Congenital and Inherited Cataracts

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Abstract

Congenital cataracts cause approximately one-third of blindness in infants worldwide. If untreated they can cause permanent blindness by interfering with the sharp focus of light onto the retina and thus fail to establish appropriate synaptic connections between the retina and the visual cortex. Between 8 and 30% (see later) of congenital cataracts are inherited, and our understanding of their genetic architecture is increasing. Delineating the relationship between the genes and mutations causing cataracts and their phenotypic presentation can help us to understand the biology of the lens and provide a framework for the clinical approach to diagnosis and treatment.

Keywords

Cataract · Lens · Congenital · Genetic

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22.1 Introduction

The main functions of the lens are to transmit and focus light onto the retina. The lens transmits light with wavelengths from 390 to 1200 nm efficiently, extending above the limit of visual perception (about 720 nm). Lens transparency results from appropriate architecture of lens cells and tight packing of their proteins, resulting in a constant refractive index over distances approximating the wavelength of light [1, 2]. There is a gradual increase in the refractive index of the human lens from the cortex (1.38) to the nucleus (1.41) where there is an enrichment of tightly packed γ-crystallins.

Cataracts have multiple causes, but are often associated with breakdown of the lens microarchitecture [3, 4], possibly including vacuole formation, which can cause large fluctuations in density resulting in light scattering. In addition, light scattering and opacity will occur if there is a significant amount of high molecular weight protein aggregates 1000 Å or more in size [5, 6]. The short-range ordered packing of the crystallins is important in this regard. For transparency, crystallins must exist in a homogeneous phase.

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22.2 Epidemiology and Global Perspective

Hereditary cataracts are estimated to account for between 8.3 and 30 (see later) percent of congenital cataracts, depending on the population and study [7–9]. For the most part, these differences relate to the higher frequencies of environmental and infectious etiologies in developing nations, lowering the fraction of inherited cataracts, with underlying mutation rates relatively constant. Frequencies of inheritance patterns also relate to marriage patterns in specific populations. For example, about 85% of reported inherited cataracts worldwide are autosomal dominant (see below), while in Pakistan, which has a high rate of consanguineous marriages, about 87% of genetic cataracts are inherited as an autosomal recessive trait [10]. Similarly, it has been estimated that 71% of inherited congenital cataracts in Saudi Arabia are autosomal recessive [11].

22.3 Etiology

In contrast to age-related cataracts, which have a strong environmental component, hereditary congenital cataracts are almost completely determined by germline mutations, which may present as autosomal dominant, autosomal recessive, or X-linked traits. Clinically identical cataracts can result from different mutations and even involving different genes and be inherited in different patterns. Conversely, morphologically distinct and variable cataracts can result from a single mutant gene in a single large family [12]. The number of known cataract loci has increased dramatically in the last few years to well over 60 loci at which mutations in over 40 genes have been demonstrated to cause inherited human cataracts, with the best indications being that approximately 40% of cataract loci have been identified. Obviously, much remains to be learned about the genetic contributions to inherited congenital cataracts.

The genetic architecture of Mendelian cataracts largely comprises a limited number of functional groups making up biological pathways or processes critical for lens development, homeostasis, and transparency (Table 22.1). About a third of cataracts result from mutations in lens crystallins; about a quarter result from mutations in transcription or growth factors; slightly less than one-seventh result from mutations in connexins, about one-tenth result from mutations in membrane proteins or components, and somewhat less than 5% show mutations in chaperone or protein degradation components each, about 2% result from mutations in a mixed group of other genes while the genes at about 3% of known cataract loci have not been identified yet (Fig. 22.1). A more complete list with detailed descriptions and references can be found in CATMAP [13].

The lens has a single layer of anterior epithelial cells overlaying the fiber cells wrapped onion-like around the lens nucleus [14]. Cell division occurs in the germinative zone just anterior to the equator, and the cells then move laterally toward the equator, where the anterior epithelial cells begin to elongate and form secondary fibers [15]. The organelle-rich anterior epithelial cells are connected by gap junctions [16], which facilitate exchange of ions and other low molecular weight metabolites, but tend to lack tight junctions, which would seal the extracellular spaces to these molecules [17]. Differentiating lens fiber cells move toward the lens core and lose their organelles, including the cell nuclei, mitochondria, Golgi bodies, and both rough and smooth ER. Fiber cells, have many interdigitations with minimal extracellular space [18] and are joined by frequent junctional complexes allowing for intercellular transfer of metabolites [19]. Both the anterior epithelial cells and especially the fiber cells contain large amounts of crystallins, as well as cytoskeletal proteins. The process of lens differentiation with its changing protein components are largely under transcriptional control.

Table 22.1 Loci, genes, and phenotypes for nonsyndromic cataract

Gene	Inheritance	Associated extralenticular phenotypes	MIM no.	Gene/locus MIM no.	Locus
1. Transcription and developmental factors					
PITX3	AD	Anterior segment mesenchymal dysgenesis, microphthalmia, neurodevelopmental abnormalities	610623	602669	10q24.32
EPHA2	AD/AR	Susceptibility to age-related cortical cataract	116600	176946	1p36.13
HSF4	AD/AR		116800	602438	16q21
MAF	AD	With or without microcornea	610202	177075	16q22-q23
SIPA1L3	AR		616851	616655	19q13.1-13.2
NHS	X-linked	Nance-Horan (cataract dental) syndrome	302200	300457	Xp22.13
2. Lens crystallins					
CRYGB	AD		615188	123670	2q34
CRYBA2	AD		115900	600836	2q34
CRYGC	AD	With or without microcornea	604307	123680	2q33.3
CRYGD	AD	With or without microcornea	115700	123690	2q33.3
CRYGS	AD		116100	123730	3q27.3
CRYAB	AD/AR	Myopathy, multiple types	613763	123590	11q22.3
CRYBA1	AD		600881	123610	17q11.2
CRYAA	AD/AR	With or without microcornea, susceptibility to age-related nuclear cataract	604219	123580	21q22.3
CRYBB2	AD	With or without microcornea	601547	123620	22q11.23
CRYBB3	AD/AR		609741	123630	22q11.23
CRYBB1	AD/AR		611544	6009291	22q12.1
CRYBA4	AD		610425	123631	22q12.1
3. Gap junction proteins (Connexins)					
GJA8	AD/AR	With or without microcornea	116200	600897	1q21.1
GJA3	AD		601885	121015	13q12.1
4. Membranes and their proteins					
WFS1	AD	Wolfram syndrome (DIDMOAD)	116400	606201	4p16.1
LEMD2	AR		212500	616312	6p21.31
AGK	AR	Senger's syndrome	614691	610345	7q34
MIP	AD		615274	154050	12q13.3
LIM2	AR		615277	154045	19q13.41
LSS	AR		616509	600909	21q22.3
5. Besded filament and other intermediate filament proteins					
BFSP2	AD	Myopia	611597	603212	3q22.1
VIM	AD		116300	193060	10p13
BFSP1	AR		611391	603307	20p12.1
6. Chaperones and protein degradation					
FYCO1	AR		610019	607182	3p21.31
UNC45B	AD		616279	611220	17q12
CHMP4B	AD		605387	610897	20q11.21
7. Other genes and pathways					
TDRD7	AR		613887	611258	9q22.33
GCNT2	AR	Adult i blood group phenotype	110800	600429	6p24
8. Unknown loci					
?	AD		115665	NA	1pter-p36.13
?	AR	With or without microcornea	612968	NA	1p34.3-p32.2
?	AD		115800	NA	2pter-p24

(continued)

Table 22.1 (continued)

Gene	Inheritance	Associated extralenticular phenotypes	MIM no.	Gene/locus MIM no.	Locus
?	AD		607304	NA	2p12
?	?	Susceptibility to age-related cortical cataract	609026	NA	6p12-q12
?	AR		605749	NA	9q13-q22
?	AD		614422	NA	12q24.2-q24.3
?	AD		115650%	NA	14q22-q23
?	AD		605728	NA	15q21-q22
?	AD		601202	NA	17p13
?	AD		115660	NA	17q24
?	AR		609376	NA	19q13

Further information and references can be found at CAT-MAP: https://cat-map.wustl.edu/ [13]

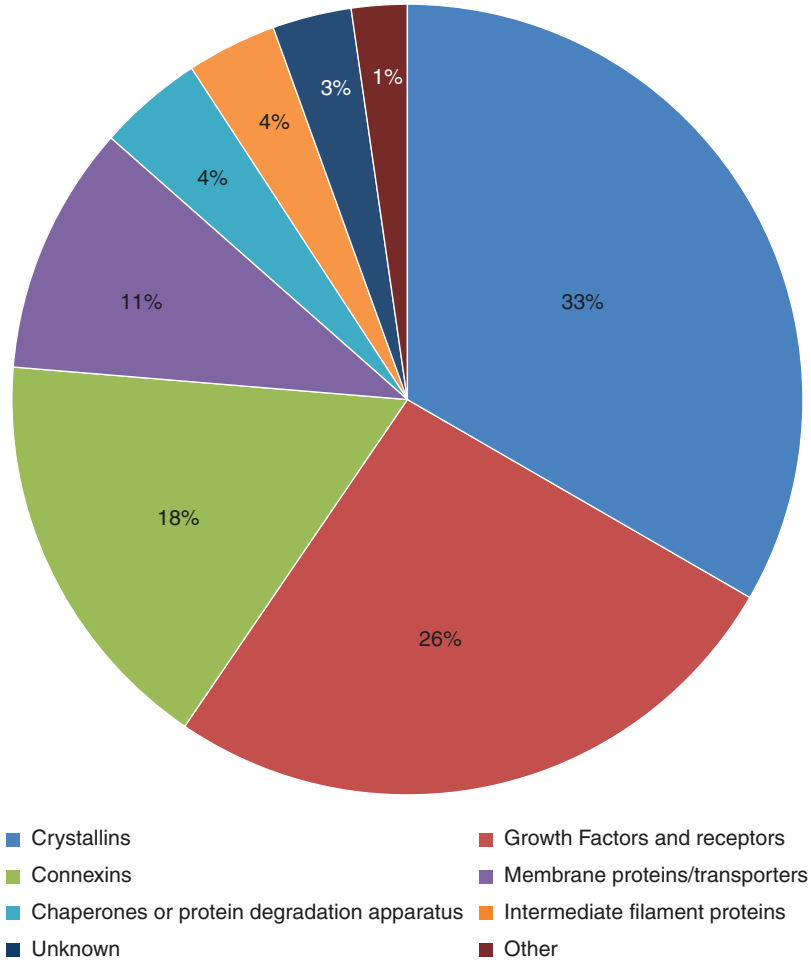

Fig. 22.1 Fraction of cataract families with mutations in genes belonging to specific pathways, processes, or protein families. Crystallins are the most commonly mutated genes in congenital cataract, followed closely by growth factors, connexins, and then membrane proteins. The remainder is caused by additional groups of genes important in a variety of metabolic and functional processes in the lens

22.4 Transcription and Developmental Factors

Although the process and mechanisms of lens development are still being elucidated, a number of transcription and developmental factors including *Pax6*, Rx, VSX2, MAF, FOXE3, EYA1, and PITX3 are critical for lens development [20–25]. Mutations in Pax6, which is expressed in the entire developing eye field, often are associated with aniridia, which is often accompanied by cataracts [26]. Mutations in PITX3 often cause posterior polar cataracts (70%), often associated with anterior segment mesenchymal dysgenesis (ASMD or ASD, affecting the lens, cornea, and iris). Mutations in NHS most often cause the Nance Horan syndrome (NHS), which includes cataracts, facial dysmorphism, dental abnormalities, and often developmental delay and mental retardation. Mutations in NHS often cause nuclear (39%) or sutural (39%) cataracts. In contrast, although it is expressed across most ocular tissues, mutations in HSF4 (heat shock factor 4) tend to cause isolated nuclear or lamellar cataracts as do mutations in *SIPAIL3*, which functions in epithelial cell morphogenesis and polarity. Overall, most mutations in transcription and developmental factors tend to result in autosomal dominant cataracts with a ratio of about 2.5/1, an interesting exception being MAF, which shows no autosomal recessive inheritance in ten independent families identified. Mutations in *TDRD7*, a widely expressed Tudor domain RNA binding protein of RNA granules that interact with STAU-1 ribonucleoproteins also cause cataract, probably related to the high levels of mRNA synthesis required during lens differentiation. Also included in this group is the ephrin receptor EPHA2, which, while not actually a transcription factor, but plays a major role in developmental processes in the eye and nervous system. Mutations in EPHA2 can cause both dominant and recessive congenital cataracts, as well as contributing to age-related cataracts [27–32].

22.5 Lens Crystallins

Crystallins are the most highly expressed proteins in the lens, comprising about 90% of the soluble protein. Their physical properties, especially close packing and stability, are critical for lens transparency. Both of these characteristics are probably responsible for the crystallins being the most commonly mutated genes implicated in human congenital cataracts. There are three classes of crystallins in humans encoded by multiple genes. The β-, and γ-crystallins are part of a large gene superfamily including spore coat protreins. The α-crystallins, comprising αA- and αB-crystallins, part of the small heat shock protein family, have chaperone-like activity binding but not recycling partially denatured proteins and forming large protein complexes with a protective role in the lens. In contrast to αA-crystallinα, which is largely confined to the lens, αB-crystallin is is found in multiple other tissues as well, binding but not recycling partially denatured proteins.

As damaged or mutant β- and γ-crystallins start to form irreversible aggregates that would eventually precipitate out of solution, they are bound by α-crystallins and held in soluble aggregates. However, if the mutation is severe enough to result in rapid denaturation without an intermediate molten globule state, they can escape binding by the α-crystallins and other chaperones in the lens, causing direct damage to the lens cells or initiating cellular processes such as the unfolded protein response (UPR) and apoptosis [33]. Similarly, although most pertinent to age-related cataracts, denaturation and binding of large amounts of crystallins can lead to high molecular weight aggregates large enough to scatter light themselves, and eventually overwhelm the α-crystallin chaperone system causing cataract [34]. Thus, denatured crystallins can lead to cataract directly by scattering light or more catastrophically by toxic effects on the lens cells and micro-architecture perhaps inducing the UPR and/or apoptosis [35].

As would be expected from the discussion above, most cataracts resulting from mutations in crystallins are autosomal dominant, with a

ratio of about 12:1 dominant to recessive. They are heavily biased toward nuclear or lamellar cataracts except for CRYAB cataracts of which 40% are posterior polar and CRYBB3 cataracts, 50% of which are cortical (Table 22.2). This is consistent with most crystallin mutations causing cataract by the proteins gaining a deleterious function, e.g., denaturing and precipitating with a toxic effect on the lens cell, thus inducing the UPR. There is growing support for this mechanism for a variety of crystallin and other mutations [36–40], although some crystallin mutations cause autosomal recessive cataracts. These include CRYAA (3 of 41), CRYAB (5 of 16), CRYBB1 (6 of 19), and CRYBA4 (1 of 5), suggesting that these crystallins might have additional functions in the lens than that of a structural crystallin. The α-crystallins are well known to function as molecular chaperones, but additional functions for the β-crystallins remain to be identified, and no recessive mutations have been identified for any γ-crystallin. Alternatively, mere haploinsufficiency for the crystallins causing autosomal recessive cataracts might be sufficient to impair lens transparency and function.

22.6 Gap Junction Proteins (Connexins)

Lacking blood vessels, the lens is dependent on gap junctions, intercellular channels composed of hexameric hemichannels from two adjacent cells joined to create gap junction channels, for communication and transfer of nutrients, especially between fiber cells. Lens junctions con-

Table 22.2 Clinician characteristics of cataracts by their genetic cause. (**a**) Fraction of mutations in specific genes resulting in cataracts of various morphologies. (**b**) Inheritance patterns for cataracts caused by specific genes

a

	GJA8	GJA3	CRYAA	CRYAB	CRYBB1	CRYBB2	CRYBB3	CRYBA3	CRYBA4	CRYGC	CRYGD
nuclear	0.56	0.51	0.59	0.40	0.75	0.33	0.50	0.47	0.50	0.76	0.43
lamellar [a]	0.26	0.29	0.22	0.20	0.00	0.17	0.00	0.22	0.33	0.24	0.07
sutural	0.06	0.05	0.02	0.00	0.06	0.04	0.00	0.19	0.00	0.00	0.02
cortical	0.00	0.02	0.02	0.00	0.13	0.13	0.50	0.08	0.00	0.00	0.02
PP[b]	0.06	0.05	0.05	0.40	0.06	0.00	0.00	0.03	0.00	0.00	0.05
AP[c]	0.00	0.00	0.10	0.00	0.00	0.00	0.00	0.00	0.17	0.00	0.02
corralliform	0.00	0.07	0.00	0.00	0.00	0.04	0.00	0.00	0.00	0.00	0.32
cerulean	0.00	0.00	0.00	0.00	0.00	0.25	0.00	0.00	0.00	0.00	0.07
PSC	0.06	0.00	0.00	0.00	0.00	0.04	0.00	0.00	0.00	0.00	0.00
% defined[d]	0.58	0.77	0.89	0.56	0.55	0.65	0.50	0.91	0.75	0.62	0.79
% other[e]	0.42	0.23	0.11	0.44	0.45	0.35	0.50	0.00	0.25	0.38	0.21

CRYGS	NHS	HSF4	EPHA2	FOXE3	MAF	PITX3	BFSP1	BFSP2	AQP0	GCNT2	FYCO1
0.11	0.39	0.25	0.50	0.25	0.33	0.06	0.50	0.17	0.45	0.50	1.00
0.33	0.00	0.45	0.05	0.00	0.25	0.00	0.25	0.17	0.15	0.25	0.00
0.22	0.39	0.05	0.00	0.00	0.00	0.00	0.00	0.42	0.15	0.00	0.00
0.33	0.18	0.20	0.27	0.38	0.00	0.06	0.25	0.25	0.15	0.00	0.00
0.00	0.00	0.00	0.09	0.00	0.25	0.71	0.00	0.00	0.05	0.00	0.00
0.00	0.00	0.05	0.05	0.00	0.08	0.00	0.00	0.00	0.00	0.25	0.00
0.00	0.04	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.00	0.00	0.00	0.00	0.38	0.08	0.00	0.00	0.00	0.05	0.00	0.00
0.00	0.00	0.00	0.05	0.00	0.00	0.18	0.00	0.00	0.00	0.00	0.00
1.13	0.50	0.71	0.96	0.42	0.63	0.61	0.57	1.00	0.61	0.27	0.67
0.00	0.50	0.29	0.04	0.58	0.37	0.39	0.43	0.00	0.39	0.73	0.33

Table 22.2 (continued)

b

	GJA8	GJA3	CRYAA	CRYAB	CRYBB1	CRYBB2	CRYBB3	CRYBA3	CRYBA4	CRYGC	CRYGD
AD	49	44	38	11	13	28	3	26	4	30	51
AR	4	1	3	5	6	0	2	0	1	0	0
AD/AR	12.25	44.00	12.67	2.20	2.17	na	1.50	na	4.00	na	na
group ratio	18.60		12.47								
% AD	0.92	0.98	0.93	0.69	0.68	1.00	0.60	1.00	0.80	1.00	1.00

CRYGS	NHS	HSF4	EPHA2	FOXE3	MAF	PITX3	BFSP1	BFSP2	AQP0	GCNT2	FYCO1	Total
8	0	16	18	6	10	27	2	8	29	0	0	421
0	0	7	5	11	0	1	2	2	1	12	14	77
na	na	2.29	3.60	0.55	na	27.00	1.00	4.00	29.00	0.00	0.00	5.47
			2.54				2.50		varied			
1.00	na	0.70	0.78	0.35	1.00	0.96	0.50	0.80	0.97	0.00	0.00	0.85

[a]Lamellar or zonular
[b]Posterior polar
[c]Anterior polar
[d]Described as one of the above morphologies
[e]Not described or other morphology

tain *GJA3* (encoding connexin 46) and *GJA8* (encoding connexin 50) [41, 42]. Mutations in *GJA3* and *GJA8* have been implicated largely in autosomal dominant human cataract (92% and 98%, respectively) with a few autosomal recessive families reported for each. They also usually cause nuclear or lamellar cataracts (Table 22.2). Because of their multimeric nature, some missense mutations in connexins can have a dominant negative effect on gap junction function as exemplified by the p.P88S change in GJA8, [43]. The mutant protein is incorporated into the gap junction structure and inactivates the entire junction [44]. Other connexin mutations do not inhibit channel function by normal connexins synthesized from unaffected genes but might be retained in or near the endoplasmic reticulum such as the p.46fs380 change or fail to be incorporated into the gap junction at all [45] such as a p.N63S missense mutation, both in GJA3. Some gap junction mutations causing retention in the endoplasmic reticulum can induce the UPR [46], and conversely, mutations causing enhanced hemichannel function also can lead to cell death and cataract [47]. GJA8 mutant cataracts have also been associated with microcornea with or without myopia and occasionally with microphthalmia while GJA3 mutations are usually isolated.

22.7 Membranes and Their Proteins

In addition to the Gap Junction Proteins, lens epithelia require large amounts of membranes when they elongate to form fiber cells and must synthesize the lipids making up the membranes as well as the protein components required for circulation of water and small molecules critical for lens fiber cell homeostasis and function. Mutations in *SLC16A12*, a transmembrane protein functioning in creatine transport can cause dominant cataracts, sometimes accompanied by microcornea or renal glycosuria. Aquaporins are integral membrane proteins that generally act as water channels. Mutations in aquaporin 0 (*AQP0*, also known as major intrinsic protein, *MIP*) are also a major contributor to inherited congenital cataracts, usually nuclear, with some lamellar, sutural, or cortical (Table 22.2). Similar to some gap junction mutations, autosomal dominant

E134G and T138R mutations inhibit normal trafficking of AQP0 to the plasma membrane [48] and also interfere with water channel activity by normal AQP0, consistent with a dominant negative mechanism. *LIM2* is required for cell junctions in lens fiber cells.

TMEM114, a transmembrane glycoprotein member of a group of calcium channel gamma subunits, can also cause cataracts when mutated. Mutations in LEMD2, a transmembrane protein found in the nuclear membrane important for nuclear organization and cell signaling, can also cause autosomal recessive cataracts. While mutations in the wolframin ER transmembrane glycoprotein (WFS1) usually cause Wolfram syndrome, they have also been described in a family with isolated cataracts. Mutations in acylglycerol kinase (*AGK*), a mitochondrial membrane protein, acts as a lipid kinase required for synthesis of phosphatidic and lysophosphatidic acids are associated with autosomal recessive cataracts, as are mutations in lanosterol synthase (LSS), which is required for synthesis of cholesterol. These are possibly related to the large amounts of membrane components required to be synthesized during fiber cell differentiation, although lanosterol has been shown to act as a chaperone for denatured crystallins [49].

22.8 Beaded Filament and Other Intermediate Filament Proteins

Intermediate filaments are cytoskeletal proteins with an average diameter of around 10 nm. In the lens, these include vimentin filaments, which are present in the anterior epithelial cells but are replaced by lens-specific beaded filaments as the cells differentiate into fiber cells. Beaded filaments are composed of BFSP1 (CP115, filensin) and BFSP2 (CP49, phakinin), both highly divergent members of the intermediate filament protein family. About 50% of mutations in BFSP1 cause nuclear cataracts while about 42% of mutations in BFSP2 cause sutural cataracts (Table 22.2). Mutations in vimentin can cause autosomal dominant cataracts, while those in BFSPs can be either dominant or recessive, with missense mutations tending to cause dominant cataracts, while nonsense mutations and frameshift causing deletions resulting in premature termination tend to cause recessive cataracts. Mutations in COL4A1 can cause dominant cataracts, and mutations in prolyl 3-hydroxylase 2 (P3H2, also known as LEPREL1), which is active in collagen chain crosslinking, can cause cataracts, sometimes accompanied by ectopia lentis and high myopia.

22.9 Chaperones and Protein Degradation

As lens fiber cells lack nuclei, they also lack protein synthesis and their proteins must last for the lifetime of the individual. In order to facilitate this, the lens contains high levels of chaperones such as the α-crystallins, although these also perform a more standard role as crystallin structural proteins in the lens. In this light, a mutation in UNC45B, a co-chaperone for HSP90 has been implicated in congenital cataract. Conversely, lens fiber cell differentiation also requires elimination of all organelles and their associated proteins, requiring highly active protein degradation systems. Mutations in *CHMP4B*, part of the endosomal sorting complex required for transport and autophagy, have been shown to cause autosomal dominant posterior polar or subcapsular cataract. Mutations in Ras-related GTP binding A (RRAGA), a component of the mTORC pathway, have been implicated in autosomal dominant cataracts. Mutations in the mitochondrial chaperone and protein degradation protease lon peptidase 1(LONP1) can also cause recessive cataracts, emphasizing the importance of mitochondrial function in the lens epithelia for lens transparency. *FYCO1 is* a scaffolding protein active in microtubule transport of lysosomes including autophagic vesicles. Mutations in *FYCO1* can cause autosomal recessive cataracts, consistent with an important role for autophagic vesicles in organelle degradation as equatorial epithelia differentiate into lens fiber cells. Interestingly,

all cataracts resulting from FYCO1 so far are nuclear. Finally, mutations in *EPG5*, a key regulator of autophagy that is active in autolysosome formation, while they have not been shown to cause isolated cataracts, do cause Vici syndrome, which includes cataracts [50].

22.10 Other Genes and Pathways

GCNT2 is the I-branching enzyme for poly-N-acetyllactosaminoglycans. In addition to determining the I (usually seen in children) and I (usually seen in adults) blood types it influences the epithelial-to-mesenchymal transition and cell migration, probably by influencing E-cadherin expression, and can cause autosomal recessive cataracts when mutated, about 50% of which are nuclear and 25% are lamellar and anterior polar, each. Mutations in *TAPT1*, which can disrupt Golgi structure and trafficking, can cause autosomal recessive cataracts, as can mutations in aldo-keto reductase family 1 member E2 (*AKR1E2*) and renalase (*RNLS*, FAD-dependent amine oxidase). Interestingly, mutations in the iron-responsive element of ferritin L (light chain, *FTL*) cause the hyperferritinemia-cataract syndrome in which loss of translational control results in massive overexpression of FTL that crystallizes in the lens and gives granular opacities in the nucleus and cortex. This example of an extraneous protein expressed at high levels in the lens emphasizes the requirement that crystallins or other proteins must be exceptionally soluble and stable to be expressed at crystallin-like levels without causing dysfunction. Finally, *TDRD7* is a widely expressed Tudor domain RNA binding and processing protein of RNA granules that also causes cataract when mutated, probably related to the high levels of mRNA synthesis required during lens differentiation.

22.11 Pathology

As mentioned above, cataracts have multiple causes, and thus present with different pathological findings. However, these can basically be grouped into two broad categories. Some congenital cataracts result from mutations with catastrophic effects on the protein, causing gross structural changes and precipitation or changes of similar impact in other lens components. The denatured proteins either escape or overwhelm binding by α-crystallin or other lens chaperones and are toxic to lens cells interfering with their proper differentiation and causing death and degeneration, often through the unfolded protein response (UPR) and apoptosis. These mutations are often associated with breakdown of the lens microarchitecture, including degeneration and perhaps calcification of lens fiber cells and eventually formation of large lacunae filled with proteinaceous debris with rupture of the lens capsule in the most severe cases. These cause large fluctuations in optical density with resultant light scattering. These are best studied in animal models of inherited congenital cataracts, with one example being a c.215+1G >A splice mutation in *CRYBA1* causing a p.Ile33_Ala119del mutant βA3/A1-crystallin protein [37], and many others also being well studied [36, 38, 51, 52].

In addition, light scattering and opacity will occur if there is a significant amount of high molecular weight (HMW) protein aggregates 1000 Å or more in size, even though the microarchitecture of the lens is well preserved [13, 14]. The short-range ordered packing of the crystallins, which must exist in a homogeneous phase for transparency, is important as is their stability over time. As increasing amounts of unstable mutant crystallins begin to denature and are bound by α-crystallins the size of the aggregates increases toward the 1000 Å limit. Eventually, the limit is passed, and light scattering begins, progressing to a clinically significant cataract when vision is impaired, although this mechanism appears to be more common in age-related cataracts. This can occur with normal lens histology, but eventually the α-crystallin is saturated, and HMW aggregates begin to come out of solution [34]. This can result in toxic effects on the lens fiber cells, with cellular degeneration and calcification, as seen in a rapamycin-induced model [53].

22.12 Clinical Features and Classification of Congenital Cataracts

Human cataracts can be classified using a variety of characteristics such as their age of onset, location in the lens, size, pattern or shape, density, and rate of progression. They can also be classified by their etiology, with about 30% of congenital cataracts in developed countries of genetic etiology, with most of the remainder idiopathic and a few percent due to intrauterine infection [9], although the fraction associated with infections and trauma can increase considerably in less developed nations [54]. Cataracts can also be classified by age at onset. Cataracts visible within the first year of life are generally considered congenital or infantile cataracts, the subject of this chapter. Juvenile cataracts are visible within the first decade of life, presenile cataracts are seen before the age of 45–55 years, and age-related cataracts with onset after 45–55 years.

Perhaps most usefully, cataracts can be classified by their appearance and anatomic location in the lens. The most commonly used system is that described by Merin, in which the cataract is classified as total (mature or complete), polar (including anterior or posterior), zonular (including nuclear, lamellar, and sutural), and capsular or membranous [55]. Since equatorial epithelia migrate laterally and then elongate and invert before moving into the nucleus in a concentrically ordered fashion during lens development, the location of a lens opacity can suggest the time at which the pathology initiated. When correlated the developmental expression of lens genes can suggest the genetic cause of the cataract. Nuclear opacities are likely to result from genes active during formation of the embryonic (months 1–3), fetal (months 3–9), or infantile (after birth), nucleus. Lens fiber cells continue to be laid down throughout life, so that lens opacities developing postnatally tend to present as cortical opacities or sometimes subcapsular opacities, which are also often associated with topical steroid drugs or radiation.

Polar opacities involve either the anterior (Fig. 22.2a) or the posterior (Fig. 22.2b) pole of the lens and may include the posterior subcapsular lens cortex (Fig. 22.2c) extending to the lens capsule. In addition to genetic causes, posterior subcapsular cataracts can occur secondarily to a variety of insults. Although posterior subcapsular cataracts have been associated with proliferation of Wedl cells (dysplastic bladder-like fiber cells) at least some posterior subcapsular cataracts are caused by abnormalities of the posterior fiber ends [46]. Polar opacities affecting both anterior and posterior poles are called bipolar. About 40% of Isolated anterior polar cataracts are caused by mutations in CRYAA and 30% of posterior polar cataracts are caused by mutations in *PITX3*, while 43% of posterior subcapsular cataracts are caused by mutations in *PITX3* and 29% by mutations in *GJA8*. (Table 22.3). Anterior polar cataracts are usually small, bilateral, and nonprogressive and do not impair vision. Anterior polar cataracts can be associated with microphthalmos, persistent pupillary membrane, or anterior lenticonus, while posterior polar cataracts can be associated with abnormalities of the posterior capsule including lentiglobus, lenticonus or with remnants of the tunica vasculosa. Although they are usually stable over time, they may progress, and can be associated with capsular fragility.

Nuclear cataracts show opacities in the fetal or fetal and embryonic lens nucleus (Fig. 22.2d, e). They can show a wide variation in severity, from dense opacities involving the entire nucleus to pulverulent (or dusty appearing) cataracts involving only the central nucleus or discrete layers (see below) and can be caused by mutations in a wide variety of genes.

Lamellar cataracts (Fig. 22.2f, g) affect lens fibers, which are formed at the same time, resulting in a shell-like opacity at the level at which the fibers were laid down at the time of the presumed insult. They are the most common type of congenital cataract and can be caused by a wide variety of genes (Table 22.3). Some cataracts have associated arcuate opacities within the cortex called cortical riders (Fig. 22.2g).

Sutural or stellate cataracts (Fig. 22.2h, i) affect the regions of the fetal nucleus on which the ends (or feet) of the lens fibers converge, called the Y sutures. Even in normal lenses, the sutures are visible by slit lamp biomicroscopy

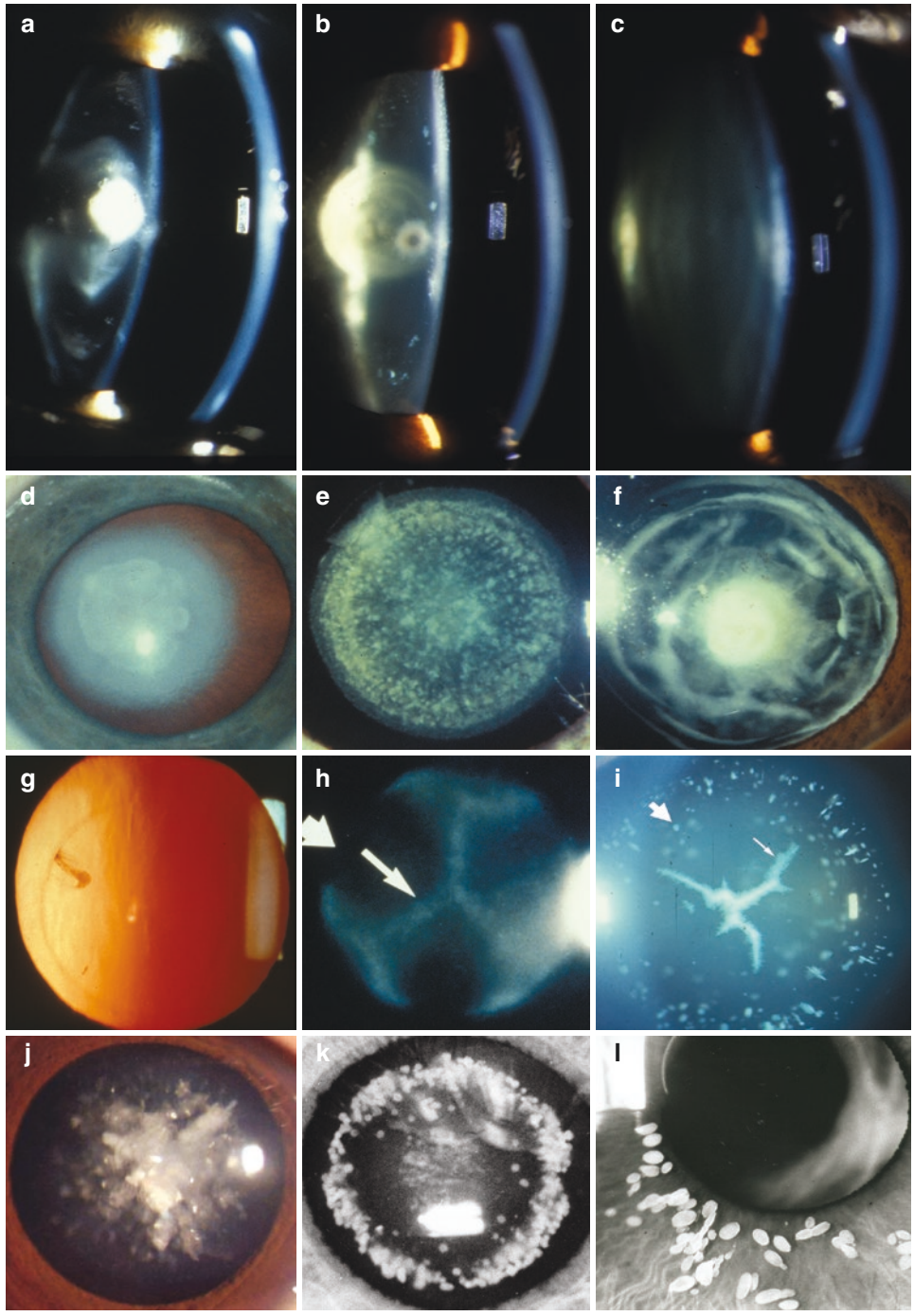

Fig. 22.2 Examples of cataract morphologies. (**a**) Dense anterior polar cataract visible on slit lamp examination. Some opacification of the lens nucleus is also visible. (**b**) Dense posterior polar cataract is visible on slit lamp examination. A smaller anterior polar cataract is also visible so that this would be termed a bipolar cataract. (**c**) Posterior subcapsular cataract. (**d**) Dense nuclear cataract. The macula and optic nerves are obscured by this cataract. (**e**) Punctate nuclear cataract. (**f**) Multi-lamellar cataract with an anterior polar component. (**g**) Very fine nuclear lamellar pulverulent cataract viewed by retroillumination with a cortical rider at 10 o'clock. (**h**) Sutural cataract with a nuclear lamellar component. (**i**) Sutural cataract with a cortical cerulean or blue dot component. (**j**) Corraliform cataract (courtesy of Li et al. [67]). (**k**, **l**) Ant's egg cataract (courtesy of Hansen et al. [56])

Table 22.3 Fractions of cataract types caused by specific genes

	nuclear	lamellar[a]	sutural	cortical	PP[b]	AP[c]	corralliform	cerulean	PSC
GJA8	0.09	0.12	0.05	0.00	0.06	0.00	0.00	0.00	0.29
GJA3	0.10	0.16	0.05	0.02	0.06	0.00	0.16	0.00	0.00
CRYAA	0.12	0.12	0.03	0.02	0.06	0.40	0.00	0.00	0.00
CRYAB	0.02	0.03	0.00	0.00	0.13	0.00	0.00	0.00	0.00
CRYBB1	0.06	0.00	0.03	0.05	0.03	0.00	0.00	0.00	0.00
CRYBB2	0.04	0.05	0.03	0.07	0.00	0.00	0.05	0.43	0.14
CRYBB3	0.01	0.00	0.00	0.05	0.00	0.00	0.00	0.00	0.00
CRYBA3	0.08	0.10	0.19	0.07	0.03	0.00	0.00	0.00	0.00
CRYBA4	0.01	0.03	0.00	0.00	0.00	0.10	0.00	0.00	0.00
CRYGC	0.08	0.06	0.00	0.00	0.00	0.00	0.00	0.00	0.00
CRYGD	0.09	0.04	0.03	0.02	0.06	0.10	0.74	0.21	0.00
CRYGS	0.00	0.04	0.05	0.07	0.00	0.00	0.00	0.00	0.00
NHS	0.05	0.00	0.30	0.12	0.00	0.00	0.05	0.00	0.00
HSF4	0.02	0.12	0.03	0.10	0.00	0.10	0.00	0.00	0.00
EPHA2	0.05	0.01	0.00	0.14	0.06	0.10	0.00	0.00	0.14
FOXE3	0.01	0.00	0.00	0.07	0.00	0.00	0.00	0.21	0.00
MAF	0.02	0.04	0.00	0.00	0.09	0.10	0.00	0.07	0.00
PITX3	0.00	0.00	0.00	0.02	0.38	0.00	0.00	0.00	0.43
EYA1	0.01	0.01	0.00	0.02	0.00	0.00	0.00	0.00	0.00
BFSP2	0.01	0.03	0.14	0.07	0.00	0.00	0.00	0.00	0.00
AQP0	0.04	0.04	0.08	0.07	0.03	0.00	0.00	0.07	0.00
CHMP4B	0.01	0.01	0.00	0.00	0.00	0.10	0.00	0.00	0.00
FYCO1	0.05	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Frequencies are calculated from CAT-MAP
[a]Lamellar or zonular
[b]Posterior polar
[c]Anterior polar

as an upright Y anteriorly and an inverted Y posteriorly. About 30% of sutural cataracts result from mutations in NHS, while the remainder are caused by multiple additional genes, with 19% associated with mutations in CRYBA3 and 4% with mutations in BFSP2 (Table 22.3). Cerulean, or blue dot cataracts are characterized by numerous small bluish opacities in the cortical and nuclear areas of the lens (Fig. 22.2i). About 43% of cerulean cataracts are caused by mutations in CRYBB2 while another 21% are caused by mutations in CRYGD and FOXE3 each (Table 22.3). Coralliform cataracts are dispersed popcorn or coral-like cataracts primarily in the nuclear area (Fig. 22.2j). About 74% of coralliform cataracts are caused by mutations in CRYGD, with about 16% caused by mutations in GJA3 (Table 22.3). Other varieties of cataract can usually be described through a combination of the above terms, although there are some specialized cataracts that have unique characteristics, such as the ant's egg cataract (Fig. 22.2k, l), in which a mutation in connexin 46 causes beaded structures like ants eggs to form from the lens [56, 57].

Mature or total cataracts may represent a late stage of any of the above types of cataracts, in which the entire lens is opacified. Membranous cataracts result from resorption of lens proteins, often from a traumatized lens, with resulting fusion of the anterior and posterior lens capsules to form a dense white membrane. They usually cause severe loss of vision.

22.13 Genetic Aspects of Congenital Cataracts

As has been mentioned above, about 85% of inherited congenital cataracts show an autosomal dominant inheritance pattern, although this varies significantly depending on the population and study (Table 22.2b). In addition, there

is a significant variation in inheritance patterns among the various genes. All cataracts caused by CRYBB2, CRYBA3, CRYGC, CRYGD, CRYGS, and MAF are dominant, which suggests that there might be redundant biological systems for these proteins in the lens so that their absence by itself would not disrupt lens biology and transparency. In contrast, the presence of autosomal recessive inheritance patterns of cataracts caused by CRYBB3 and CRYBA4 suggests that they might have an irreplaceable role in lens biology in addition to that of structural lens crystallins. In contrast, the absence of autosomal dominantly inherited cataracts resulting from GCNT2 and FYCO1 suggests that these cataracts all result from the absence of the functional protein, implying a unique and necessary role for these genes in the lens.

22.14 Clinical Aspects of Congenital Cataracts

Cataracts that interfere with vision significantly, require early diagnosis and prompt evaluation to determine their etiology if possible. As one example, treatment of galactosemia in early life will permit recovery of the lens to normal clarity. Conversely, if lens clarity is significantly compromised, surgical treatment might be required. However, in general, severe congenital cataracts require surgical treatment to allow the functional retinal–cortical connections required for vision to form successfully.

Because unequal ocular input into cortical neurons due to unilateral form deprivation results in more severe visual deficits than does bilateral deprivation [58–60] a unilateral dense congenital cataract is generally considered to be a surgical emergency while bilateral dense cataracts allow more routine scheduling. Thus, unilateral dense cataracts can be operated successfully in the first weeks of life, while bilateral cataracts can be operated successfully until 3 months of age. With prompt surgery, the visual prognosis is better for bilateral as compared with unilateral cases and in less dense cataracts as compared with total opacities. Chronic dilation of the pupil in small centrally located congenital cataracts, allowing the infant to see around the cataract, may be useful in some cases when cataract surgery may not be immediately feasible. When congenital cataracts are associated with other ocular abnormalities and/or systemic disease, a poorer visual outcome often results [60–62]. Finally, it should be emphasized that communication between clinicians, therapists, and teachers combined with counseling of patients is very important in the treatment of young cataract patients and their families [63]. More recently, there has been much interest in small molecule chaperones that might stabilize or even renature damaged crystallins [49, 64], although these would probably be more relevant for treatment of age-related cataracts. Finally, promising results have been obtained by using lens regeneration rather than inserting an intraocular lens, although this approach is still highly experimental [65].

22.15 Molecular Biology of Congenital Cataracts

As described briefly above, congenital cataracts tend to result from mutations with severe functional consequences for the mutant protein structure and function and are often accompanied by significant disarray of the lens microarchitecture, as shown in a number of model systems [36–38, 51, 52]. This breakdown in lens microarchitecture is usually accompanied by induction of the unfolded protein response with subsequent activation of apoptotic processes. This pathological process contrasts with that seen in most age-related cataracts, which are characterized by increased sensitivity of mutant or variant proteins being acted on by environmental factors to give a gradual decrease in stability followed by denaturation and binding by α-crystallin [66]. These two mechanisms are not exclusive, as potentially toxic high molecular weight protein aggregates can form when the lens cell α-crystallin becomes saturated with denatured crystallins, resulting in damage to lens cells.

22.16 Laboratory and Clinical Evaluation of Congenital Cataracts

Cataracts may be examined clinically in a variety of ways. Looking at the pupil with a handlight, will show a white opacity (termed leukocoria). Direct ophthalmoscopy can suggest the effect of the cataract on visual function since sharp visualization of retinal components such as the optic nerve and macula suggest that the patient can see out as well. In addition, a lens opacity can be silhouetted in the red reflex using either direct or retroillumination. However, a more definitive description of the lens opacity requires slit lamp biomicroscopy pupillary dilation, allowing both direct and retroillumination with magnification sufficient to visualize the lens opacity and define its morphological features.

After establishing the significance and classification of the cataract by type, the evaluation of a cataract consists of a careful assessment of its effect on the visual acuity and function. In very young children from 0 to 3 years old observation-fixing, following, covering alternative eyes, and observing the response are useful. If more accurate evaluation is required, visually evoked cortical responses, preferential looking, or the forced choice method may be used. As children grow older, the illiterate E or Allen cards using picture differentiation can be used, and once the child has mastered the alphabet a logEDTRS or Snellen chart may be used.

Not all congenital cataracts are genetic in origin, with perhaps the most common differential diagnosis being prenatal infections by viruses or other infectious diseases. Of these, rubella directly involves the lens while other infectious diseases such as toxoplasmosis, mumps, measles, chickenpox, herpes simplex, herpes zoster, influenza, echovirus type 3, and cytomegalovirus, cause uveitis (ocular inflammation). A good screen for these diseases is TORCH titers. Developmental disorders due to prematurity, with birth anoxia, low birth weight, central nervous system involvement characterized by seizures, cerebral palsy or hemiplegia, and retinopathy of prematurity. Multisystem syndromes including chromosomal abnormalities can be suggested by the clinical examination and tested by chromosome analysis or blood and urine chemistries specific for the disorder suspected. Some perinatal–postnatal problems such as hyperglycemia (associated with signs of diabetes) and hypocalcemia (usually characterized by tetany), can cause cataracts and can be detected using serum chemistries. Finally, cataracts may be associated with other ocular abnormalities including anterior chamber abnormalities such as Reiger syndrome, primary hyperplastic vitreous, and aniridia, or with retinopathies such as retinal dysplasia, Norrie disease, and microphthalmia.

22.17 Summary

Inherited congenital cataracts affect all populations throughout the world and are a significant cause of blindness in infants that require early diagnosis and prompt treatment. While clinically identical cataracts can be caused by mutations in different genes and identical mutations in the same gene can cause clinically different cataracts, it is possible to identify general correlations between some of the causative genes and specific cataract morphologies, which might be useful in guiding genetic diagnosis. Genes associated with congenital cataracts tend to belong to molecular or biochemical pathways important for lens development and homeostasis. While we have identified many genes, there remains much work to be done both in identifying the remaining causative genes and in understanding the molecular pathologies that lead to the common endpoint of lens opacity or cataract.

References

1. Benedek GB. Theory of transparency of the eye. Appl Opt. 1971;10:459–73.
2. Delaye M, Tardieu A. Short-range order of crystallin proteins accounts for eye lens transparency. Nature. 1983;302:415–7.
3. Vrensen G, Kappelhof J, Willikens B. Aging of the human lens. Lens Eye Toxicol Res. 1990;7:1–30.

4. Harding CV, Maisel H, Chylack LT. The structure of the human cataractous lens. In: Maisel H, editor. The ocular lens. New York: Marcel Dekker; 1985. p. 405–33.
5. Benedek GB, Chylack LT, Libondi T, Magnante P, Pennett M. Quantitative detection of the molecular changes associated with early cararactogenesis in the living human lens using quasielastic light scattering. Curr Eye Res. 1987;6:1421–32.
6. Bettelheim FA. Physical basis of lens transparency. In: Maisel H, editor. The ocular lens. New York: Marcil Dekker; 1985. p. 265–300.
7. Francois J. Genetics of cataract. Ophthalmologica. 1982;184:61–71.
8. Merin S. Inherited cataracts. In: Merin S, editor. Inherited eye diseases. New York: Marcel Dekker; 1991. p. 86–120.
9. Haargaard B, Wohlfahrt J, Fledelius HC, Rosenberg T, Melbye M. A nationwide Danish study of 1027 cases of congenital/infantile cataracts: etiological and clinical classifications. Ophthalmology. 2004;111(12):2292–8.
10. Chen J, Wang Q, Cabrera PE, Zhong Z, Sun W, Jiao X, et al. Molecular genetic analysis of pakistani families with autosomal recessive congenital cataracts by homozygosity screening. Invest Ophthalmol Vis Sci. 2017;58(4):2207–17.
11. Aldahmesh MA, Khan AO, Mohamed JY, Hijazi H, Al-Owain M, Alswaid A, et al. Genomic analysis of pediatric cataract in Saudi Arabia reveals novel candidate disease genes. Genet Med. 2012 Dec;14(12):955–62.
12. Scott MH, Hejtmancik JF, Wozencraft LA, Reuter LM, Parks MM, Kaiser-Kupfer MI. Autosomal dominant congenital cataract: Interocular phenotypic heterogeneity. Ophthalmology. 1994;101(5):866–71.
13. Shiels A, Bennett TM, Hejtmancik JF. Cat-Map: putting cataract on the map. Mol Vis. 2010;16:2007–15.
14. Rafferty NS. Lens morphology. In: Maisel H, editor. The ocular lens. New York: Marcel Dekker; 1985. p. 1–60.
15. Brown NAP, Bron AJ. Lens structure. In: Brown NAP, Bron AJ, editors. Lens disorders: a clinical manual of cataract diagnosis. Oxford: Butterworth-Heinemann; 1996. p. 32–47.
16. Goodenough DA, Dick JSB, Lyons JE. Lens metabolic cooperation: a study of mouse lens transport and permeability visualized with freeze-substitution autoradiography and electron microscopy. J Cell Biol. 1980;86:576–89.
17. Gorthy WC, Snavely MR, Berrong ND. Some aspects of transport and digestion in the lens of the normal young adult rat. Exp Eye Res. 1971;12:112–9.
18. Kuszak JR. Embryology and anatomy of the lens. In: Tasman W, Jaeger EA, editors. Duane's clinical ophthalmology. Philadelphia: J.B. Lippincott; 1990. p. 1–9.
19. Alcala H, Maisel H. Biochemistry of lens plasma membranes and cytoskeleton. In: Maisel H, editor. The ocular lens. New York: Marcel Dekker; 1985. p. 169–222.
20. Halder G, Callaerts P, Gehring WJ. Induction of ectopic eyes by targeted expression of the eyeless gene in Drosophila [see comments]. Science. 1995;267:1788–92.
21. Mathers PH, Grinberg A, Mahon KA, Jamrich M. The Rx homeobox gene is essential for vertebrate eye development. Nature. 1997;387(6633):603–7.
22. Hanson I, Churchill A, Love J, Axton R, Moore T, Clarke M, et al. Missense mutations in the most ancient residues of the PAX6 paired domain underlie a spectrum of human congenital eye malformations. Hum Mol Genet. 1999;8(2):165–72.
23. Walther C, Gruss P. Pax-6, a murine paired box gene, is expressed in the developing CNS. Development. 1991;113:1435–49.
24. Fujiwara M, Uchida T, Osumi-Yamashita N, Eto K. Uchida rat (rSey): a new mutant rat with craniofacial abnormalities resembling those of the mouse Sey mutant. Differentiation. 1994;57:31–8.
25. Inoue M, Kamachi Y, Matsunami H, Imada K, Uchikawa M, Kondoh H. PAX6 and SOX2-dependent regulation of the Sox2 enhancer N-3 involved in embryonic visual system development. Genes Cells. 2007;12(9):1049–61.
26. Brewer C, Holloway S, Zawalnyski P, Schinzel A, FitzPatrick D. A chromosomal deletion map of human malformations. Am J Hum Genet. 1998;63(4):1153–9.
27. Shiels A, Bennett TM, Knopf HL, Maraini G, Li A, Jiao X, et al. The EPHA2 gene is associated with cataracts linked to chromosome 1p. Mol Vis. 2008;14:2042–55.
28. Zhang T, Hua R, Xiao W, Burdon KP, Bhattacharya SS, Craig JE, et al. Mutations of the EPHA2 receptor tyrosine kinase gene cause autosomal dominant congenital cataract. Hum Mutat. 2009;30(5):E603–E11.
29. Jun G, Guo H, Klein BE, Klein R, Wang JJ, Mitchell P, et al. EPHA2 is associated with age-related cortical cataract in mice and humans. PLoS Genet. 2009;5(7):e1000584.
30. Kaul H, Riazuddin SA, Shahid M, Kousar S, Butt NH, Zafar AU, et al. Autosomal recessive congenital cataract linked to EPHA2 in a consanguineous Pakistani family. Mol Vis. 2010;16:511–7.
31. Sundaresan P, Ravindran RD, Vashist P, Shanker A, Nitsch D, Talwar B, et al. EPHA2 Polymorphisms and Age-Related Cataract in India. PLoS One. 2012;7(3):e33001.
32. Tan W, Hou S, Jiang Z, Hu Z, Yang P, Ye J. Association of EPHA2 polymorphisms and age-related cortical cataract in a Han Chinese population. Mol Vis. 2011;17:1553–8.
33. Moreau KL, King JA. Cataract-causing defect of a mutant gamma-crystallin proceeds through an aggregation pathway which bypasses recognition by the alpha-crystallin chaperone. PLoS One. 2012;7(5):e37256.

34. Datiles MB, 3rd, Ansari RR, Yoshida J, Brown H, Zambrano AI, Tian J, et al. Longitudinal study of age-related cataract using dynamic light scattering: loss of alpha-crystallin leads to nuclear cataract development. Ophthalmology. 2016;123(2):248-254.
35. Shiels A, Hejtmancik JF. Mutations and mechanisms in congenital and age-related cataracts. Exp Eye Res. 2017;156:95–102.
36. Andley UP, Goldman JW. Autophagy and UPR in alpha-crystallin mutant knock-in mouse models of hereditary cataracts. Biochim Biophys Acta. 2015;1860(1):234–9.
37. Ma Z, Yao W, Chan CC, Kannabiran C, Wawrousek E, Hejtmancik JF. Human betaA3/A1-crystallin splicing mutation causes cataracts by activating the unfolded protein response and inducing apoptosis in differentiating lens fiber cells. Biochim Biophys Acta. 2016;1862:1214–27.
38. Zhou Y, Bennett TM, Shiels A. Lens ER-stress response during cataract development in Mip-mutant mice. Biochim Biophys Acta. 2016;1862(8):1433–42.
39. Berthoud VM, Minogue PJ, Lambert PA, Snabb JI, Beyer EC. The cataract-linked mutant Connexin50D47A causes endoplasmic reticulum stress in mouse lenses. J Biol Chem. 2016;291(34):17569–78.
40. Li L, Fan DB, Zhao YT, Li Y, Kong DQ, Cai FF, et al. Two novel mutations identified in ADCC families impair crystallin protein distribution and induce apoptosis in human lens epithelial cells. Sci Rep. 2017;7(1):17848.
41. Zampighi GA, Hall JE, Kreman M. Purified lens junctional protein forms channels in planner lipid films. Proc Natl Acad SciUSA. 1985;82:8468–72.
42. Jiang JX, Goodenough DA. Heteromeric connexons in lens gap junction channels. Proc Natl Acad Sci USA. 1996;93:1287–91.
43. Minogue PJ, Liu X, Ebihara L, Beyer EC, Berthoud VM. An aberrant sequence in a connexin46 mutant underlies congenital cataracts. J Biol Chem. 2005;280(49):40788–95.
44. Berthoud VM, Minogue PJ, Guo J, Williamson EK, Xu X, Ebihara L, et al. Loss of function and impaired degradation of a cataract-associated mutant connexin50. Eur J Cell Biol. 2003;82(5):209–21.
45. Pal JD, Liu X, Mackay D, Shiels A, Berthoud VM, Beyer EC, et al. Connexin46 mutations linked to congenital cataract show loss of gap junction channel function. Am J Physiol Cell Physiol. 2000;279(3):C596–602.
46. Alapure BV, Stull JK, Firtina Z, Duncan MK. The unfolded protein response is activated in connexin 50 mutant mouse lenses. Exp Eye Res. 2012;102:28–37.
47. Minogue PJ, Tong JJ, Arora A, Russell-Eggitt I, Hunt DM, Moore AT, et al. A mutant connexin50 with enhanced hemichannel function leads to cell death. Invest Ophthalmol Vis Sci. 2009;50(12):5837–45.
48. Francis P, Chung JJ, Yasui M, Berry V, Moore A, Wyatt MK, et al. Functional impairment of lens aquaporin in two families with dominantly inherited cataracts. Hum Mol Genet. 2000;9(15):2329–34.
49. Zhao L, Chen XJ, Zhu J, Xi YB, Yang X, Hu LD, et al. Lanosterol reverses protein aggregation in cataracts. Nature. 2015;523(7562):607–11.
50. Cullup T, Kho AL, Dionisi-Vici C, Brandmeier B, Smith F, Urry Z, et al. Recessive mutations in EPG5 cause Vici syndrome, a multisystem disorder with defective autophagy. Nat Genet. 2013;45(1):83–7.
51. Ma Z, Yao W, Theendakara V, Chan CC, Wawrousek E, Hejtmancik JF. Overexpression of human γC-crystallin 5bp duplication disrupts lens morphology in transgenic mice. Invest Ophthalmol Vis Sci. 2011;52(8):5269–375.
52. Watson GW, Andley UP. Activation of the unfolded protein response by a cataract-associated alphaA-crystallin mutation. Biochem Biophys Res Commun. 2010;401(2):192–6.
53. Wilkinson JE, Burmeister L, Brooks SV, Chan CC, Friedline S, Harrison DE, et al. Rapamycin slows aging in mice. Aging Cell. 2012;11:675–82.
54. Singh MP, Ram J, Kumar A, Khurana J, Marbaniang M, Ratho RK. Infectious agents in congenital cataract in a tertiary care referral center in North India. Diagn Microbiol Infect Dis. 2016;85(4):477–81.
55. Merin S. Congenital cataracts. In: Goldberg MF, editor. Genetic and metabolic eye disease. Boston: Little, Brown; 1974. p. 337–55.
56. Hansen L, Yao W, Eiberg H, Funding M, Riise R, Kjaer KW, et al. The congenital "ant-egg" cataract phenotype is caused by a missense mutation in connexin46. Mol Vis. 2006;12:1033–9.
57. Riise R. Hereditary "ant-egg-cataract". Acta Ophthalmol (Copenh). 1967;45(3):341–6.
58. Weisel TN, Hubel DH. Comparison of the effects of unilateral and bilateral eyelid closure on cortical responses in kittens. J Neurophysiol. 1965;28:1029.
59. Harwerth RS, Smith ELd, Paul AD, Crawford ML, von Noorden GK. Functional effects of bilateral form deprivation in monkeys. Invest Ophthalmol Vis Sci. 1991;32:2311–27.
60. Robb RM, Mayer DL, Moore BD. Results of early treatment of unilateral congenital cataracts. J Pediatr Ophthalmol Strabismus. 1987;24:178–81.
61. Gelbart SS, Hoyt CS, Jastrebski G, Marg E. Long-term visual results in bilateral congenital cataracts. Am J Ophthalmol. 1982;93:615–21.
62. Nelson LB. Diagnosis and management of cataracts in infancy and childhood. Ophthalmic Surg. 1984;15:688–97.
63. Burns EC, Jones RB. Long term management of congenital cataracts. Arch Dis Child. 1985;60:322–5.
64. Makley LN, McMenimen KA, DeVree BT, Goldman JW, McGlasson BN, Rajagopal P, et al. Pharmacological chaperone for alpha-crystallin

partially restores transparency in cataract models. Science. 2015;350(6261):674–7.
65. Lin H, Ouyang H, Zhu J, Huang S, Liu Z, Chen S, et al. Lens regeneration using endogenous stem cells with gain of visual function. Nature. 2016;531(7594):323–8.
66. Datiles MB III, Ansari RR, Suh KI, Vitale S, Reed GF, Zigler JS Jr, et al. Clinical detection of precataractous lens protein changes using dynamic light scattering. Arch Ophthalmol. 2008;126(12):1687–93.
67. Li F, Wang S, Gao C, Liu S, Zhao B, Zhang M, et al. Mutation G61C in the CRYGD gene causing autosomal dominant congenital coralliform cataracts. Mol Vis. 2008;14:378–86.