human age 4–5 weeks, embryo length 4–6 mm, carnegie stage 13. (C) LP invagination produces a lens pit at Carnegie stage 14, week 5, 31–35 days. (D) Lens pit detaches from the surface ectoderm and the LV is formed at human age 5–6 weeks, 7–9 mm embryo length, carnegie stage 15, day 35–38. (E) Posterior lens vesicular cells elongate toward the anterior epithelial cells to form PLFs. (F) The embryonal nucleus is formed following the obliteration of the LV lumen at human age 6 weeks, 8–11 mm embryo length, carnegie stage 16. LP, lens placode; LV, lens vesicle; OV, optic vesicle; PLE, presumptive lens ectoderm; PLF, primary lens fibre.

CATARACT PHENOTYPES AND MODES OF INHERITANCE

The congenital cataract phenotype broadly reflects spatiotemporal insults experienced by the developing lens. Broadly these phenotypes can be divided into eight distinct clinical appearances: (1) nuclear (figure 2A), (2) anterior polar (figure 2B), (3) posterior polar (figure 2C), (4) lamellar, (5) coralliform, (6) blue dot (cerulean – figure 2D), (7) cortical (figure 2E) and (8) pulverulent (figure 2F).[9–11]

There is considerable phenotypic variation in autosomal cataract, although there have been few systematic studies recording differences for specific mutations.[8] To date (August 2019), 1314 novel and recurrent disease-causing sequence variants have been identified (http://cat-map.wustl.edu/), with a well-defined

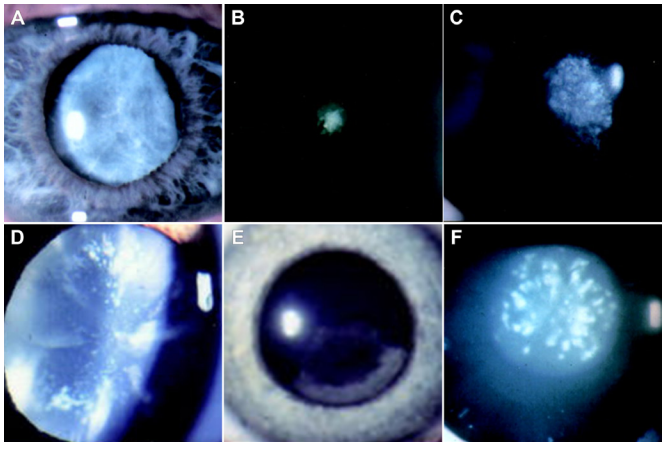

Figure 2 Slit-lamp presentation of examples of inherited cataract phenotypes. (A) Nuclear cataract, (B) anterior polar cataract, (C) posterior polar cataract, (D) blue dot cataract (Cerulean), (E) cortical cataract and (F) pulverulent cataract.

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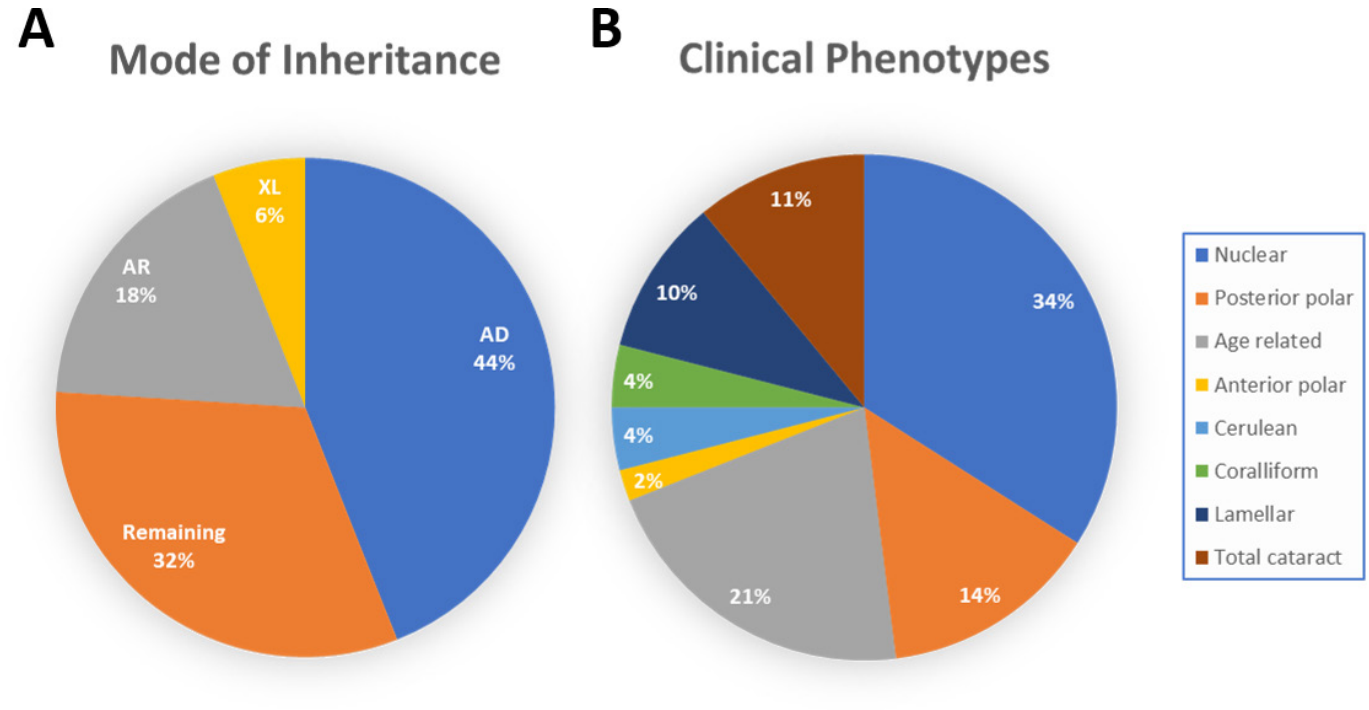

Figure 3 Frequency pie charts. (A) Frequency of various mode of inheritance. (B) Frequency of cataract phenotypes in families seen to date. AD, autosomal dominant; AR, autosomal recessive; XL, X-linked.

distinct phenotype observed in 366 cases as shown in figure 3A. Interestingly, the most frequent phenotype was nuclear cataract (34%), followed by posterior polar (14%), total cataract (11%), lamellar (10%), cerulean and coralliform both (4%), and anterior polar (2%), and the remaining were age-related cataracts (21%) (figure 3B).

The most common mode of inheritance is autosomal dominant (44%), followed by autosomal recessive (18%), X-linked recessive (6%) with the remaining 32% being sporadic with no clear family history (https://cat-map.wustl.edu/) (figure 3A).[17 18] Improvements in molecular diagnosis using next-generation sequencing will allow a better understanding of the mode of inheritance in sporadic cases, to establish whether the variant is homozygous/recessive or heterozygous/dominant.

MOLECULAR GENETICS

Disease-causing sequence variants in 115 genes have been identified in isolated and syndromic inherited cataract. Thirty-eight genes are responsible for distinct isolated cataract and can be divided into five main groups based on the encoded proteins: (1) crystallins, (2) membrane proteins, (3) transcription factors, (4) cytoskeletal proteins and (5) gene products with special roles in the lens (figure 4).

Crystallins

Crystallins (α, β and γ) account for nearly 90% of all lens proteins; they are crucial for the lens optical properties and its function, for the remarkable resilience to post-translational modifications due to ageing[19] and the environment to maintain lens transparency.[20 21]

Alpha-crystallins are members of the small heat shock protein family, which are molecular chaperones protecting lens proteins and enzymes from aggregation, which could otherwise lead to lens opacification.[20] Alpha-crystallin comprises two related subunits (αA polypeptide and αB polypeptide) encoded by *CRYAA* on chromosome 21q22.3 and *CRYAB* on chromosome 11q22-q22.3, respectively.[22] Variants in *CRYAA* cause both autosomal-dominant and autosomal-recessive cataracts and account for 25.8% of all crystallin mutations. CRYAA is primarily expressed in the lens; there is also extralenticular expression detected in mouse retina and cornea.[23–25]

CRYAB is expressed in the lens epithelial cells and in the retina, skeletal muscle, heart, kidney and brain.[24 26] Mutations in *CRYAB* cause not only cataract but also myopathies there being heart and lens-specific enhancers to regulate its expression in these tissues. In 2001, Berry and colleagues found the first dominant heterozygous mutation in a large family with posterior polar cataract.[27] To date, 22 mutations have been reported in the *CRYAB* gene in both autosomal-dominant and

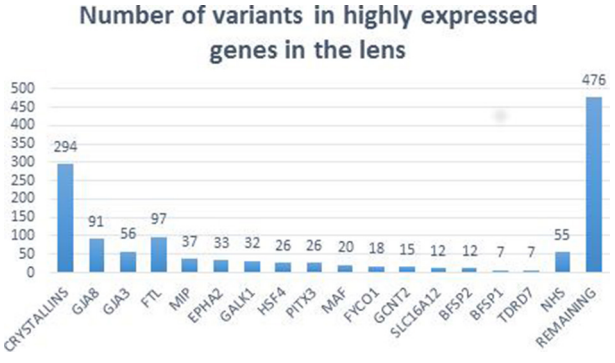

Figure 4 Cataract-causing variants by gene. Total number of 1314 disease-causing variants (novel and recurrent) are shown in various highly expressed genes to date (http://cat-map.wustl.edu/), including crystallins, gap junction proteins, membrane proteins, developmental and cytoskeletal proteins in the lens; remaining 476 variants are found in various other genes important for the normal function of the crystalline lens.

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autosomal-recessive cataract. Heterozygous missense variants have also been described in patients with desmin-related myopathies and cardiomyopathy.[28]

The βγ-crystallins are derived by gene duplication and belong to a large superfamily that includes such proteins as AIM1.[24] They consist of four homologous Greek key motifs organised into two domains. The β-crystallin family comprises four acidic (A) and three basic (B) forms encoded by genes—*CRYBA2*, *CRYBA1* and *CRYBB3*, *CRYBB2*, *CRYBB1* and *CRYBA4*, respectively. γ-Crystallin is encoded by the γ-gene cluster on chromosome 2q33–35 encompassing genes γA to γD. Fewer mutations are found in the γA (*CRYGA*) and γB (*CRYAGB*) compared with γC (*CRYGC*) and γD(*CRYGD*).[29–32] Interestingly, most of the variants in *CRYGC* and *CRYGD* genes cause nuclear cataract and coralliform phenotypes inherited dominantly. A single γs-crystallin gene resides on the long arm of chromosome 3q25-qter; mutations in this gene are mainly causing autosomal-dominant disease with various phenotypes. Crystallins is the most prevalent proteins in the lens; nearly 294 variants have been found in crystallins, which account for nearly 22.4% of all the inherited cataract variants found to date (figure 4).

Membrane proteins

Connexins

A sophisticated cell-to-cell communication network is important in maintaining lens cell homeostasis. In the developing lens, this communication is maintained via gap junction channels which allow the flow of ions, second messengers and metabolites between lens fibre cells. In the lens, these channels are made up of three connexin isoforms: GJA1 (Cx43), GJA3 (Cx46) and GJA8 (Cx50). Six connexin molecules assemble to form a hemichannel or connexon. Each connexon is either made from a single type of connexin, or from more than one type, which leads to either homomeric or heteromeric hemichannels, respectively. These hemichannels dock with a counterpart in an adjacent cell to make a gap junction channel linked by their extracellular loops.[33 34] GJA1 is expressed only in the lens epithelial cells during early stages of lens development, but not associated with lens pathology.[35 36] Fifty-five heterozygous variants and 1 homozygous variant have been found in *GJA3*, with various associated lens phenotypes, including pulverulent, nuclear, lamellar, coralliform and total (http://cat-map.wustl.edu/). To date, 90 heterozygous variants have been described in families with autosomal-dominant cataract, and a single homozygous variant in autosomal-recessive cataract has been found in *GJA8*, associated not only with inherited cataract but also age-related cataract and other eye anomalies including microcornea, microphthalmia and corneal opacification.[37]

MIP

MIP26 is the major intrinsic protein of the lens, encoded by *AQP0*, a member of the ubiquitous family of water channel proteins called aquaporins that allow rapid movements of water across cell membranes. MIP is highly expressed in terminally differentiated lens fibre, comprising nearly half of the total lens fibre cell membrane proteins.[38] Berry and colleagues[39 40] identified two autosomal-dominant variants (G134E and T138R) leading to polymorphic and lamellar cataract. So far, 37 heterozygous variants have been found in *MIP* causing autosomal-dominant cataract.[7]

LIM2

LIM2 is a lens-specific integral membrane protein, also referred to as MP19. This gene encodes an eye lens-specific protein found at the junctions of lens fibre cells, where it may contribute to cell junctional organisation. It acts as a receptor for calmodulin and may play an important role in both lens development and cataractogenesis. Mutations in *LIM2* have been associated recessive cataracts and age-related cataracts.[41–43]

Transcription factors

TFs including PAX6, FOXE3, HSF4, MAF and PITX3 among many others play an important role in lens development.[13 14] *PAX6*, the paired-box gene is one of the key players in vertebrate eye development. In the lens, PAX6 plays a key role in the regulation of lens-specific crystallins.[44 45] and thus is an important TF in lens development. Heterozygous null mutations in *PAX6* typically give rise to aniridia often with associated lens opacities but missense changes may result in milder phenotypes including foveal hypoplasia, Peters anomaly and isolated cataract.[46 47]

FOXE3 is a forkhead-box TF, required for morphogenesis and differentiation of the anterior segment of the eye.[48] Semina *et al* reported the first human variants in this gene causing anterior segment mesenchymal dysgenesis and congenital cataracts.[49] More than 20 homozygous and heterozygous variants have been reported, displaying severe developmental eye anomalies including cataract.[50]

MAF, is a basic region leucine zipper (bZIP), an oncogene, which is expressed in early lens development.[51] MAF regulates the expression of the lens crystallins.[52] Mutations in *MAF* are not only responsible for cataract and ocular abnormalities but also cause Aymé-Gripp syndrome.[53 54] Recently, a missense mutation in *MAFA* gene has been reported to cause autosomal-dominant insulinomatosis and diabetes mellitus along with cataract and glaucoma.[55]

PITX3 gene is a member of the *REIG*/*PITX* family of homeobox TFs.[56] To date, 26 variants in *PITX3* have been identified (including a hot spot in exon 4, c.640_656dup17bp) to cause mainly posterior cataracts and anterior segment dysgenesis in different ethnicities.[57]

Cytoskeletal proteins

The cytoskeleton of a cell comprises three major filaments: microfilaments, microtubules and intermediate filaments. In the lens, two beaded filaments, a type of intermediate filaments, BFSP1 (filensin) and BFSP2 (phakinin), are expressed.[58] Several variants in *BFSP2* lead to sutural opacities and nuclear cataract in association with *BFSP1* variants. NHS (Nance-Horan Syndrome) is also associated with abnormalities in the lens cytoskeleton and epithelial cell junctions. A total of 55 sequence variants in the gene underlying the X-linked dominant NHS have been identified. Affected men have dense nuclear cataracts and frequently have microcornea, whereas heterozygous women show sutural cataracts with microcornea, craniofacial dysmorphism, nystagmus, strabismus and dental anomalies[59 60](table 1).

Studies in various animal models have identified several genes and their pathways linked to lens defects and cataract that are good candidates for examining human patients; for example, iSyTE (https://research.bioinformatics.udel.edu/iSyTE/ppi/) has impacted many cataract gene discoveries both in human and animal models. Recently, Siddam *et al*[61] have shown that deficiency of Celf1 (RNA binding protein) causes cataract in fish and mouse, and serves as a potential candidate to examine in patients with cataract.

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CATARACT THERAPEUTICS AND FUTURE DIRECTION

Understanding cataractogenesis: latency and ageing

The timing of the appearance of cataract depends on whether it is due to a harmful mutation or primarily due to accumulated biomolecular damage. Both can be described as accumulated cataractogenic load, manifesting as cataract either during infancy or at other life stages. Genetic, environmental and stochastic factors all contribute to ageing of the lens and presbyopia at the end of the fourth decade of life is evidence of this. Presbyopia is both a consistent, universal, totally penetrant phenotypic change in the ageing human lens. In line with ageing hypotheses, treatment with antioxidants such as a lipoic acid derivative can reverse presbyopia in mouse models.[62] Indeed, Nacety cysteine derivatives are also effective cataract-reversing molecules in other animal models, indicating that cataract, though a histopathological endpoint, is not necessarily irreversible if treatment and timing are optimised.[63 64] For each individual, the manifestation of their cataract will depend on their accumulated cataractogenic load due to various genetic and environmental insults. This explains why the age of onset for age-related cataract is so variable and why for congenital cataract the age of onset is more consistent. This can be interpreted as representing a threshold.[65]

The lens relies on biomolecular longevity[66 67] because of the lifelong retention of its components and particularly the proteins. The lens continues to grow throughout life and as such bimolecular integrity is integral to its lifelong functions.[68] It is important to recognise that lens metabolism changes as the tissue ages, evidenced by the tissue response to growth factors[69] by metabolite accumulation (kynurenine derivatives,[70 71] by the gradual reduction in glutathione levels[72] and of course the age-dependent increased levels in racemization/isomerisation[73] and advanced glycation end-modified lens proteins.[74 75] The accumulation of polypeptides as a result of the proteolytic modification of lens proteins can also have beneficial and detrimental effects.[76] It is important to appreciate this concept when considering pharmaceutical/small molecule interventions to either arrest or even reverse cataract.

Small molecules

Cataracts are a major burden on public health, and effective therapeutic approaches are yet to be established for preventing or mitigating the process. Lens opacity triggers due to malfunction of alpha-crystallins, when they lose their chaperone properties either due to genetic basis or ageing. Due to their reduced functional capacity, crystallin tends to misfold the protein and aggregate into amyloids.[77] Several studies have suggested few compounds that can reverse the light scattering lens aggregates in vitro and in animal studies.

Recently, Makley and colleagues[78] identified a small molecule, 'compound 29', which binds to several members of the small heat shock protein family including the alpha-crystallins. This compound, an oxysterol, was shown to improve lens transparency in the mouse model and able to restore the protein solubility in the lenses of aged mice in vivo and in human lenses in vitro. These findings suggest an approach to treating cataracts by stabilising alpha-crystallins.

Another group identified variants in the *LSS* gene in two autosomal-recessive congenital cataract families. The *LSS* gene encodes lanosterol synthase, a key enzyme in the cholesterol biosynthesis pathway, is highly expressed in the lens and has water-lipid solubility properties. Lanosterol treatment has shown to reverse crystallin aggregation in vitro. It was also suggested to improve lens transparency in rabbits and dogs with naturally occurring cataract. Due to its solubility properties, lanosterol has been suggested as a possible topical eye-drop therapy for cataract.[79 80] although recent studies have cast doubt on the efficacy of the identified oxysterols lanosterol and 25-hydroxy cholesterol to treat cataract.[81] The chemical chaperone 4-phenylbutyrate was used in mouse lenses to improve lens function in the genetic model of a cataract-causing connexin mutation (Cx50D47A) with limited success.[82] The search for small molecule inhibitors has been a consistent research goal over the decades with promising effects obtained with molecules such as pantethine,[83]rosmarinic acid and polyherbal preparations[84] and multifunctional antioxidants.[85] Those that have shown the most promise are those that have met the challenge of reducing cataractogenic load and this is therefore an important mechanistic focus for future work.

Cellular therapy

Lin *et al* have developed a method that enables lens regeneration from endogenous stem cells to treat cataract, where they removed cataract lens in mammals and human infants while preserving lens capsule and lens epithelial cells[86] In the case of inherited cataracts, this method deploys further gene editing using CRISPR/Cas9 technology in order to rectify the genetic mutation in the regenerated lens.

However, small molecule therapy, for example using eye drops, seems to remain the most pragmatic solution in developing parts of the world, where immediacy and cost-effectiveness is key. The more invasive and time-consuming stem cell therapy approaches are apt in cases where gene editing is essential to correct the mutant gene, for example, inherited cataracts.

CONCLUSIONS

The identification of genetic variants causing congenital cataract has not only improved our understanding of the pathogenesis of infantile cataract, the most frequently treatable cause of blindness in childhood, but also its more common counterpart, adult-onset cataract. For example, *LIM2*, *EPHA2* and *TDRD7* that have variants described in both congenital and age-related cataract. It is thus pivotal to identify genetic variations associated with a high risk of developing cataract. This may lead towards new strategies for the prevention of cataract or mitigating the progression of early lens opacity, thus reducing the global huge demand for surgery. There is immense potential in cataract research to elucidate the relationship between neurological and vascular diseases.[87]

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REFERENCES

1 Solebo AL, Teoh L, Rahi J. Epidemiology of blindness in children. *Arch Dis Child* 2017;102:853–7.
2 Sheeladevi S, Lawrenson JG, Fielder AR, *et al*. Global prevalence of childhood cataract: a systematic review. *Eye* 2016;30:1160–9.
3 Gogate P, Kalua K, Courtright P. Blindness in childhood in developing countries: time for a reassessment? *PLoS Med* 2009;6:e1000177.
4 Messina-Baas O, Cuevas-Covarrubias SA. Inherited congenital cataract: a guide to suspect the genetic etiology in the cataract genesis. *Mol Syndromol* 2017;8:58–78.
5 Renwick JH, Lawler SD. Probable linkage between a congenital cataract locus and the Duffy blood group locus. *Ann Hum Genet* 1963;27:67–76.
6 Graw J. The genetic and molecular basis of congenital eye defects. *Nat Rev Genet* 2003;4:876–88.
7 Shiels A, Bennett TM, Hejtmancik JF. Cat-Map: putting cataract on the MAP. *Mol Vis* 2010;16:2007–15.
8 Shiels A, Hejtmancik JF. Mutations and mechanisms in congenital and age-related cataracts. *Exp Eye Res* 2017;156:95–102.
9 Ionides A, Francis P, Berry V, *et al*. Clinical and genetic heterogeneity in autosomal dominant cataract. *Br J Ophthalmol* 1999;83:802–8.
10 Francis PJ, Berry V, Bhattacharya SS, *et al*. The genetics of childhood cataract. *J Med Genet* 2000;37:481–8.
11 Churchill A, Graw J. Clinical and experimental advances in congenital and paediatric cataracts. *Philos Trans R Soc Lond B Biol Sci* 2011;366:1234–49.
12 Musleh M, Ashworth J, Black G, *et al*. Improving diagnosis for congenital cataract by introducing NGS genetic testing. *BMJ Qual Improv Rep* 2016;5:u211094.w4602.
13 Sinn R, Wittbrodt J. An eye on eye development. *Mech Dev* 2013;130:347–58.
14 Cvekl A, Ashery-Padan R. The cellular and molecular mechanisms of vertebrate lens development. *Development* 2014;141:4432–47.
15 Lovicu FJ, McAvoy JW. Growth factor regulation of lens development. *Dev Biol* 2005;280:1–14.
16 Murphy P, Kabir MH, Srivastava T, *et al*. Light-focusing human micro-lenses generated from pluripotent stem cells model lens development and drug-induced cataract *in vitro*. *Development* 2018;145:dev155838.
17 Li R, Johnson AB, Salomons G, *et al*. Glial fibrillary acidic protein mutations in infantile, juvenile, and adult forms of Alexander disease. *Ann Neurol* 2005;57:310–26.
18 Sakumi K. Germline mutation: de novo mutation in reproductive lineage cells. *Genes Genet Syst* 2019;94:3–12.
19 Nielsen J, Hedeholm RB, Heinemeier J, *et al*. Eye lens radiocarbon reveals centuries of longevity in the Greenland shark (Somniosus microcephalus). *Science* 2016;353:702–4.
20 Wistow GJ, Piatigorsky J. Lens crystallins: the evolution and expression of proteins for a highly specialized tissue. *Annu Rev Biochem* 1988;57:479–504.
21 Horwitz J. Alpha-Crystallin. *Exp Eye Res* 2003;76:145–53.
22 Bhat SP. Crystallins, genes and cataract. *Prog Drug Res* 2003;60:205–62.
23 Kato K, Shinohara H, Kurobe N, *et al*. Immunoreactive alpha a crystallin in rat non-lenticular tissues detected with a sensitive immunoassay method. *Biochim Biophys Acta* 1991;1080:173–80.
24 Slingsby C, Wistow GJ. Functions of crystallins in and out of lens: roles in elongated and post-mitotic cells. *Prog Biophys Mol Biol* 2014;115:52–67.
25 Piri N, Kwong JMK, Caprioli J. Crystallins in retinal ganglion cell survival and regeneration. *Mol Neurobiol* 2013;48:819–28.
26 Graw J. Genetics of crystallins: cataract and beyond. *Exp Eye Res* 2009;88:173–89.
27 Berry V, Francis P, Reddy MA, *et al*. Alpha-B crystallin gene (CRYAB) mutation causes dominant congenital posterior polar cataract in humans. *Am J Hum Genet* 2001;69:1141–5.
28 Vicart P, Caron A, Guicheney P, *et al*. A missense mutation in the alphaB-crystallin chaperone gene causes a desmin-related myopathy. *Nat Genet* 1998;20:92–5.
29 Sandilands A, Hutcheson AM, Long HA, *et al*. Altered aggregation properties of mutant gamma-crystallins cause inherited cataract. *Embo J* 2002;21:6005–14.
30 Wistow G. Lens crystallins: gene recruitment and evolutionary dynamism. *Trends Biochem Sci* 1993;18:301–6.
31 Andley UP. Crystallins in the eye: function and pathology. *Prog Retin Eye Res* 2007;26:78–98.
32 Reis LM, Tyler RC, Muheisen S, *et al*. Whole exome sequencing in dominant cataract identifies a new causative factor, CRYBA2, and a variety of novel alleles in known genes. *Hum Genet* 2013;132:761–70.
33 Goodenough DA. The crystalline lens. A system networked by gap junctional intercellular communication. *Semin Cell Biol* 1992;3:49–58.
34 Mathias RT, White TW, Gong X. Lens gap junctions in growth, differentiation, and homeostasis. *Physiol Rev* 2010;90:179–206.
35 Musil LS, Beyer EC, Goodenough DA. Expression of the gap junction protein connexin43 in embryonic chick lens: molecular cloning, ultrastructural localization, and post-translational phosphorylation. *J Membr Biol* 1990;116:163–75.
36 Yancey SB, Biswal S, Revel JP. Spatial and temporal patterns of distribution of the gap junction protein connexin43 during mouse gastrulation and organogenesis. *Development* 1992;114:203–12.
37 Ceroni F, Aguilera-Garcia D, Chassaing N, *et al*. New GJA8 variants and phenotypes highlight its critical role in a broad spectrum of eye anomalies. *Hum Genet* 2019;138:1027–42.
38 Agre P, Bonhivers M, Borgnia MJ. The aquaporins, blueprints for cellular plumbing systems. *J Biol Chem* 1998;273:14659–62.
39 Berry V, Francis P, Kaushal S, *et al*. Missense mutations in MIP underlie autosomal dominant 'polymorphic' and lamellar cataracts linked to 12q. *Nat Genet* 2000;25:15–17.
40 Francis P, Chung JJ, Yasui M, *et al*. Functional impairment of lens aquaporin in two families with dominantly inherited cataracts. *Hum Mol Genet* 2000;9:2329–34.
41 Pras E, Levy-Nissenbaum E, Bakhan T, *et al*. A missense mutation in the LIM2 gene is associated with autosomal recessive presenile cataract in an inbred Iraqi Jewish family. *Am J Hum Genet* 2002;70:1363–7.
42 Zhou Z, Wang B, Hu S, *et al*. Genetic variations in GJA3, GJA8, LIM2, and age-related cataract in the Chinese population: a mutation screening study. *Mol Vis* 2011;17:621–6.
43 Irum B, Khan SY, Ali M, *et al*. Mutation in LIM2 is responsible for autosomal recessive congenital cataracts. *PLoS One* 2016;11:e0162620.
44 Cvekl A, Piatigorsky J. Lens development and crystallin gene expression: many roles for Pax-6. *Bioessays* 1996;18:621–30.
45 Walther C, Gruss P. Pax-6, a murine paired box gene, is expressed in the developing CNS. *Development* 1991;113:1435–49.
46 Hever AM, Williamson KA, van Heyningen V. Developmental malformations of the eye: the role of Pax6, Sox2 and Otx2. *Clin Genet* 2006;69:459–70.
47 Davis LK, Meyer KJ, Rudd DS, *et al*. Pax6 3' deletion results in aniridia, autism and mental retardation. *Hum Genet* 2008;123:371–8.
48 Blixt A, Landgren H, Johansson BR, *et al*. Foxe3 is required for morphogenesis and differentiation of the anterior segment of the eye and is sensitive to Pax6 gene dosage. *Dev Biol* 2007;302:218–29.
49 Semina EV, Brownell I, Mintz-Hittner HA, *et al*. Mutations in the human forkhead transcription factor FOXE3 associated with anterior segment ocular dysgenesis and cataracts. *Hum Mol Genet* 2001;10:231–6.
50 Anand D, Agrawal SA, Slavotinek A, *et al*. Mutation update of transcription factor genes *FOXE3*, *HSF4*, Maf, and Pitx3 causing cataracts and other developmental ocular defects. *Hum Mutat* 2018;39:471–94.
51 Nishizawa M, Kataoka K, Goto N, *et al*. v-maf, a viral oncogene that encodes a "leucine zipper" motif. *Proc Natl Acad Sci U S A* 1989;86:7711–5.
52 Kim JI, Li T, Ho IC, *et al*. Requirement for the c-Maf transcription factor in crystallin gene regulation and lens development. *Proc Natl Acad Sci U S A* 1999;96:3781–5.
53 Jamieson RV, Perveen R, Kerr B, *et al*. Domain disruption and mutation of the bZIP transcription factor, Maf, associated with cataract, ocular anterior segment dysgenesis and coloboma. *Hum Mol Genet* 2002;11:33–42.
54 Niceta M, Stellacci E, Gripp KW, *et al*. Mutations impairing GSK3-mediated Maf phosphorylation cause cataract, deafness, intellectual disability, seizures, and a Down syndrome-like facies. *Am J Hum Genet* 2015;96:816–25.
55 Iacovazzo D, Flanagan SE, Walker E, *et al*. *MAFA* missense mutation causes familial insulinomatosis and diabetes mellitus. *Proc Natl Acad Sci U S A* 2018;115:1027–32.
56 Semina EV, Ferrell RE, Mintz-Hittner HA, *et al*. A novel homeobox gene Pitx3 is mutated in families with autosomal-dominant cataracts and ASMD. *Nat Genet* 1998;19:167–70.
57 Berry V, Yang Z, Addison PKF, *et al*. Recurrent 17 bp duplication in Pitx3 is primarily associated with posterior polar cataract (CPP4). *J Med Genet* 2004;41:e109.
58 Song S, Landsbury A, Dahm R, *et al*. Functions of the intermediate filament cytoskeleton in the eye lens. *J Clin Invest* 2009;119:1837–48.
59 Ramprasad VL, Thool A, Murugan S, *et al*. Truncating mutation in the *NHS* gene: phenotypic heterogeneity of Nance-Horan syndrome in an Asian Indian family. *Invest Ophthalmol Vis Sci* 2005;46:17–23.
60 Florijn RJ, Loves W, Maillette de Buy Wenniger-Prick LJJM, *et al*. New mutations in the NHS gene in Nance-Horan syndrome families from the Netherlands. *Eur J Hum Genet* 2006;14:986–90.
61 Siddam AD, Gautier-Courteille C, Perez-Campos L, *et al*. The RNA-binding protein CELF1 post-transcriptionally regulates p27Kip1 and Dnase2b to control fiber cell nuclear degradation in lens development. *PLoS Genet* 2018;14:e1007278.
62 Pescosolido N, Barbato A, Giannotti R, *et al*. Age-Related changes in the kinetics of human lenses: prevention of the cataract. *Int J Ophthalmol* 2016;9:1506–17.
63 Garner WH, Garner MH. Protein disulfide levels and lens elasticity modulation: applications for presbyopia. *Invest Ophthalmol Vis Sci* 2016;57:2851.
64 Maddirala Y, Tobwala S, Karacal H, *et al*. Prevention and reversal of selenite-induced cataracts by N-acetylcysteine amide in Wistar rats. *BMC Ophthalmol* 2017;17:54.
65 Uwineza A, Kalligeraki AA, Hamada N, *et al*. Cataractogenic load - A concept to study the contribution of ionizing radiation to accelerated aging in the eye lens. *Mutat Res* 2019;779:68–81.
66 Stewart DN, Lango J, Nambiar KP, *et al*. Carbon turnover in the water-soluble protein of the adult human lens. *Mol Vis* 2013;19:463–75.
67 Hughes JR, Levchenko VA, Blanksby SJ, *et al*. Correction: no turnover in lens lipids for the entire human lifespan. *Elife* 2015;4:e08186.
68 Michael R, Bron AJ. The ageing lens and cataract: a model of normal and pathological ageing. *Philos Trans R Soc Lond B Biol Sci* 2011;366:1278–92.

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69 Dawes LJ, Duncan G, Wormstone IM. Age-Related differences in signaling efficiency of human lens cells underpin differential wound healing response rates following cataract surgery. *Invest Ophthalmol Vis Sci* 2013;54:333.
70 Linetsky M, Raghavan CT, Johar K, *et al*. Uva light-excited kynurenines oxidize ascorbate and modify lens proteins through the formation of advanced glycation end products: implications for human lens aging and cataract formation. *J Biol Chem* 2014;289:17111–23.
71 Hood BD, Garner B, Truscott RJW. Human lens coloration and aging. *J Biol Chem* 1999;274:32547–50.
72 Friedrich MG, Wang Z, Schey KL, *et al*. DehydroalanylGly, a new post translational modification resulting from the breakdown of glutathione. *Biochim Biophys Acta Gen Subj* 2018;1862:907–13.
73 Fujii N, Takata T, Fujii N, *et al*. D-Amino acids in protein: the mirror of life as a molecular index of aging. *Biochim Biophys Acta Proteins Proteom* 2018;1866:840–7.
74 Nagaraj RH, Linetsky M, Stitt AW. The pathogenic role of Maillard reaction in the aging eye. *Amino Acids* 2012;42:1205–20.
75 Cheng R, Lin B, Ortwerth BJ. Rate of formation of ages during ascorbate glycation and during aging in human lens tissue. *Biochim Biophys Acta* 2002;1587:65–74.
76 Kumarasamy A, Jeyarajan S, Cheon J, *et al*. Retracted: peptide-induced formation of protein aggregates and amyloid fibrils in human and guinea pig αA-crystallins under physiological conditions of temperature and pH. *Exp Eye Res* 2019;179:193–205.
77 Nagaraj RH, Nahomi RB, Mueller NH, *et al*. Therapeutic potential of α-crystallin. *Biochim Biophys Acta* 2016;1860:252–7.
78 Makley LN, McMenimen KA, DeVree BT, *et al*. Pharmacological chaperone for α-crystallin partially restores transparency in cataract models. *Science* 2015;350:674–7.
79 Zhao L, Chen X-J, Zhu J, *et al*. Lanosterol reverses protein aggregation in cataracts. *Nature* 2015;523:607–11.
80 Quinlan RA. A new dawn for cataracts. *Science* 2015;350:636–7.
81 Daszynski DM, Santhoshkumar P, Phadte AS, *et al*. Failure of oxysterols such as lanosterol to restore lens clarity from cataracts. *Sci Rep* 2019;9:8459.
82 Jara O, Minogue PJ, Berthoud VM, *et al*. Chemical chaperone treatment improves levels and distributions of connexins in Cx50D47A mouse lenses. *Exp Eye Res* 2018;175:192–8.
83 Clark JI, Livesey JC, Steele JE. Delay or inhibition of rat lens opacification using pantethine and WR-77913. *Exp Eye Res* 1996;62:75–84.
84 Velpandian T, Gupta P, Ravi AK, *et al*. Evaluation of pharmacological activities and assessment of intraocular penetration of an Ayurvedic polyherbal eye drop (Itone™) in experimental models. *BMC Complement Altern Med* 2013;13:1.
85 Randazzo J, Zhang P, Makita J, *et al*. Orally active multi-functional antioxidants delay cataract formation in streptozotocin (type 1) diabetic and gamma-irradiated rats. *PLoS One* 2011;6:e18980.
86 Lin H, Ouyang H, Zhu J, *et al*. Lens regeneration using endogenous stem cells with gain of visual function. *Nature* 2016;531:323–8.
87 Graw J. From eyeless to neurological diseases. *Exp Eye Res* 2017;156:5–9.

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