Congenital Cataracts and their Molecular Genetics

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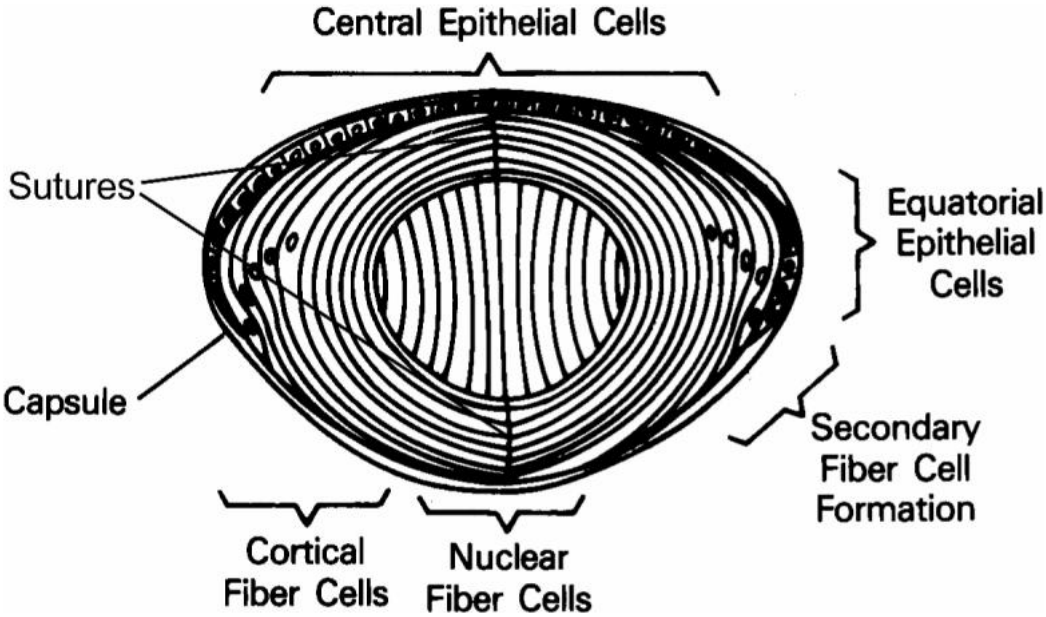
Abstract

Cataract can be defined as any opacity of the crystalline lens. Congenital cataract is particularly serious because it has the potential for inhibiting visual development, resulting in permanent blindness. Inherited cataracts represent a major contribution to congenital cataracts, especially in developed countries. While cataract represents a common end stage of mutations in a potentially large number of genes acting through varied mechanisms in practice most inherited cataracts have been associated with a subgroup of genes encoding proteins of particular importance for the maintenance of lens transparency and homeostasis. The increasing availability of more detailed information about these proteins and their functions and is making it possible to understand the pathophysiology of cataracts and the biology of the lens in general.

Transparency and the Lens

The lens transmits light with wavelengths from 390 nm to 1200 nm efficiently, extending well 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]. Ultrastructurally, the lens comprises an anterior layer of organelle rich cuboidal epithelial cells covering a large fiber cell mass making up the bulk of the lens (Fig. 1). Layers of nucleated cortical fiber cells form highly ordered concentric shells around the nonnucleated and essentially organelle-free central fiber cells which make up the lens nucleus. The ends of the more peripheral fiber cells abut in branched anterior and posterior sutures. The cellular architecture and arrangement of the fiber cells and particularly their sutures are critical for light transmission and lens transparency [3]. In addition, the stability and close ordering of lens crystallins, which make up 80−90% of the soluble proteins in the lens, are critical for lens transparency. The high protein content of the lens and especially the lens nucleus, approximately 60% of the wet weight -- the highest of any tissue, is particularly important for refraction and focusing of light. Solutions of lens crystallins are highly transparent, and as they are concentrated to levels above 450 mg/ml, light scattering actually decreases [4], [5].

Figure 1



Structure of the mature human lens. Cell division occurs in the 10 and 2 O'clock positions of the anterior epithelia, and cells move laterally until they invert in the bow region of the lens and begin loosing their organelles to form cortical fiber cells. Nuclear fiber cells are laid down relatively early in development. The ends of the more peripheral fiber cells meet atn the sutures, shown here as vertical lines but seen clinically as anterior and posterior Y structures.

Cataracts, which can be defined as lens opacities, have multiple causes, but are often associated with breakdown of the lens microarchitecture [3], [6], possibly including vacuole formation and disarray of lens cells, 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 of approximately 1000 Å or more in size [7], [8]. The short-range ordered packing of the lens crystallins is important in this regard. For transparency, crystallins must exist in a homogeneous phase with significant short-range spatial ordering [2]. This condition will be abrogated in the presence of aggregates of partially denatured or even native proteins. In fact, disruption of lens microarchitecture and protein denaturation are not mutually exclusive events, and both may play a part in some cataracts. The physical basis of lens transparency can be complex, and has been reviewed elsewhere [1], [7], [8], [9].

When mutations in crystallins are sufficient in and of themselves to cause aggregation they usually result in congenital cataract, while if they merely increase susceptibility to environmental insults such as light, hyperglycemic or oxidative damage they might contribute to age related cataract [10]. Similarly a mutation causing a severe insult to the lens cell that results in major and immediate disruption of cell homeostasis tends to cause congenital cataracts, while milder insults tend to become evident only with added stress imposed by time and environmental factors. Thus, congenital cataracts tend to be inherited in a Mendelian fashion with high penetrance, while age-related cataracts tend to be multifactorial, with both multiple genes and environmental factors influencing the phenotype.

The Lens and Cornea: Transparency and Refraction

The lens and cornea function together to transmit and refract light. While the cornea has additional protective functions, the main functions of the lens are to transmit light and focus it on the retina. Because of the large change in refractive index at the air-cornea interface in terrestrial species, about 80 percent of total refraction results from the cornea. However in mammals the lens is the only tissue capable of accurately focusing light onto the retina, in a process called accommodation [8], [4]. In addition, there is a gradual increase in the refractive index of the human lens from the cortex (1.38, 73 to 80 percent H2O) to the nucleus (1.41, 68 percent H2O), where there is an enrichment of tightly packed Y-crystallins (see below). The human lens is colorless when young, and a gradual increase in yellow pigmentation occurs with age, resulting in some decrease in perception of blue light[11].

There are two general fashions in which cataracts are associated with other ocular anomalies, especially abnormalities of the cornea and anterior chamber. While in some cases inherited cataracts caused by mutations in growth or transcription factors are associated with extralenticular abnormalities because those growth factors are directly necessary for development of both the lens and the other affected tissues, representing a true pleiotropic effect of the mutant gene. In other cases, e.g. some α- and β-crystallin mutations, inherited congenital cataracts are associated with microcornea and microphakia, probably because severe and early damage to the lens interferes with development of the anterior chamber [12]. In this case, the damaged lens is unable to support development of the anterior chamber, resulting in a developmental cascade of abnormalities. That microcornea is among the most common abnormalities associated with congenital cataracts further emphasizes the interdependence of the lens and cornea in development and metabolism. Indeed, as elaborated in the refraction hypothesis[13] and discussed in other articles in this journal issue, there are many similarities between the lens and cornea. Included among these are transparency, a refractive role in vision, and the accumulation of multifunctional crystallins as well as their metabolic and developmental interdependence leasing to the association of congenital cataracts and corneal anomalies. This review centers primarily on lens cataract; however, similar considerations may apply to corneal opacification in some cases.

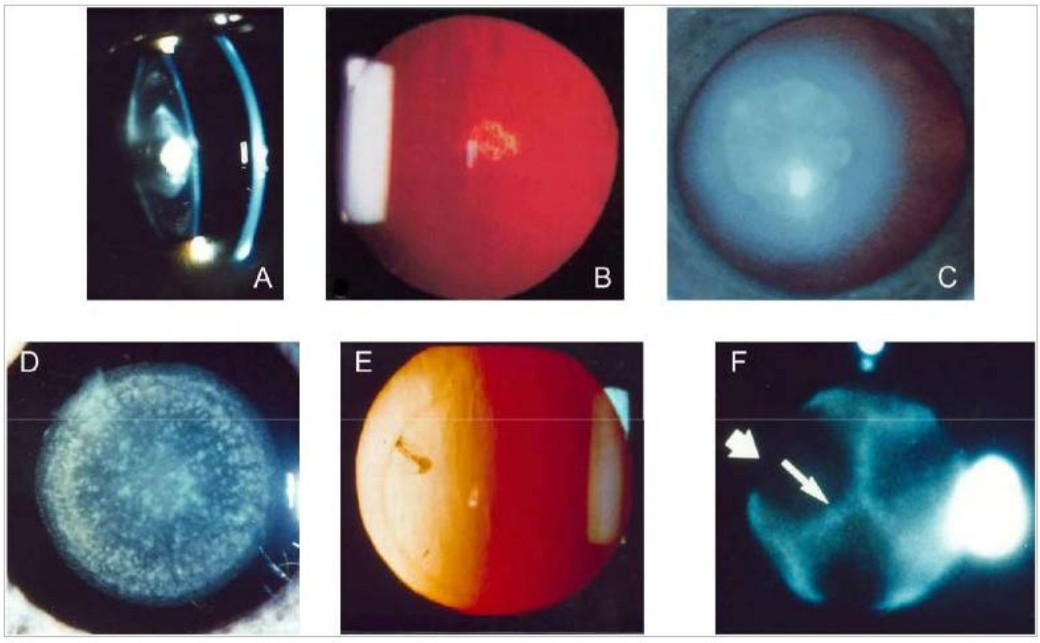
Congenital Cataracts

Cataracts can be defined by the age at onset: a congenital or infantile cataract presents within the first year of life; a juvenile cataract presents within the first decade of life; a presenile cataract presents before the age of about 45 years, and senile or age-related cataract after that. Between 8.3 and 25 percent of congenital cataracts are believed to be inherited [14], [15], [16]. The lens alone may be involved, accounting for approximately 70% of congenital cataracts [16]. Conversely, lens opacities may be associated with other ocular anomalies such as microphthalmia, aniridia, other anterior chamber developmental anomalies, or retinal degenerations, seen in approximately 15% of cases. Cataracts may also be part of multisystem genetic disorders such as chromosome abnormalities, Lowe syndrome or neurofibromatosis type 2, also accounting for approximately 15% of congenital cataracts. In some cases this distinction can be blurred, e.g. in the developmental abnormality anterior segment mesenchymal dysgenesis resulting from abnormalities in the PITX3 gene, inherited cataracts may be isolated in some family members and associated with additional findings in others [17].

Hereditary (Mendelian) cataracts are most frequently inherited as autosomal dominant traits, but also can be inherited in an autosomal recessive, or X-linked fashion. Phenotypically identical cataracts can result from mutations at different genetic loci and may have different inheritance patterns, while phenotypically variable cataracts can be found in a single large family [18]. There are several classification systems which have been developed based on the anatomic location, size, density, and progression of the opacity.

In an attempt to develop a logical classification of congenital cataracts, Merin has proposed a system based on morphological classification [19]. Examples are shown in Fig. 2. Polar opacities involve either the anterior or posterior pole of the lens (or both, in which case they are referred to as bipolar) and may include the posterior subcapsular lens cortex (PSC) extending to the lens capsule. Posterior subcapsular cataracts can occur secondarily to a variety of insults including steroid treatment. Zonular cataracts include specific regions of the lens and include nuclear cataracts, which affect the fetal or embryonic lens nucleus and lamellar cataracts. These tend to affect lens fibers that are formed at the same time, resulting in a shell like opacity. Zonular cataracts can also be characterized as dense or pulverulent (dusty appearing), and can be accompanied by arcuate opacities extending into the lens cortex, called cortical riders. Sutural cataracts, also called stellate, affect the sutural regions of the fetal nucleus, at which the ends of the lens fiber cells converge. Cerulean cataracts, also called blue dot cataracts, have numerous small bluish opacities in the lens cortex and nucleus. Finally, membranous or capsular cataracts can result from resorprption of lens proteins after capsular rupture, often from a traumatized or severely dysfunctional lens. In addition, there are a number of morphologically distinctive types of cataract such as the ant egg cataract and corraliform cataracts (see below).

Fig. 2



A. Slit lamp view of a dense anterior polar cataract.. B. Reflex view of posterior subcapsular cataract. C. Dense nuclear cataract. D. Punctate nuclear cataract. E. Reflex view of a lamellar pulverulent cataract with a cortical rider in the upper right. F. Sutural cataract with a pulverulent nuclear lamellar component.

Cataracts can be isolated or can occur in association with a large number of metabolic diseases and genetic syndromes[18]. Isolated congenital cataracts tend to be highly penetrant Mendelian traits, with autosomal dominant more common than autosomal recessive cataracts. Currently, there are about 39 genetic loci to which isolated or primary cataracts have been mapped, although the number is constantly increasing and depends to some extent on definition (Table 1). Of these, several are associated with additional abnormalities, mostly as part of developmental syndromes. These tend to result from mutations in genes encoding transcriptional activators, and most of these have been identified by sequencing candidate genes in patients with developmental anomalies. A notable exception is the αB-crystallin gene, CRYAB, which is widely expressed in various tissues, especially muscle. Mutations in CRYAB can cause a spectrum of abnormalities ranging from isolated cataracts to mild cataracts associated with myopathy. A second counterexample is the ferritin gene, which causes the hyperferritinemia-cataract syndrome (Table 1).

Table 1

Mapped human cataracts. Specific mutations are described below the entry for the gene or locus. The cDNA sequence changes are given in reference to the NCBI sequence identifier in the Locus column. Chrom: chromosomal location. Inh: inheritance pattern. cDNA: changes in the NCBI DNA sequence listed in the Locus column. AA: changes in the protein sequence. Ref: reference number. MIM: Mendelian Inheritance in Man reference. Specific mutations identified are listed below the gene. AD: autosomal dominant. AR: autosomal recessive. XL: X-linked. S: sporadic. MIM: Mendelian Inheritance in Man identifier. Genes and locs are shown in bold, while individual mutations and their descriptions are shown in small lettering below.

Locus	Chrom	Inh	Morphology	cDNA	AA	Ref	MIM
CCV (Volkmann)	**1p36**	**AD**	**variable (progressive central and zonular nuclear cataract with sutural component), Rh linked cataracts not well described**			[89]	**115665**
CTPP	**1p34-p36**	**AD**	**posterior polar, complete (2904)**			[91], [92]	**116600**
FOXE3 NM_012186	**1p32**	**AD**					**107250, 601094**
		AD	ASMD and cataracts	c.699insG	fs = 111 aa's	[24]	
GJA8 NM_005267	**1q21-q25**					[93]	**116200**
		AD	zonular pulverulent	c.262C>T	P88S	[94], [55]	
		AD	zonular pulverulent	c.142G>A	E48K	[95]	
		AD	zonular pulverulent	c.741T>G	1247M	[96]	
		AD	progressive nuclear	c.68G>C	R23T	[97]	
		AD	congenital nuclear	c.191T>G	V64G	[98]	
		AD	lamellar pulverulent	c.263C>A	P88Q	[99]	
		AD	congenital total	c.131T>A	V44E	[51]	
		AD	posterior subcapsular	c.593G>A	R198Q	[51]	
		AR	total congenital cataracts with nystagmus	c.607insA	203fs	[100]	
		AD	star shaped nuclear opacity with a whitish central core	c.566C>T	P189L	[30]	
	2p24	**AD**	**corraliform**			[101]	
CCNP	**2p12**	**AD**	**congenital embryonic nuclear (congenital cataract nuclear progressive)**			[102]	**607304**
CRYGC NM_020989	**2q33-q35**					[103], [104], [105], [106]	**123660, 123680, 601286**
		AD	Coppock (nuclear lamellar	c.125A>C	T5P	[41]	
		AD	variable zonular pulverulent	c.126insGC GGC,	p.C42fs	[102]	
		AD	lamellar	c.502C>T	R168W	[108]	
CRYGD NM_006891	**2q33–35**	**AD**				[109]	**115700, 123690**
		AD	punctate progressive	c43C>t	R15C	[110]	
		AD	aciuliform	c.176G>A	R59H	[41]	
		AD	crystalline	c.110G>A	R37S	[40]	
		AD	lamellar	c.70C>A	P24T	[108]	
		AD	central nuclear	c.466G>A	W156X	[108]	
		AD	cerulean	c.70C>A	P24T	[111]	
		AD	?	c.70C>A	P24T	[112]	
		AD	coralliform	c.70C>A	P24T	[113]	
		AD	fasciculiform	c.70C>A	P24T	[114]	
		AD	coralliform	c.70C>A	P24T	[115]	
		AD	Nuclear coralliform	c.43C>t	R14C	[39]	
		AD	Nuclear	c.320A>C	E107A	[116]	
		AD	polymorphic	c.70C>T	P24S	[76]	
		AD		c.402C>A	Y134X	[80]	
	3p22-p24.2	**AR**				[117]	
BFSP2 NM_003571	**3q21-q22**					[118]	**603212**
		AD	congenital nuclear and sutural cataracts unknown myopia	c.697–699delGAA	E233del	[66]	
		AD	juvenile progressive lamellar	c.859C>T	R287W	[63]	
		AD	congenital progressive sutural with myopia	c.697–699delGAA	E233del	[67]	
		AD	progressive congenital sutural (no myopia)	c.697–699delGAA	E233del	[68]	
CRYGS NM_017541	**3q26.3-qter**						**123730**
		AD	progressive polymorphic cortical cataract	c.53G>T	G18V	[119]	
GCNT2 NM_001491	**6p24-p23**					[120], [121]	**110800**
		AR	i associated	c.1043G>A	G348E	[70]	
		AR	i associated	c.1148G>A	R383H	[70]	
		AR		total deletion of gene	total deletion of gene	[70]	
		AR	congenital	c.978G>A	W326X	[80]	
EYA1 NM_172060	**8q13.3**						**601653**
		AD	congenital cataracts	c.1320G>A	R407Q	[75]	
		AD	congenital cataracts and anterior segment anomalies	c.988G>A	E330K	[75]	
			congenital nuclear cataract with nystagmus	c.1177G>A	G393S	[75]	
CAAR	**9q13-q22**	**AR**	**adult onset pulverulent**			[122]	**212500**
PITX3 NM_005029	**10q25**						**602669**
		AD	ASD and congenital cataracts	c.656ins1 7bp	17bpdup	[17]	
		AD	congenital cataracts	c38G>A	S13N	[17]	
		AD	posterior polar congenital	c.656ins1 7bp	17bpdup	[123]	
		AD	posterior polar congenital	650delG	G217Afs90	[123]	
CRYAB NM_001885	**11q23.3–24.2**						**123590**
		AD	mild "discrete" opacities	c.358A>G	R120G	[31]	
		AD	posterior polar congenital	c.450delA	K150fs	[34]	
		AD	lamellar congenital	c.418G>A	D140N	[124]	
		AD	congenital posterior polar	c.58C>T	P20S	[125]	
AQP0 NM_012064	**12q12–14.1**					[126]	**601286**
		AD	polymorphic, discrete, congenital, progressive, punctate in mid and peripheral lamellae, some with anterior and posterior opacification	c.401A>G	E134G	[127], [128], [58]	
		AD	fine non-progressive congenital lamellar and sutural	c.413C>G	T138R	[127]	
		AD	radiating, vacuolar, or dense opacities in the embryonal nucleus	c.638delG	G213VfsX44	[129]	
GJA3 NM_021954	**13q11–13**	**AD**				[130], [131]	**601885**
		AD	zonular pulverulent	c.188A>G	N63S	[132], [52]	
			zonular pulverulent	c.1138insC	S380fs	[132]	
		AD	zonular pulverulent	c.560C>T	P187L	[133]	
		AD	nuclear pulverulent	c.114C>A	F32L	[134]	
		AD	nuclear pulverulent with faint lamellar opacity and incomplete penetrance	c.227G>A	R76H	[135]	
		AD	congenital nuclear pulverulent	c.563A>C	N188T	[136]	
		AD	nuclear	c.134G>C	W45S	[98]	
		AD	total	c.226C>G	R76G	[137]	
			variable age, cortical and capsular	c.82G>A	V28M	[137]	

		AD	nuclear punctate	c.176C>T	P59L	[138]	
		AD	zonular pulverulent	c.7G>T	D3Y	[139]	
		AD	aut egg	c.32T>C	L11S	[140]	
		AD	pearl box (lamellar with fine white nuclear spots)	c.260C>T	T87M	[141]	
CHX10 NM_182894	**14q24.3**						**142993**
		AR	congenital cataracts	c.599G>A	R200Q	[142]	
		AR	congenital cataract	c.599G>C	R200P	[142]	
CCSSO	**15q21-q22**	**AD**	**central pouchlike with sutural opacities**			[143]	605728
HSF4 NM_001538	**16q22.1**					[144], [71]	**602438**
		AD	lamellar	c.341T>C	L114P	[70]	
		AD	Marner (zonular stellate with anterior polar opacity) early childhood onset	c.355C>T	R120C	[70]	
		S	lamellar	c.56C>A	A20D	[70]	
		S	lamellar	c.1152A>G	187V	[70]	
		AR	early total (with nystagmus)	splice mutation intron 12 (c.1234 +4A>G)	splice mutation intron 12 (c.1234 +4A>G)	[73]	
		AR	nuclear with cortical extension in severe cases	c.524G>C	R175P	[72]	
		AR	?	(c.595_599delGGGCC	(c.595_599delGGGCC	[72]	
		AD	congenital total	c.218G>A	R73H	[145]	
MAF NM_001031804	**16q23**		**cataract, iris coloboma, microcornea**				**177074**
		AD	juvenile onset lamellar pulverulent	c.863G>C	R288P	[77], [146]	
		AD	congenital cerulean	c.890A>G	K297R	[78]	
CTAA2	**17p13**	**AD**	**anterior polar**			[147], [148]	**601202**
CRYBA3 NM_005208	**17q11-q12**		**nuclear lamellar with sutural component**			[149]	**600881**
		AD	zonular with sutural opacities	c.215+2T>A	splice mutation in intron 3	[150]	
		AD	pulverulent embryonal nucleus and sutural	c.215+1G>C	splice mutation in intron 3	[151]	
		AD	nuclear congenital	c.271delGG A	G91del	[152]	
		AD	variable nuclear, sutural, and cortical opacity	c.215+1G>A	splice mutation in intron 3	[112]	
		AD	congenital nuclear lactescent with sutural sparing	c.271delGG A	G91del	[153]	
CCA1 (Cerulean - blue dot)	**17q24**	**AD**	**cerulean (nuclear and cortical)**			[154]	**115660**
	19q13	**AD**	**cortical, irregular or spherical vacuolated white opacities**			[155]	
	19q13.4	**AR**	**bilateral congenital nuclear**			[156]	
FTL NM_000146	**19q13.4**	**AD**	**Multiple bread crumblike nuclear and cortical lens opacities**			[157]	
LIM2 NM_002316	**19q**						**154045**
		AR	presenile	c.310T>G	F104V	[61]	
BFSP1 NM_001195	**20p11.23-p12.1**						**603307**
		AR	developmental	c736−1384_c.957−66del	T246fsX7	[64]	
CPP3	**20p12-q12**	**AD**	**progressive, discshaped, posterior subcapsular opacity; congenital zonular nuclear**			[158], [159]	**605587**
CHMP4B NM_176812	**20q11.22**	**AD**	**progressive childhood posterior subcapsular**				**610897**
		AD	progressive childhood posterior subcapsular	c.386A>T	D129V	[160]	
		AD	posterior polar	c.481G>A	E161K	[160]	
CRVAA NM_000394	**21q22.3**						**123580**
		AD	congenital zonular central nuclear, some with microcornea	c.346C>T	R116C (C>T)	[23]	
		AR	congenital (xed first 3 mo)	c.27G>A	W9X	[23]	
		AD	nuclear	c.145C>T	R49C	[26]	
		Spo radi c	nuclear, with fundus hypoplasia (mutation in P)	c.62C>G	R21L	[27]	
		AD	fan shaped with microcornea	c.346C>T	R116C	[28]	
		AD	presenile progressing from lamellar to total	c.247G>A	G98R	[29]	
		AD	posterior polar progressing to dense nuclear and laminar, with involvement of anterior and posterior poles	c.1134C>T	R12C	[30]	
		AD	central and laminar with varying anterior and posterior polar components	c.130C>T	R21W	[30]	
		AD	nuclear with polar and/or equatorial ramification	c.347G>A	R116H	[30]	
CRYBB2 NM_00496	**22q11.2**					[50]	**123620**
		AD	cerulean	c.463C>T	Q155X	[161]	
		AD	Coppock (nuclear lamellar	c.463C>T	Q155X	[162]	
		AD	Sutural and cerulean	c.463C>T	Q155X	[44]	
		AD	?	c.453C>T	W151C	[163]	
		AD	congenital nuclear with cortical ring	c.383A>T	D128V	[164]	-
		AD	?	c.463C>T	Q155X	[165]	-
		AD	Progressive polymorphic congenital	c.463C>T	Q155X	[166]	
CRYBB1 NM_001887	**22q11.2**	**AD**	**pulverulent**				**600929**
		AD	pulverulent	c.658G>T	G220X	[167]	
		AD	dense nuclear with cortical riders and anterior and posterior polar opacities and microcornea	c.757T>C	X235R	[168]	
		AD	?	c.682T>C	S228P	[169]	
		AR	nuclear	c.171delG	N58T6X106	[48]	
CRYBB3 NM_004076	**22q11.2**						**123630**
		AR	nuclear	c.493G>C	G165R	[49]	
CRYBA4 NM_001886	**22q11.2**						**123631**
		AD	congenital lamellar	c.206T>C	L69P	[170]	-
CXN	**Xp22**	**XL**	**Nuclear, fan shaped**			[171]	**300457**
NHS NM_198270	**Xp22.13**	**XL**	**Congenital**				**300457**
		XL	congenital, total	c.2387insC	A796fs	[83]	
		XL	congenital,, total	c.3459fs	A1153fs	[83]	
		XL, *de novo*	congenital, total	c.1117C>T	R373X	[83]	
		XL	congenital, total	c.718insG, c.719−3C>G	E240fs, 3' acceptor splice site, intron 2	[83]	
		XL	congenital, total	c.400delC	R134fsX261	[83], [86]	
		XL	congenital, total	c.3738delT G	C1246AfsX15	[86]	
		XL	congenital, total	c.2687delA	Q896fsX10	[86]	
		XL	congenital, total	c.115C>T	Q39X	[172]	
		XL	congenital, total	c.853−2A>G	3' acceptor splice site, intron 3	[173]	
		XL	congenital, total	c.2601insG	K868EfsX5	[173]	
		XL	congenital, total	c.1117C>T	R373X	[173]	
		XL	congenital, total	c.2635C>T	R879X	[173]	
		XL	congenital, total	c.3624C>A	C1208X	[174]	
		XL	congenital, total	c.1108C>T	Q370X	[174]	
		XL	prenatal	c.3908del11	T1303RfsX4	[89]	

Genes and Mutations Causing Congenital Cataracts

Over 26 of the 39 mapped loci for isolated congenital or infantile cataracts have been associated with mutations in specific genes. Of the cataract families for whom the mutant gene is known, about half have mutations in crystallins, about a quarter have mutations in connexins, with the remainder divided among the genes for heat shock transcription factor-4 (HSF4), aquaporin-0 (AQP0, MIP), and beaded filament structural protein-2 (BFSP2). There is often some correlation between the pattern of expression of the mutant protein and the morphology of the resulting cataract. However, as has been mentioned previously, inheritance of the same mutation in different families or even the same mutation within the same family can result in radically different cataract morphologies and severities. This suggests that additional genes or environmental factors might modify the expression of the primary mutation associated with the cataracts. Conversely, cataracts with similar or identical clinical presentations can result from mutations in completely different genes.

Lens Crystallins

Three major classes of ubiquitous crystallins are found in the vertebrate eye lens [20], [21]. The α-crystallins are related to the small heat-shock protein family and have chaperone-like activity [22]. Mutations in the αA-crystallin gene have been implicated both in autosomal recessive and autosomal dominant cataract. Autosomal recessive cataracts have been associated with a chain termination mutation near the beginning of the protein, converting the tryptophan codon at position 9 into a termination codon [23]. These findings are consistent with data from knock-out mice in which expression of the αA-crystallin gene is disrupted. In these mice the lenses are somewhat smaller in size and develop cataracts associated with the presence of inclusion bodies containing αB-crystallin [24]. The early chain termination mutation would be expected to cause loss of function of the mutant protein without affecting protein synthesized from the normal gene, suggesting that half the normal level of α-crystallin can provide sufficient chaperone-like activity and structural crystallin packing to establish and maintain lens transparency, although the complete absence of αA-crystallin results in opacity. Presumably, either the mRNA undergoes nonsense-mediated decay, the small peptide synthesized from the mutant gene is degraded rapidly, or is at least not toxic to lens cells. An interesting question is whether heterozygosity for this mutation might increase carriers risk for age related cataracts, although answering this question could require examination of many individuals.

Autosomal dominant cataracts tend to be associated with nonconservative missense mutations in αA-crystallin, many of them involving changes of a neutral or hydrophobic amino acid to or from arginine [25], [26], [27], [28], [29]. The high level of involvement of arginine in these cataracts would tend to support the hypothesis that the molecular charge dispersion at the surface of the α-crystallin molecule is critical for chaperone action, and perhaps even stability. The occurrence of dominant cataracts with the missense mutations suggests that the mutant αA-crystallin protein exerts a deleterious effect that actively damages the lens cell or its constituent proteins, or inhibits the function of the remaining normal α-crystallin, rather than acting through loss of chaperone function as the recessive cataract appears to do. Five of the 8 described autosomal dominant mutations in CRYAA are also associated with microcornea [25], [28], [30].

Because αA- and αB-crystallin are found in the lens associated into large multimeric complexes and function similarly in vitro, one might expect that mutations in αB-crystallin would have a similar effect to those in αA-crystallin, at least in the lens. However, the first human mutation reported in αB-crystallin was associated with desmin-related myopathy and only "discrete" cataracts [31]. This was a missense mutation that reduced αB-crystallin chaperone activity dramatically, causing aggregation and precipitation of the protein under stress [32]. The myopathy associated with this mutation is probably related to the high level of expression of αB-crystallin, but not αA-crystallin, in muscle cells, where it binds and presumably stabilizes desmin [33]. Similarly, an αB-crystallin knockout mouse exhibits myopathy without cataracts [33]. In contrast, a deletion in the αB-crystallin gene resulting in a frame-shift and expression of an aberrant 184 amino acid protein causes autosomal dominant cataracts in the absence of myopathy [34]. This seems more similar to the dominant αA-crystallin associated cataract, with the aberrant protein likely to have a toxic effect on the lens cells. While the reason for the absence of myopathy from this mutation is unclear, it might relate to the decreased ability of the lens to turn over proteins, especially once the cell nuclei and other organelles have been lost in the transition of fiber cells from the lens cortex to the nucleus.

The βY-crystallins are members of a protein family that includes bacterial spore-coat protein S and Spherulin 3A [35]. These structural proteins share a highly stable structure comprising two domains connected by a connecting peptide. Each domain comprises motifs, each forming a Greek key fold forming a β-sandwich structure. The Y-crystallins are found as monomers while the β-crystallins associate into higher order complexes. Most mutations described in the βγ-crystallins would be expected to cause major abnormalities in the protein structure, presumably resulting in an unstable protein that precipitates from solution and serves as a nidus for additional protein denaturation and precipitation, eventually resulting in cataract formation. This mechanism has been demonstrated for a number of inherited cataracts [36], [37]. These include missense mutations, insertions changing the reading frame and causing expression of aberrant peptides with premature termination, and splice mutations as shown in Table 1. Although the resulting phenotypes can vary significantly, mutations in γ-crystallins tend to produce nuclear or zonular cataracts, consistent with their high level of expression in the lens nucleus. Presumably central nuclear cataracts reflect high level expression of the mutant gene early in lens development while zonular cataracts reflect synthesis somewhat later and for a limited period of time, resulting in a shell of opaque cells surrounded internally and externally by relatively clear lens. This interpretation is supported by mouse data that shows YB-crystallin with an I4F mutation looses stability and forms large aggregates with α-crystallin, which is presumably acting as a molecular chaperone. The inner fiber cells where YB-crystallin is highly expressed show darkly stained aggregates, enlarged interfiber spaces, and disorganized and smaller fibers which would be expected to scatter light and cause cataract [38]. One mutation in YD-crystallin has been shown to cause nuclear and coralliform cataracts associated with high myopia [39], while a second is associated with microcornea [30].

Recently, two mutations in γD-crystallin, R36S and R58H, have been shown not to alter the protein fold, but rather to alter the surface characteristics of the protein [40], [41], [42]. This, in turn, lowers the solubility and enhances the crystal nucleation rate of these mutants so that they precipitate out of solution, or in at least one case actually form crystals in the lens. In a third mutation in γD-crystallin, R14C, the protein also maintains a normal protein fold, but is

susceptible to thiol-mediated aggregation [43]. These results emphasize that crystallins need not undergo denaturation or other major changes in their protein folds to cause cataracts.

The cataract phenotypes reported with mutations in the β-crystallins are somewhat more varied, ranging in different families from zonular pulverulent with or without involvement of the sutures to cerulean cataracts (Table 1). The association of identical mutations in βB2-crystallin in different families with nuclear lamellar Coppock-like and cerulean cataracts emphasizes the importance of modifying genes in the phenotypic expression of these mutations. There are multiple reports of Q155X mutations in the βB2-crystallin gene. These occur in families that are unrelated, but show a common sequence of 9−104 bp around the mutation that is consistent with that of the nearby and highly homologous pseudogene, CRYBP1 [44]. It is of interest that the β-crystallins, like αB-crystallins, are found in a variety of tissues outside of the lens and even the eye. This is particularly the case for βB2-crystallin, which is expressed in the brain and gonads among other tissues [45]. At least some strains of the Philly mouse, which has a mutation in βB2-crystallin causing cataracts, has been shown to have decreased fertility as well [46], and βB2-crystallin has been shown to promote regeneration of retinal ganglion axons in vitro [47]. These observations suggest that βBB2-crystallin has an important biological function in addition to the structural and refractive role of a crystallin. This is supported when taken in conjunction with the existence of autosomal recessive forms of cataract resulting from mutations in βB1- and βB3-crystallins [48], [49] and the mild nature of heterozygous βB2-crystallin cataracts when compared to the homozygous state [50]. These findings suggest that this might be the case for the other basic β-crystallins as well. At a minimum, it is obvious that current information is only beginning to illuminate the biological roles of the β-crystallins in the lens and elsewhere. In addition, these mutations emphasize the requirement that crystallins must be exceptionally soluble to be expressed at such high levels in the lens without causing dysfunction.

Gap Junction Proteins

Connexins 46 (GJA3, cx46) and 50 (GJA8, cx50) are constituents of gap junctions, especially important for nutrition and intercellular communication in the avascular lens. Cataract causing mutations in connexin 46 proteins have been associated with microcornea [30] in three families and in a couple of these with mild myopia and microcornea as well [51]. Two mutations in connexin 46, one with an N63S missense mutation in the first extracellular domain and a second with a frame-shift mutation at residue 380 causing read-through into the 3'-untranslated region until an in-frame stop codon 90 nucleotides downstream from the wild-type stop codon, have been shown not to form intercellular channels in paired Xenopus oocytes [52]. However, these mutant connexins are unable to participate in gap junction formation at all, and thus do not inhibit channel function by products of the normal gene. The S380fs mutation in connexin 46 ends in 87 aberrant amino acids and the mutant protein localizes to the endoplasmic reticulum and Golgi [53]. One cataract associated mutation in the connexin 50 gene, the P88S missense mutation in the second transmembrane domain, has also been shown to result in a connexin that fails to form functional gap junctional channels [54]. Incorporation of even a single mutant protein molecule into a gap junction in Xenopus oocytes inhibits channel function [55]. Since gap junction channels are formed of a double ring of 6 connexin molecules from each cell, this provides an example of a true dominant negative disease mechanism. Mutations in both connexin

46 and connexin 50 tend to produce phenotypically similar autosomal dominant nuclear and especially zonular pulverulent cataracts.

Membrane Proteins

AQP0 is an integral membrane protein member of the aquaporin family of water transporters and distantly related to soybean nodulin-26 and E. coli glycerol facilitator [56]. It is the most highly expressed membrane protein in the lens, accounting for its earlier name, major intrinsic protein (MIP). While AQP0 has only weak water channel activity at neutral pH, this increases to levels typical of other aquaporins at low calcium concentrations and at pH 6.5, which is fairly close to physiological pH for the lens [57]. Lamellar and polymorphic cataracts have been associated with missense mutations in the AQP0 (MIP) gene. One mutation, E134G, is associated with a non-progressive congenital lamellar and sutural cataract, and the second T138R is associated with multifocal opacities that increase in severity throughout life. Both of these mutations appear to act by interfering with normal trafficking of AQP0 to the plasma membrane and thus with water channel activity [58]. In addition, both mutant proteins appear to interfere with water channel activity by normal AQP0, consistent with a dominant negative mechanism for the autosomal dominant inheritance of the cataracts. Perhaps this relates to the presence of AQP0 in thin (11 to 13 nm) junctions present in both single membranes as well as junctional areas between cells [59], [60], where it shows a tetragonal arrangement. Mutations in LIM2, another lens membrane protein junctional component that binds calmodulin, can also cause presenile cataracts [61].

Beaded Filament Proteins

Beaded filaments are a type of intermediate filament unique to the lens fiber cells. They are made up of BFSP1 (also called CP115 or filensin) and BFSP2 (also called CP49 or phakinin), highly divergent intermediate filament proteins that combine in the presence of α-crystallin to form the appropriate beaded structure. Beaded filaments are not present in the anterior epithelial cells but emerge after the fiber cells have begun to differentiate, initially near the plasma membrane, but becoming more cytoplasmic as fiber cells age [62], [63]. This is consistent with the nuclear, nuclear lamellar, and sutural nature of cataracts associated with mutations in the beaded filament proteins, although BFSP1 associated cataracts can be cortical. Developmental cataracts have been associated with deletion of exon 6 of the BFSP1 gene, predicted to result absence of functional BFSP1, consistent with the recessive inheritance seen in this family [64]. Cataracts have also been associated with mutations in BFSP2. In one family the cataracts are associated with a nonconservative missense mutation in exon 4 substituting a tryptophan for an evolutionarily conserved arginine in the central rod domain of the protein [65]. A deletion resulting in loss of Glu233 in this protein has also been associated with cataracts in three families, one of whom also had associated myopia [66], [67], [68].

Growth and Transcription Factors

HSF4 is a member of the heat-shock transcription factor family, which regulate expression of heat-shock proteins, including lens αB-crystallin [69], in response to elevated temperature and other stress stimuli. Mutations in HSF4 have been associated with both autosomal dominant and

recessive cataracts. The dominant cataracts present in early childhood and are described as lamellar [70], including the historically important Marner family cataract [71], whereas, the recessive cataracts had a congenital onset and ranged in severity from nuclear with some cortical involvement [72] to total lens opacities at birth with associated nystagmus [73]. Interestingly, the dominant mutations in HSF4 lie within the α-helical DNA-binding domain, whereas, the recessive mutations lie outside this highly conserved functional domain. It is somewhat unclear why mutations in HSF4, which is widely expressed in many tissues including the heart, muscle, lung and brain, should cause isolated cataracts, although this might relate to the highly variable alternative splicing seen in a tissue specific pattern [73].

In addition to HSF4, mutations in a number of additional growth factors are associated with isolated congenital cataracts. These also tend to cause extralenticular defects, suggesting they cause cataracts as part of a broader developmental malformation. These include FOXE3 which causes cataracts as part of an anterior segment mesenchymal dysgenesis (ASMD) spectrum [74]. EYA1 is necessary for the formation of compound eyes in Drosophila, and mutations in humans also cause cataracts with dysgenesis of the anterior segment of the eye, sometimes associated with branchio-oto-renal syndrome [75]. PITX3 mutations cause predominantly posterior polar cataracts associated with ASMD including corneal opacity, iris adhesions, and optic nerve abnormalities. CHX10 mutations can cause cataracts associated with microphthalmia and iris defects, although it is also highly expressed in the developing neuroretina [76]. Mutations in MAF can cause cataracts associated with ASD in some families [77] but isolated in others [78]. Finally, while not listed in Table 1 as a cause of isolated cataracts, mutations in PAX6 certainly can cause anterior segment malformations including cataracts [27].

Other Proteins

In addition to the above classes of genes, an interesting and varied set of genes can cause cataracts when mutated. GCNT2 encodes β-1, 6-N-acetylglucosaminyltransferase, the I-branching enzyme responsible for the change from the fetal i antigen to the adult I antigen on human erythrocytes. The GCNT2 gene expresses 3 forms, A, B, and C, by alternative splicing of the first of three exons, exons 2 and 3 being constant in all forms. While the C form is expressed in erythrocytes, the B form is expressed in lens cells. Homozygous mutations in exon 2, frequently found in Asian individuals with the i blood trait, thus result in cataracts as well. Mutations in the C form exon 1, frequently found in Western individuals with the i trait do not result in cataracts [79]. In addition, a termination mutation has been described in Arab families with autosomal recessive congenital cataracts [80]. CHMP4B is a human ortholog of yeast Snf7/Vps32 (sucrose non-fermenting-7 or vacuolar protein sorting-32), which functions in protein sorting and transport in the endosome-lysosome pathway and facilitates formation of multivesicular bodies as part of the endosomal-sorting complex [81]. The cataract-associated CHMP4 mutation changes the subcellular distribution of a truncated form of a D129W mutant, which also inhibited VLP release from cells cotransfected with HIV-1 Gag polyprotein.

The hyperferritinemia-cataract syndrome is a disorder in which cataracts are associated with hyperferritinemia without iron overload. Ferritin L (light chain) levels in the lens can increase dramatically to levels approaching that of a crystallin. The molecular pathology lies in the ferritin L iron responsive element, a stem loop structure in the 5’ untranslated region of the

ferritin mRNA. Normally, this structure binds a cytoplasmic protein, the iron regulatory protein, which then inhibits translation of ferritin mRNA. Mutation of this structure and overexpression of ferritin by loss of translational control in the hyperferritinemia-cataract syndrome results in crystallization of ferritin in the lens, similar to that described above for the R36S and R58H γ-crystallin mutations, and the appearance of bread crumb like opacities in the cortex and nucleus [82]. Although only the original paper describing this syndrome is referenced in Table 1, many affected families, individuals and mutations have been reported. The X-linked Nance-Horan syndrome (NHS), which includes nuclear cataracts, microcornea, and dental abnormalities, with occasional mental retardation and dysmorphic features, results from mutations in the NHS gene [83]. While the function of the NHS protein hasn't been determined precisely, it has been shown to have two isoforms differing by alternative splicing of exon 1 or 1A. One of which is cytoplasmic while the second localizes to the apical cell membrane in association with the tight junction protein Z0−1 [84]. Similarly, decrease of the cytoplasmic form of this protein causes cataracts in the Xcat mouse [85]. These findings suggest that Nance-Horan syndrome is caused by abnormalities of tight junction function. Cataracts in another family map to a region overlapping NHS, but are accompanied by ventricular septal defects in some patients and the NHS gene in this family does not show mutations, suggesting that it might represent a second locus [86].

The above overview of hereditary congenital cataracts provides some insight into those biological systems most important for developing and maintaining lens transparency, or at least those which are most easily disrupted. While a more complete description of the molecular biology of the normal lens and the clinical aspects of cataracts is beyond the scope of this review, more detailed reviews are available [87], [88]. As suggested by their high expression levels in the lens, the crystallins are the most common group of proteins mutated in inherited congenital cataracts. Other important functional systems include cytoskeletal and membrane proteins, especially those limited to or favored in the lens. Growth and differentiation factors also frequently are seen causing congenital cataracts, often in association with other findings in their developmental spectra. Finally, a varied group of proteins can also cause congenital cataracts. Together these studies provide insights into lens biology easily accessible in no other way. They can also be of direct clinical benefit in some families [89]. In addition, while the pathophysiology of congenital and hereditary cataracts differs in fundamental ways from that of age related cataracts, the study of congenital cataracts can provide insights into the mechanisms of lens transparency and to some of the ways in which it can be lost as the lens ages.

Footnotes

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