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ORIGINAL INVESTIGATION

Genetic landscape of isolated pediatric cataracts: extreme heterogeneity and variable inheritance patterns within genes

Linda M. Reis[1] · **Elena V. Semina**[1,2]

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Abstract

Pediatric cataract represents an important cause of pediatric visual impairment. While both genetic and environmental causes for pediatric cataract are known, a large proportion remains idiopathic. The purpose of this review is to discuss genes involved in isolated pediatric cataract, with a focus on variable inheritance patterns within genes. Mutations in over 52 genes are known to cause isolated pediatric cataract, with a major contribution from genes encoding for crystallins, transcription factors, membrane proteins, and cytoskeletal proteins. Interestingly, both dominant and recessive inheritance patterns have been reported for mutations in 13 different cataract genes. For some genes, dominant and recessive alleles represent distinct types of mutations, but for many, especially missense variants, there are no clear patterns to distinguish between dominant and recessive alleles. Further research into the functional effects of these mutations, as well as additional data on the frequency of the identified variants, is needed to clarify variant pathogenicity. Exome sequencing continues to be successful in identifying novel genes associated with congenital cataract but is hindered by the extreme genetic heterogeneity of this condition. The large number of idiopathic cases suggests that more genes and potentially novel mechanisms of gene disruption remain to be identified.

Introduction

Cataracts are light-scattering opacities in the lens of the eye that often result in vision impairment and affect individuals of all age groups. Pediatric cataracts, particularly congenital or infantile (onset within the first year of life), exemplify the most severe end of the spectrum (Fig. 1a); congenital/infantile cataracts currently explain ~ 10% of childhood blindness worldwide and represent the primary cause of blindness in some countries with a prevalence of 2.2–13.6 per 10,000 births (Khandekar 2008; Wu et al. 2016). Timely diagnosis and prompt surgical intervention in affected children are critical to avoid irreversible amblyopia and allow for normal visual development. Cataracts may be unilateral or bilateral and globally cases are split evenly between the two groups (Wu et al. 2016). Other ocular features that frequently coincide with cataracts in pediatric cases [microcornea, anterior segment defects (Fig. 1b), microphthalmia, persistent fetal vasculature] as well as surgical complications [inflammatory response, secondary glaucoma, posterior capsule opacification (Fig. 1c)] present additional challenges and affect visual prognosis (Lawrence et al. 2005; Whitman and Vanderveen 2014).

Based on their position and morphology, pediatric cataracts can be further classified into total/complete, nuclear, anterior polar, posterior (cortical/subcapsular or polar), and other subtypes (punctate, sutural, lamellar); of these groups, total, nuclear, and posterior subcapsular are the most commonly reported (Haargaard et al. 2004; Wu et al. 2016). While visually significant cataracts need to be removed to preserve visual development, some subtypes of cataract, such as anterior polar, do not interfere with vision in most cases (Dixit et al. 2017). A cataract type may be indicative of gene's expression and function during lens development; however, significant genetic and phenotypic heterogeneity is observed with family members sharing the same mutation displaying differing types of cataract and identical types of cataracts being caused by mutations in different genes (Shiels and Hejtmancik 2017).

Approximately 10–29% of pediatric cataract cases are currently attributed to genetic causes (Haargaard et al. 2004;

✉ Elena V. Semina
esemina@mcw.edu

[1] Department of Pediatrics and Children's Research Institute, Medical College of Wisconsin, Milwaukee, WI 53226, USA

[2] Department of Ophthalmology, Medical College of Wisconsin, Milwaukee, WI 53226, USA

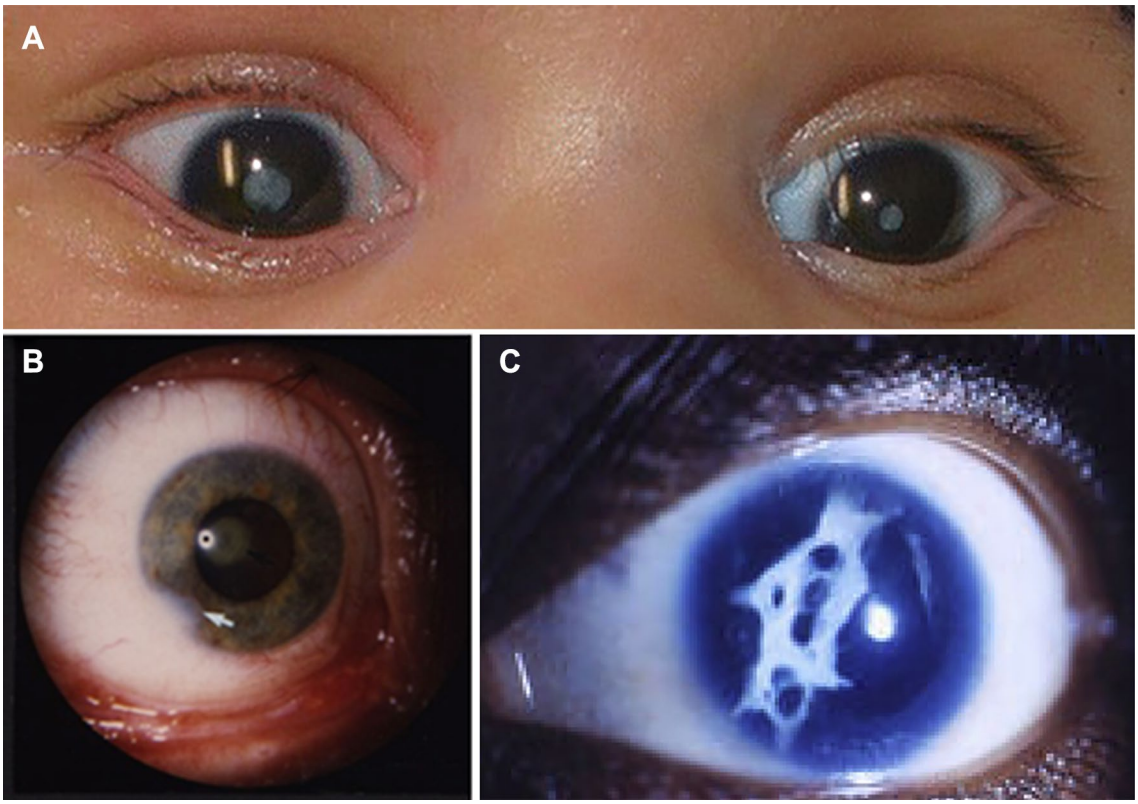

Fig. 1 Ocular photographs of previously reported patients with cataracts. **a** Photograph showing bilateral dense central congenital cataract in an individual with a homozygous deletion of *GCNT2* (reprinted with permission from Fig. 1A of Happ et al. 2016); **b** Photograph of the eye of an individual affected with a heterozygous mutation in *PITX3* showing cataracts and corneal defects (white arrow) (reprinted with permission from Fig. 1 of Semina et al. 1998); **c** Photograph showing development of a fibrous posterior capsular reaction after lens removal for cataract in an individual with aniridia and cataract due to a nonsense mutation in *PAX6* (reprinted with permission from Fig. 2 of Bremond-Gignac et al. 2010)

Trumler 2011). Known environmental causes of cataracts include intrauterine infections, especially by so-called TORCH agents [toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus (CMV), and herpes simplex], trauma, inflammation, metabolic disease (i.e., diabetes), and steroid or radiation treatments (Lloyd et al. 1992; Lu and Yang 2016). A large portion of pediatric cataract cases (up to 2/3 in some studies) remain idiopathic; while unilateral and bilateral cases are evenly distributed overall, unilateral cases are much more likely to be idiopathic compared to bilateral cases (Haargaard et al. 2004; Wu et al. 2016). With the recent successes in next-generation sequencing-based genetic testing and an increasing number of newly identified factors with a significant role in lens development/function, it is likely that the number of cataract cases attributed to genetic causes will grow and explain some of the currently idiopathic disease.

General overview of genes associated with pediatric cataracts

Over 200 syndromes have been associated with pediatric cataract in at least some cases, including numerous metabolic disorders such as lysosomal storage diseases, mitochondrial conditions, and congenital disorders of glycosylation. For some syndromes, such as oculofaciocardiodental (*BCOR*), Marinesco–Sjogren (*SIL1*), and Lowe (*OCRL*) syndromes, congenital cataract is the major ocular finding (Bokenkamp and Ludwig 2016; Krieger et al. 2013; Zhou et al. 2017), while for others, such as branchiooculofacial syndrome (*TFAP2A*), Norrie disease (*NDP*) and Warburg Micro syndrome (*RAB3GAP1, RAB3GAP2, RAB18*, or *TBC1D20*) cataracts are seen as part of generalized ocular dysgenesis along with other

developmental ocular anomalies such as microphthalmia, anterior segment dysgenesis, and coloboma (Al-Dosari et al. 2010; Handley and Sheridan 1993; Sims 1999). Pediatric cataracts can also be seen in many chromosomal disorders, including Down syndrome (Trisomy 21) (Haargaard and Fledelius 2006), Cri-du-chat syndrome (5p deletion) (Farrell et al. 1988), Trisomy 18 (Correia et al. 2017), and 22q11.2 deletion syndrome (McDonald-McGinn et al. 1993), and in retinal disorders such as retinitis pigmentosa (Fahim et al. 1993). For nonsyndromic cases, cataracts may accompany a more complex ocular condition such as, for example, microcornea, myopic chorioretinal atrophy, and telecanthus (MMCAT) associated with mutations in *ADAMTS18* (Aldahmesh et al. 2013), or appear as a more specific finding. Since others have reviewed syndromic causes of pediatric cataract (Trumler 2011), for the purposes of this review, we will focus on genes reported to cause isolated pediatric cataract in at least one family or for which isolated pediatric cataract may be the initially presenting feature.

Mutations in over 52 genes are known to cause isolated pediatric cataract (Table 1). Of these, 35 are significantly associated with isolated pediatric cataract (Table 1A), either only reported in isolated cataract or in multiple families with isolated cataracts while being syndromic in other cases [*CRYAB* (myopathy), *GCNT2* (blood group i), *MAF* (Ayme-Gripp syndrome), *TDRD7* (azoospermia)]. Inheritance is variable with dominant inheritance only reported for 15 of these genes, recessive inheritance only for 7 factors, and both dominant and recessive inheritance patterns described for 13 genes. Mutations in crystallin genes are the most frequently identified genetic cause of isolated cataracts. Crystallin proteins are an important component of the human lens and provide both transparency as well as refractive power (Bassnett et al. 2011). Crystallins are categorized as α-, β-, and γ-crystallins, and each crystallin is further subdivided into individual protein components, e.g., αA and αB crystallin proteins are encoded by separate genes, *CRYAA* and *CRYAB*. Mutations within crystallin genes that result in congenital cataract are thought to cause rapid protein aggregation (Shiels and Hejtmancik 2017). Other major gene families involved in isolated pediatric cataract include transcription factors (*HSF4, PITX3, MAF, PAX6, FOXE3*), membrane proteins (*GJA8, GJA3, MIP, LIM2, CHMP4B, EPHA2, SLC16A12*), cytoskeletal proteins (*VIM, BFSP2, BFSP2*), and numerous additional genes with other/unknown functions (Anand et al. 2018; Evers et al. 2015; Shiels et al. 2010).

An additional 17 genes that typically result in syndromic cataract or broader developmental ocular anomalies have been occasionally reported to cause isolated pediatric cataracts or may have isolated pediatric cataract as the first clinical condition diagnosed with additional features identifiable only through specific testing or developing with time (Table 1B). It is important for ophthalmologists to be aware of syndromic conditions which may initially present as isolated pediatric cataract since correct diagnosis will allow for prompt management of possible additional features. Two conditions deserve special attention as there are specific and effective treatments available. Cerebrotendinous xanthomatosis, caused by mutation in *CYP27A1*, is a disorder which affects the metabolism of cholesterol and bile acid and leads to progressive clinical features including cataract, diarrhea, cognitive/neurological impairment, and xanthomas. Treatment with oral chenodeoxycholic acid (CDCA) therapy improves the syndromic features of the condition, but is most effective if begun early, before significant neurological disease is present. Because early-onset cataract is one of the most specific and consistent early signs of this condition, it should be considered in the differential for pediatric cataract, especially in a patient with diarrhea (Duell et al. 2018). Galactokinase deficiency, caused by recessive mutations in the *GALK1* gene, results in cataracts which are generally reversible (or preventable) with initiation of a lactose-free, galactose-restricted diet (Hennermann et al. 2011). While some regions include galactokinase deficiency in newborn screening panels, this is not universal and thus cannot be assumed to be ruled out in all children with pediatric cataract.

The proportion of cataracts that can be explained by currently known genes has varied between studies. Exome sequencing of hereditary pediatric cataracts identified causative mutations in 43–50% of cases in two studies (Reis et al. 2013; Sun et al. 2014) while next-generation sequencing panels of cataract genes have indicated success rates of 63–75% (Gillespie et al. 2014; Ma et al. 2016; Zhai et al. 2017); it is not clear whether this discrepancy reflects a true increase in detection rates for panels over exome sequencing or variable criteria for pathogenicity and/or population differences. Additional possible loci for isolated pediatric cataracts have been identified through linkage studies or chromosomal rearrangements and are still awaiting gene discovery (Shiels et al. 2010).

Variable inheritance patterns within genes causing pediatric cataracts

The presence of both dominant and recessive alleles in the same gene is observed in a high proportion of genes associated with isolated pediatric cataracts—13/35 (37%). Genes from each of the four major gene families (transcription factors, crystallins, cytoskeletal proteins, and membrane proteins) have been reported to be associated with both dominant and recessive inheritance and specific inheritance/allele types are compared below for each family with a focus on

Table 1 Current summary of genes reported to cause isolated pediatric cataracts

Gene	Full name	OMIM	Locus	Inheritance	References (AD and/or AR)
A: Genes significantly associated with isolated pediatric cataracts					
BFSP1	Beaded filament structural protein 1	603307	20p12.1	AR, AD	Ramachandran et al. (2007), Wang et al. (2013)
BFSP2	Beaded filament structural protein 2	603212	3q22.1	AR, AD	Aldahmesh et al. (2011), Conley et al. (2000)
CHMP4B	CHMP family, chromatin-modifying protein 4b	610897	20q11.22	AD	Shiels et al. 2007)
CRYAA	Crystallin, alpha-a	123580	21q22.3	AD, AR	Litt et al. (1998), Pras et al. (2000)
CRYAB[a]	Crystallin, alpha-b	123590	11q23.1	AD, AR	Berry et al. (2001), Safieh et al. (2009)
CRYBA1	Crystallin, beta-a1	123610	17q11.2	AD, AR	Gillespie et al. (2014), Kannabiran et al. (1998)
CRYBA2	Crystallin, beta-a2	600836	2q35	AD	Reis et al. (2013)
CRYBA4	Crystallin, beta-a4	123631	22q12.1	AD	Billingsley et al. (2006)
CRYBB1	Crystallin, beta-b1	600929	22q12.1	AD, AR	Cohen et al. (2007), Mackay et al. (2002)
CRYBB2	Crystallin, beta-b2	123620	22q11.23	AD	Litt et al. (1997)
CRYBB3	Crystallin, beta-b3	123630	22q11.23	AR, AD	Reis et al. (2013), Riazuddin et al. (2005)
CRYGB	Crystallin, gamma-b	123670	2q33.3	AD	AlFadhli et al. (2012)
CRYGC	Crystallin, gamma-c	123680	2q33.3	AD	Heon et al. (1999)
CRYGD	Crystallin, gamma-d	123690	2q33.3	AD	Stephan et al. (1999)
CRYGS	Crystallin, gamma-s	123730	3q27.3	AD	Sun et al. (2005)
EPHA2	Ephrin receptor epha2	176946	1p36.13	AD, AR	Aldahmesh et al. (2012), Shiels et al. (2008)
FOXE3	Forkhead box e3	601094	1p33	AD, AR	Semina et al. (2001), Valleix et al. (2006)
FYCO1	Fyve and coiled-coil domain-containing 1	607182	3p21.31	AR	Chen et al. (2011)
GCNT2[a]	Glucosaminyl (*n*-acetyl) transferase 2, i-branching enzyme	600429	6p24.3-p24.2	AR	Yu et al. (2001)
GJA3	Gap junction protein, alpha-3	121015	13q12.11	AD	Mackay et al. (1999)
GJA8	Gap junction protein, alpha-8	600897	1q21.2	AD, AR	Ponnam et al. (2007), Shiels et al. (1998)
HSF4	Heat-shock transcription factor 4	602438	16q22.1	AD, AR	Bu et al. (2002), Smaoui et al. (2004)
LEMD2	Lem domain-containing protein 2	616312	6p21.31	AR	Boone et al. (2015)
LIM2	Lens intrinsic membrane protein 2, 19-kd	154045	19q13.41	AR	Pras et al. (2002)
LSS	Lanosterol synthase	600909	21q22.3	AR	Zhao et al. (2015)
MAF[a]	V-MAF avian musculoaponeurotic fibrosarcoma oncogene homolog	177075	16q23.2	AD	Jamieson et al. (2002)
MIP	Major intrinsic protein of lens fiber	154050	12q13.3	AD, AR	Berry et al. (2000), Chen et al. (2017)
PITX3	Paired-like homeodomain transcription factor 3	602669	10q24.32	AD, AR	Aldahmesh et al. (2011), Semina et al. (1998)
RRAGA	Ras-related gtp-binding protein a	612194	9p22.1	AD	Chen et al. (2016)
SIPA1L3	Sipa1-like protein 3	616655	19q13.1	AR, AD?	Evers et al. (2015), Greenlees et al. (2015)
SLC16A12	Solute carrier family 16 (monocarboxylic acid transporter), member 12	611910	10q23.31	AD	Kloeckener-Gruissem et al. 2008)
TDRD7[a]	Tudor domain-containing protein 7	611258	9q22.33	AR	Lachke et al. (2011)
TRPM3	Transient receptor potential cation channel, subfamily m, member 3	608961	9q21.12-q21.13	AD	Bennett et al. (2014)
UNC45B	Unc45, *C. elegans*, homolog of, b	611220	17q12	AD	Hansen et al. (2014)
VIM	Vimentin	193060	10p13	AD	Muller et al. (2009)
B: Genes associated with syndromic/panocular conditions with occasional reports of isolated pediatric cataract					
AGK	Acylglycerol kinase	610345	7q34	AR	Aldahmesh et al. (2012a, b)
COL4A1	Collagen, type IV, alpha-1	120130	13q34	AD	Coupry et al. (2010)
COL4A2	Collagen, type IV, alpha-2	120090	13q34	AD	Ha et al. (2016)
CTDP1	C-terminal domain of rna polymerase II subunit a, phosphatase of, subunit 1	604927	18q23	AR	Tzifi et al. (2011)

Table 1 (continued)

Gene	Full name	OMIM	Locus	Inheritance	References (AD and/or AR)
CYP27A1	Cytochrome p450, subfamily XXVIIa, polypeptide 1	606530	2q35	AR	Khan et al. (2015)
EYA1	Eyes absent 1	601653	8q13.3	AD	Azuma et al. (2000)
FTL	Ferritin light chain	134790	19q13.33	AD	Beaumont et al. (1995)
GALK1	Galactokinase 1	604313	17q25.1	AR	Stambolian et al. (1995)
LONP1	Lon peptidase 1, mitochondrial	605490	19p13.3	AR	Khan et al. (2015)
NF2	Neurofibromin 2	607379	22q12.2	AD	Ragge et al. (1997)
NHS	NHS gene	300457	Xp22.2	XL	Sun et al. (2014)
PAX6	Paired box gene 6	607108	11p13	AD	Ma et al. (2016)
PEX7	Rhizomelic chondrodysplasia punctate, type 1/adult Refsum disease	215100	6q23.3	AR	Braverman et al. (2002)
PEX11B	Peroxisome biogenesis factor 11b	603867	1q21.1	AR	Taylor et al. (2017)
SIL1	Sil1, *S. cerevisiae*, homolog of	608005	5q31.2	AR	Krieger et al. (2013)
SLC40A1	Solute carrier family 40 (iron-regulated transporter), member 1	604653	2q32.2	AD	Yamakawa et al. (2016)
WFS1	WFS1 gene	606201	4p16.1	AD	Berry et al. (2013)

[a]Non-ocular anomalies present in some cases

transcription factors as this group demonstrates more distinguishable patterns. Interestingly, C-terminal extension alleles in genes from different families (*FOXE3, PITX3, CRYBB1, CRYBB3*, and *EPHA2*), are universally reported to cause dominant cataracts.

Transcription factors

FOXE3 was one of the first ocular genes to show both dominant and recessive mutations (Table 2; Fig. 2a). Heterozygous dominant mutations resulting in an erroneous protein extension have been identified in families affected with congenital cataract with or without anterior segment dysgenesis (ASD) (Bremond-Gignac et al. 2010; Doucette et al. 2011; Iseri et al. 2009; Semina et al. 2001). To date, four different extension mutations have been identified; three affect the stop codon directly and the fourth occurs four amino acids before the stop codon but results in a slightly longer erroneous extension. These alleles are clearly deleterious and not present in control populations. The contribution of heterozygous *FOXE3* missense mutations to congenital cataract/ASD is less clear. Four heterozygous missense mutations have been reported as possibly associated with ocular disease. Two rare alleles, c.269G>T, p.(Arg90Leu) and c.289A>G, p.(Ile97Val), were initially reported as disease-causing in patients with Peters anomaly or congenital cataract (Gillespie et al. 2014; Ormestad et al. 2002), but were subsequently identified in heterozygote state in unaffected individuals (Islam et al. 2015; Plaisancie et al. 2017; Ullah et al. 2016). The other two heterozygous alleles noted in some cases with ocular disease appear to be population-specific variants of uncertain significance. The first, c.146G>C, p.(Gly49Ala), has a 4.3% allele frequency in African populations (including five homozygotes) in gnomAD (Lek et al. 2016) and is predicted benign by 4/5 in silico programs. The second, c.601G>A, p.(Val201Met), is seen in 4% of Hispanic alleles in gnomAD (including six homozygotes) and is similarly predicted benign by 4/5 programs. Both alleles have been reported to show possible increased frequency in cases affected with ocular disorders, but their significance is unclear (Reis et al. 2010; Garcia-Montalvo et al. 2014; Iseri et al. 2009). Recessive mutations in *FOXE3* typically result in microphthalmia, aphakia, and/or sclerocornea with glaucoma in many cases (Valleix et al. 2006). Seventeen different recessive mutations have been reported to date, including 6 truncating and 11 missense mutations (The Human Gene Mutation Database (HGMD at http://www.hgmd.cf.ac.uk, Stenson et al. 2014; Plaisancie et al. 2017); all pathogenic recessive variants are very rare (allele frequency < 0.02%) and predicted damaging by in silico programs (Table 2). Functional analysis of several recessive alleles (truncating and missense) and two dominant extension alleles showed reduced transactivation function for all mutants, loss of DNA binding for three of the four recessive mutations (with the exception of p.(Arg90Leu) also reported as dominant, see above), and normal DNA binding but abnormal migration pattern for dominant extension alleles (Islam et al. 2015); these data suggest that while loss of function is the most likely disease mechanism for recessive alleles, dominant extension mutations may result in a yet undiscovered gain of function.

PITX3 shows a similar pattern of dominant mutations associated with cataract/ASD and homozygous mutations associated with microphthalmia with corneal opacity

Table 2 Summary of disease-associated alleles in *FOXE3*

Mode	DNA effect[a]	Protein effect	Phenotype	Functional prediction	gnomAD frequency	References
REC	c.21_24delGGAT	p.(Met7Ilefs*216)	Microphthalmia, aphakia, sclerocornea, ASD	Premature truncation	1/65338 (0.002%)	Iseri et al. (2009)
VUS	c.146G>C	p.(Gly49Ala)	Microphthalmia, coloboma	Damaging by 1/5 (F)	361/26504 (1.4%); 355/8250 African (4.3%); 5 homozygotes	Iseri et al. (2009)
REC	c.232G>A	p.(Ala78Thr)	Microphthalmia, sclerocornea	Damaging by 5/5 (S, PP, F, MA, MT)	NP	Plaisancie et al. (2017)
REC	c.244A>G	p.(Met82Val)	Microphthalmia, sclerocornea, aphakia, ASD	Damaging by 5/5 (S, PP, F, MA, MT)	24/259912 (0.009%)	Iseri et al. (2009)
DOM[b] REC	c.269G>T	p.(Arg90Leu)	Peter's anomaly Aphakia, corneal opacity	Damaging by 5/5 (S, PP, F, MA, MT)	24/268362 (0.009%)	Ormestad et al. (2002) Islam et al. (2015)
DOM[b] REC	c.289A>G	p.(Ile97Val)	Cataract, syndromic Microphthalmia, corneal opacity	Damaging by 5/5 (S, PP, F, MA, MT)	5/243212 (0.002%)	Gillespie et al. 2014), Ullah et al. (2016) Ullah et al. (2016)
REC	c.292T>C	p.(Tyr98His)	Sclerocornea, non-syndromic, bilateral, total	Damaging by 5/5 (S, PP, F, MA, MT)	NP	Ali et al. (2010)
REC	c.307G>A	p.(Glu103Lys)	Congenital cataract	Damaging by 4/5 (S, PP, F, MT)	1/29030 (0.003%)	Khan et al. (2016)
REC	c.310C>T	p.(Arg104Cys)	Microphthalmia, sclerocornea	Damaging by 5/5 (S, PP, F, MA, MT)	1/244576 (0.0004%)	Plaisancie et al. 2017)
REC	c.345G>A	p.(Trp115*)	Microphthalmia, sclerocornea	Premature truncation	NP	Plaisancie et al. (2017)
REC	c.351C>G	p.(Asn117Lys)	Congenital cataract	Damaging by 5/5 (S, PP, F, MA, MT)	NP	Khan et al. (2016)
REC	c.358C>G	p.(Arg120Gly)	Aphakia, corneal opacity	Damaging by 5/5 (S, PP, F, MA, MT)	1/245968 (0.0004%)	Islam et al. (2015)
REC	c.387C>G	p.(Phe129Leu)	Abnormality of the eye	Damaging by 5/5 (S, PP, F, MA, MT)	NP	Retterer et al.(2016)
DOM	c.410G>A	p.(Gly137Asp)	*Thoracic aortic aneurysms and dissections*	Damaging by 4/5 (S, PP, F, MT)	6/244140 (0.002%)	Kuang et al. (2016)
DOM	c.457G>C	p.(Asp153His)	*Thoracic aortic aneurysms and dissections*	Damaging by 4/5 (S, PP, F, MT)	1/29224 (0.003%)	Kuang et al. (2016)
DOM	c.466G>A	p.(Asp156Asn)	*Thoracic aortic aneurysms and dissections*	Damaging by 5/5 (S, PP, F, MA, MT)	76/262358 (0.03%)	Kuang et al. (2016)
REC	c.472G>C	p.(Gly158Arg)	Microphthalmia, aphakia, staphyloma malformation	Damaging by 5/5 (S, PP, F, MA, MT)	1/29234 (0.003%)	Saboo et al. (2017)
DOM	c.490C>A	p.(Arg164Ser)	*Thoracic aortic aneurysms and dissections*	Damaging by 4/5 (PP, F, MA, MT)	NP	Kuang et al. (2016)
REC	c.557delT	p.(Phe186Serfs*38)	Microphthalmia, aphakia, sclerocornea	Premature truncation	NP	Reis et al. (2010)
VUS	c.601G>A	p.(Val201Met)	Possible risk factor for eye malformations	Damaging by 1/5 (F)	272/86326 (0.3%); 236/5842 Hispanic (4.0%); 7 homozygotes	Garcia-Montalvo et al. (2014)
REC	c.679_686dup	p.(Ala230Argfs*3)	Microphthalmia, sclerocornea	Premature truncation	NP	Chassaing et al. (2014)

Table 2 (continued)

Mode	DNA effect[a]	Protein effect	Phenotype	Functional prediction	gnomAD frequency	References
REC	c.705delC	p.(Glu236Serfs*71)	Microphthalmia, aphakia, sclerocornea	Premature truncation	NP	Reis et al. (2010)
REC	c.720C>A	p.(Cys240*)	Microphthalmia, aphakia, sclerocornea	Premature truncation	7/42902 (0.02%)	Valleix et al. (2006)
DOM	c.942dupG	p.(Leu315Alafs*117)	Anterior segment ocular dysgenesis and cataracts	Erroneous extension	NP	Semina et al. (2001)
DOM	c.958T>C	p.(*320Argext*72)	Cataract, ASD, unilateral micro	Erroneous extension	NP	Iseri et al. (2009)
DOM	c.959G>C	p.(*320Serext*72)	Cataract, congenital	Erroneous extension	NP	Bremond-Gignac et al. (2010)
DOM	c.959G>T	p.(*320Leuext*72)	Anterior segment dysgenesis	Erroneous extension	NP	Doucette et al. (2011)

DOM dominant, *REC* recessive, *VUS* heterozygous variant of uncertain significance reported as causative/associated in at least one paper, *PP* PolyPhen-2, *S* SIFT, *F* FATHMM, *MA* mutation assessor, *MT* Mutation Taster, *NP* not present

[a]Reference sequence: NM_012186.2; non-ocular anomalies indicated in italics

[b]Heterozygous alleles also reported in unaffected individuals

(Table 3; Fig. 2b). The majority of reported cases are dominant mutations resulting in congenital cataract with or without ASD, including one early missense and five frameshift mutations which all result in truncation of the normal protein sequence and addition of a long erroneous protein tail that leads to an extension of the total protein length by 5–11 amino acids (to 307–313 amino acids). The most commonly seen pathogenic allele is a recurrent 17-bp duplication reported in 12 families (Reis and Semina 2011; Verdin et al. 2014). Two families with homozygous mutations have been reported. The first, c.650delG, caused congenital cataract in heterozygous individuals and microphthalmia, corneal opacity, and neurological impairment in homozygous family members (Bidinost et al. 2006). The second, c.640_656del17, which deletes the same 17-bp involved in the recurrent duplication, was reported to cause microphthalmia with sclerocornea in homozygous individuals while heterozygotes were unaffected (Aldahmesh et al. 2011). It is interesting to note that while all of the frameshift mutations truncate the normal protein sequence within the C-terminal region, the 17-bp deletion is the only allele with recessive inheritance and also the only one which results in a shorter final protein product and not its extension (Fig. 2a). Functional analysis of three dominant alleles, the recurrent 17-bp deletion, a 1-bp deletion (c.573delC), and the missense allele, showed significantly decreased DNA binding and transactivation activity for the two proteins with altered protein length and mildly decreased binding/transactivation for the missense mutant protein (Sakazume et al. 2007; Verdin et al. 2014).

Both *FOXE3* and *PITX3* have also been reported to play a role in non-ocular disease. Several rare damaging heterozygous missense variants in the forkhead domain of *FOXE3* were recently linked with thoracic aortic aneurysms and dissections (TAAD) in several families (Kuang et al. 2016); no ocular defects were reported in the TAAD families and, likewise, the cardiac phenotype has not been reported in patients with *FOXE3* ocular phenotypes. The TAAD-damaging missense mutations all occur within the second half of the forkhead domain between amino acids 137–164 (Kuang et al. 2016) whereas the ocular disease-associated missense alleles typically occur in the earlier in the forkhead domain (Fig. 2a). The one exception to this pattern is a recessive missense mutation, c.472G>C, p.(Gly158Arg), reported to cause ocular disease; no cardiac phenotype is reported (Saboo et al. 2017). With regards to *PITX3*, a possible association with features of Parkinson's disease has been noted by several studies. A heterozygous ~ 310 kb deletion of *PITX3* (and seven other genes) was identified in a patient with behavioral and neurological anomalies resembling Smith–Magenis syndrome and decreased L-DOPA in cerebrospinal fluid (but no ocular anomalies) (Derwinska et al. 2012). Several studies published association of polymorphisms in *PITX3* with increased risk of Parkinson's disease but a meta-analysis did not support this association other than a possible link with early-onset Parkinson's disease in Caucasians (Jimenez-Jimenez et al. 2014). Additionally, a recent population study suggested a higher rate of dementia in patients with *PITX3* polymorphism and Parkinson's disease (Backstrom et al. 2017).

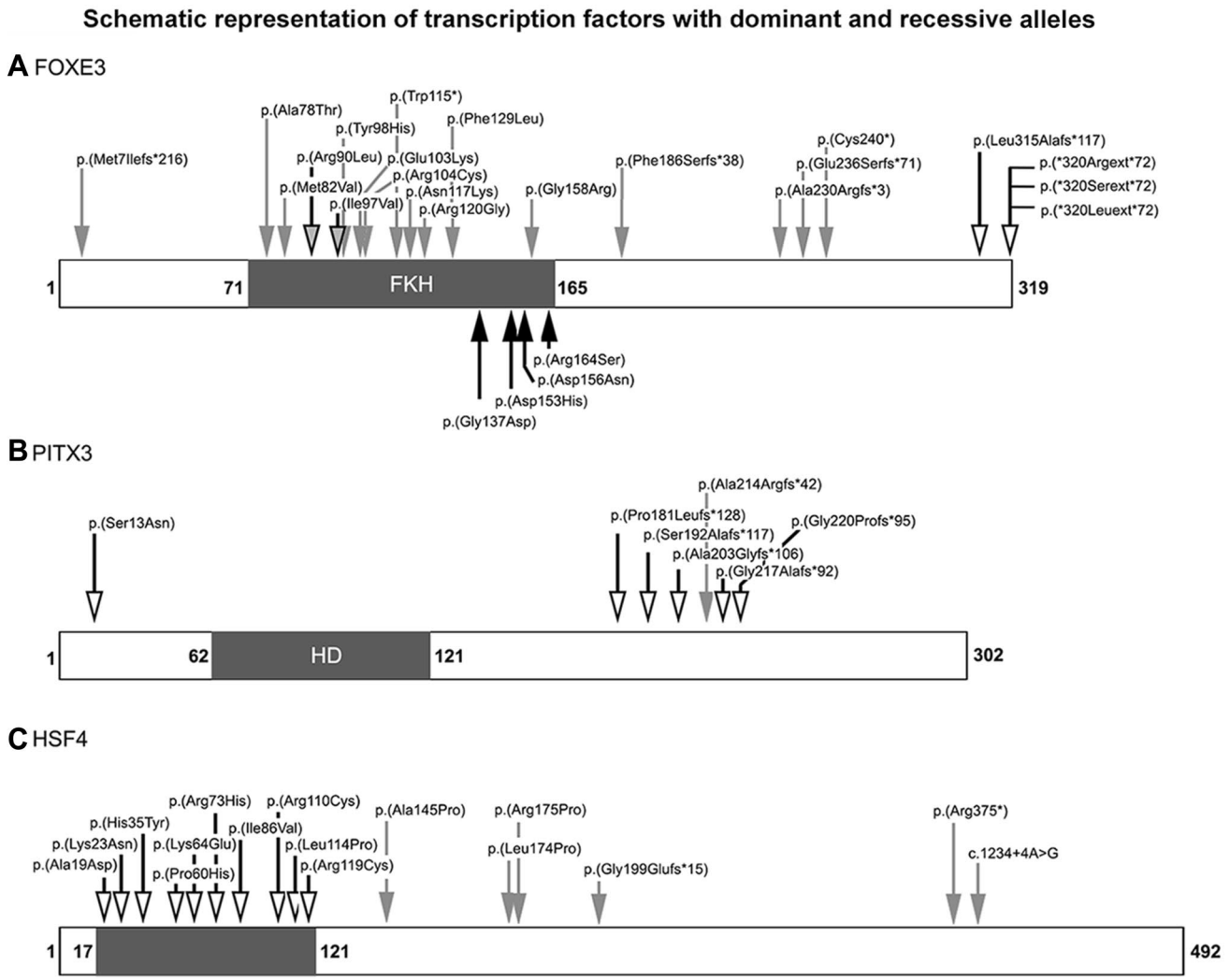

Fig. 2 Schematic representation of transcription factors with dominant and recessive alleles. Schematic representation of the FOXE3 (**a**), PITX3 (**b**), and HSF4 (**c**) proteins showing the pathogenic alleles reported in the literature and recorded in Tables 2, 3 and 4. Dominant alleles are indicated with arrows with a bold outline and an empty-head, recessive alleles are marked with gray arrows without an outline, and alleles reported as both dominant and recessive are shown with gray-headed arrows with a bold outline. Alleles associated with ocular phenotypes are indicated on the top, while thoracic aortic aneurysms and dissections (TAAD) alleles (for *FOXE3*) are marked on the bottom with black arrows

HSF4, another transcription factor, is also associated with both dominant and recessive inheritance (Table 4; Fig. 2c), but in this case both types of alleles result in isolated congenital cataract. Ten missense mutations within the first 120 amino acids have been reported in families with dominant cataracts; functional analysis of five of these variants demonstrated inhibition of DNA binding for all (Enoki et al. 2010). A heterozygous splicing variant upstream of the coding region was also reported in a small Chinese family with congenital cataract (Zhai et al. 2017), but seems likely to be a polymorphism based on the 0.4% East Asian carrier frequency in gnomAD. Three missense mutations later in the gene, within the hydrophobic repeat domain (aa 129–203) (The UniProt Consortium 2017), and three truncating mutations (one frameshift, one nonsense, and one splicing in the final intron) were reported to cause recessive cataracts; functional assessment of the truncating alleles demonstrated a loss of function for all three (Merath et al. 2013).

Crystallin genes

Dominant inheritance is reported for all 12 crystallin genes and recessive alleles have also been identified in five crystallins to date: *CRYAA, CRYAB, CRYBA1, CRYBB1*, and *CRYBB3* (Table 1). As noted above, C-terminal extension mutations are always associated with dominant disease (*CRYBB1* and *CRYBB3*).

Table 3 Summary of disease-associated alleles in *PITX3*

Mode	DNA effect[a]	Protein effect	Phenotype	Functional prediction	gnomAD frequency	References
DOM	c.38G>A	p.(Ser13Asn)	Cataract	Damaging by 3/5 (PP, MT, F)	1/225438 (0.0004%)	Semina et al. (1998)
DOM	c.542delC	p.(Pro181Leufs*128)	Cataract	Truncation of normal protein and erroneous protein tail resulting in extension (5 aa)	NP	Berry et al. (2011)
DOM	c.573delC	p.(Ser192Alafs*117)	Cataract, anterior segment dysgenesis	Truncation of normal protein and erroneous protein tail resulting in extension (5 aa)	NP	Verdin et al. (2014)
DOM	c.608delC	p.(Ala203Glyfs*106)	Cataract	Truncation of normal protein and erroneous protein tail resulting in extension (5 aa)	NP	Liu et al. (2017)
REC	c.640_656del17	p.(Ala214Argfs*42)	Microphthalmia, sclerocornea	Protein truncation	8/104350 (0.008%)	Aldahmesh et al. (2011)
DOM[b]	c.650delG	p.(Gly217Alafs*92)	Cataract [b]Microphthalmia, corneal opacity, and neurological impairment	Truncation of normal protein and erroneous protein tail resulting in extension (5 aa)	NP	Berry et al. (2004), Bidinost et al. (2006)
DOM[c]	c.640_656dup17	p.(Gly220Profs*95)	Cataract, Anterior segment dysgenesis	Truncation of normal protein and erroneous protein tail resulting in extension (11 aa)	NP	Semina et al. (1998)

DOM dominant, *REC* recessive, *PP* polyphen2, *S* S*IFT, F FATHMM, MA* mutation assessor, *MT* mutation taster, *NP* not present

[a]Reference sequence: NM_005029.3 (please note that some variants were renamed from the original publication to match their location on this transcript)

[b]Homozygous mutations resulted in more severe phenotype in children of affected parents

[c]Recurrent mutation seen in 12 families to date

As previously shown for other genes, nonsense-mediated decay (NMD) seems likely to play a role in determining whether mutant alleles result in recessive or dominant effects (Khajavi et al. 2006). For several crystallins, truncating alleles occurring early in the gene and predicted to be subject to NMD are associated with recessive disease while mutations in the final exon (or late in the penultimate exon), which are predicted to escape NMD, are linked with dominant disease. For example, early truncating mutations in *CRYAA* and *CRYBB1* are associated with recessive disease while truncating mutations in the final exon of *CRYBB1* cause dominant cataracts (no truncating mutations have been reported in the final exon *CRYAA*). Similarly, nonsense mutations in the final exon of *CRYGD* and *CRYBB2* are associated with dominant disease while an earlier truncating allele in *CRYGD*, c.51T>G, p.(Tyr17*), was shown not to co-segregate with a dominant cataract phenotype in one family (Reis et al. 2014). This pattern is not consistent among all crystallins; however, truncating mutations in both the final exon as well as exon 2 (of 3 exons) of *CRYGC* are associated with dominant inheritance and *CRYBA1* shows the opposite pattern with truncating and splicing mutations throughout the gene associated with dominant disease while a missense and possible in-frame deletion are associated with recessive cataracts (HGMD; (Stenson et al. 2014)).

The effect of missense mutations in crystallin genes is more difficult to ascertain. For some genes, such as *CRYBB1, CRYBA2, CRYBA4*, and *CRYGS* missense mutations have only been associated with dominant disease. For others, like *CRYAA, CRYAB*, and *CRYBB3*, recessive and dominant missense mutations have been reported in adjacent amino acids with no clear genotype–phenotype correlations (HGMD; Stenson et al. 2014).

Out of all crystallins, *CRYAB* is probably the most unusual as it can cause isolated congenital cataract, isolated skeletal and/or cardiac myopathy, or both. Mutations associated with

Table 4 Summary of disease-associated alleles in *HSF4*

Mode	DNA effect[a]	Protein effect	Phenotype	Functional prediction	gnomAD frequency	References
DOM	c.56C>A	p.(Ala19Asp)	Cataract	Damaging by 5/5 (S, PP, F, MA, MT)	NP	Bu et al. (2002)
DOM	c.69G>T	p.(Lys23Asn)	Cataract	Damaging by 5/5 (S, PP, F, MA, MT)	NP	Lv et al. (2014)
DOM	c.103C>T	p.(His35Tyr)	Cataract	Damaging by 5/5 (S, PP, F, MA, MT)	2/222498 (0.0009%)	Gillespie et al. (2014)
DOM[b]	c.179C>A	p.(Pro60His)	Cataract	Damaging by 5/5 (S, PP, F, MA, MT)	1/245860 (0.0004%)	Li et al. (2016)
DOM	c.190A>G	p.(Lys64Glu)	Cataract	Damaging by 5/5 (S, PP, F, MA, MT)	NP	Berry et al. (2018)
DOM	c.218G>A	p.(Arg73His)	Cataract	Damaging by 5/5 (S, PP, F, MA, MT)	NP	Ke et al. (2006)
DOM	c.256A>G	p.(Ile86Val)	Cataract	Damaging by 2/5 (F, MT)	NP	Bu et al. (2002)
DOM	c.328C>T	p.(Arg110Cys)	Cataract	Damaging by 2/5 (F, MT)	NP	Liu et al. (2015)
DOM	c.341T>C	p.(Leu114Pro)	Cataract	Damaging by 5/5 (S, PP, F, MA, MT)	NP	Bu et al. (2002)
DOM	c.355C>T	p.(Arg119Cys)	Cataract	Damaging by 5/5 (S, PP, F, MA, MT)	NP	Bu et al. (2002)
REC	c.433G>C	p.(Ala145Pro)	Cataract	Damaging by 3/5 (PP, F, MT)	NP	Chen et al. (2017)
REC	c.521T>C	p.(Leu174Pro)	Cataract	Damaging by 5/5 (S, PP, F, MA, MT)	NP	Behnam et al. (2016)
REC	c.524G>C	p.(Arg175Pro)	Cataract	Damaging by 5/5 (S, PP, F, MA, MT)	NP	Forshew et al. (2005)
REC	c.596_600delGGCCG	p.(Gly199Glufs*15)	Cataract	Protein truncation	NP	Forshew et al. (2005)
REC	c.1123C>T	p.(Arg375*)	Cataract	Protein truncation	1/245696 (0.004%)	Sajjad et al. (2008)
REC	c.1234+4A>G	Splicing disruption	Cataract	Exon skipping and protein truncation	3/273010 (0.001%)	Smaoui et al. (2004)

DOM dominant, *REC* recessive, *PP* polyphen2, *S* SIFT, *F* FATHMM, *MA* mutation assessor, *MT* mutation taster, *NP* not present

[a]Reference sequence: NM_001538.3 (please note that some variants were renamed from the original publication to match their location on this transcript)

[b]Patient also has a heterozygous *CYRGC* nonsense allele, so the significance of this allele is uncertain

myofibrillar myopathy and/or dilated cardiomyopathy consist of both truncating and missense alleles, seem to cluster in the central conserved α-crystallin domain and C-terminal region, and can be either dominant or recessive, with the recessive condition being lethal in infancy (Dimauro et al. 2017). Mutations associated with pediatric cataract are primarily missense alleles; while the majority of cataract mutations are within the N-terminal region, several, including one frameshift allele, occur in the α-crystallin domain and C-terminal region (HGMD; Stenson et al. 2014). Both recessive and dominant mutations are noted, including missense mutations in identical or adjacent amino acids which show differing inheritance patterns; a c.32G>A, p.(Arg11His) mutation co-segregated with dominant cataracts in six members of a family affected with congenital nuclear cataract while c.31C>T, p.(Arg11Cys) and c.34C>T, p.(Arg12Cys) mutations segregated with recessive congenital cataract in two consanguineous families (Chen et al. 2009; Jiao et al. 2015).

Cytoskeletal proteins

BFSP1 and *BFSP2* are components of the beaded filament, an important component of the lens cytoskeleton (Alizadeh et al. 2003). Dominant and recessive mutations resulting in congenital cataract have been reported for both genes. For *BFSP1*, there is no clear distinction between mutations types; while most truncating mutations, including in the final exon, are recessive, a splicing mutation in the final intron is reported to be dominant and both dominant and recessive missense mutations are reported. For *BFSP2*, a clearer pattern is emerging with missense/in-frame mutations associated with dominant disease and truncating alleles with recessive (HGMD; Stenson et al. 2014).

Membrane proteins

Three membrane proteins associated with congenital cataract also show both dominant and recessive mutations. For

EPHA2, extending mutations are always dominant and truncating mutations have been recessive; missense mutations can be either dominant or recessive with no discernable pattern. For *GJA8*, the majority of mutations are dominant missense mutations but several recessive truncating mutations as well as one recessive missense mutation were also reported. Similarly, the majority of mutations in *MIP* are dominant missense or truncating mutations; one recessive homozygous missense mutation was reported (HGMD; Stenson et al. 2014).

Novel cataract genes: new pathways

In the last 3 years, use of exome sequencing with or without prior linkage analysis identified several new cataract genes with possible roles in the PI3K/AKT/mTOR signaling, cholesterol biosynthesis or other pathways.

Dominant missense or splicing mutations in RagA GTPase (*RRAGA*) were identified in three unrelated families with dominant congenital or juvenile cataract (Chen et al. 2016). Rag (Ras-related GTPase) GTPases are believed to facilitate the re-localization of mTORC1 to the peri-nuclear region and/or large vesicular structures of the cell. The cellular localization of mTORC1 appears to be critical to its activation in the presence of amino acids. Consistent with this, *RRAGA* mutations were shown to disrupt mTORC1 signaling (Chen et al. 2016).

A homozygous missense mutation in *LEMD2* co-segregated in a large family affected with juvenile Hutterite cataract (initially identified in the Hutterites of North America nearly 30 years ago) and, in some individuals, sudden cardiac death. *LEMD2* is a member of the LEM domain-containing proteins which localize to the inner nuclear membrane and function in nuclear structure organization, cell signaling and differentiation. LEMD2 has been shown to directly interact with A-type lamins and help to anchor the lamina polymer to the inner nuclear membrane. Also, in mouse and cell culture models, loss of *Lemd2* led to the activation of Akt as well as Erk1/2 and other MAP kinases, with embryonic lethality in homozygous animals. Human *LEMD2* and mouse *Lemd2* genes have been shown to be expressed in the developing and postnatal lenses (Boone et al. 2015).

Linkage analysis followed by exome sequencing in a family with siblings affected with isolated congenital dense white cataracts identified nonsense mutations in signal-induced proliferation-associated 1 like 3, *SIPA1L3* (Evers et al. 2015). The SIPA1L3 protein contains several domains, including RapGAP, PDZ, two actin-binding domains, and a coiled-coil leucine zipper; the protein was shown to mediate cell adhesion/polarity and organization of the cytoskeleton. *SIPA1L3* had been identified as a candidate for cataracts through comparison of genes enriched in the lens from the iSyTE project with previously mapped cataract loci (Lachke et al. 2012); however, the previously linked family showed dominant inheritance. Concurrently, heterozygous disruption of *SIPA1L3* was identified in two families with congenital cataract including a patient with a de novo translocation disrupting *SIPA1L3* and additional ocular anomalies and a second patient with a missense variant in *SIPA1L3* (Greenlees et al. 2015). Further work in mice and zebrafish confirmed the importance of *SIPA1L3* in ocular development and lens formation (Greenlees et al. 2015; Walker et al. 2017).

Recessive missense mutations in the *LSS* gene encoding lanosterol synthase, an important enzyme in the cholesterol biosynthesis pathway, which is expressed in the lens, were identified in two families with isolated congenital cataract and in one family with additional syndromic features of small penis, baldness and absence of eyebrows (Chen and Liu 2017; Zhao et al. 2015). Interestingly, treatment of naturally occurring cataracts in rabbit lenses (in vitro) and dogs (in vivo) with lanosterol showed reduction of cataract severity and increase in lens clarity in both (Zhao et al. 2015), suggesting that while identifying new genes responsible for congenital cataract is likely to diagnose only a small number of new cases due to the extreme genetic heterogeneity, this identification may lead to new treatment options for a broader range of cataract patients. Consistent with this, a recent study used this work with lanosterol to guide their identification of pharmacological chaperones and found a novel sterol which was effective in reducing cataract in lenses with both specific crystallin mutations as well as age related cataract (Makley et al. 2015).

Additional candidate genes identified through exome sequencing of non-syndromic pediatric cataract cases include recessive genes *TAPT1, WDR87, MFSD6L, AKR1E2, RNLS*, and *CYP51A1* and dominant *EZR* (Aldahmesh et al. 2012; Patel et al. 2016; Zhai et al. 2017).

Concluding remarks and future directions

The genetics of isolated pediatric cataract is marked by extreme heterogeneity and frequently variable inheritance patterns for alleles within the same gene. This relatively rare genetic phenomenon complicates interpretation of sequencing results in dominant disease as it is not always clear whether a heterozygous variant in a proband represents a disease-causing mutation or carrier status for recessive disease. While location or functional data can distinguish between recessive and dominant alleles in some genes, for many, especially missense mutations, inheritance cannot yet be predicted. Further research will be needed to determine whether some of the reported mutations may be rare benign variants that co-segregated by chance in small families,

whether the variability of inheritance patterns is related to differing conformational/functional effects of the specific missense mutations (i.e., dominant negative vs loss of function), or whether other genetic and/or environmental factors are contributing to cataract formation and influencing whether the mutation appears dominant or recessive. Despite the significant number of new genes identified in the past 10 years with the application of exome sequencing, a large number of hereditary cataract cases/loci remain genetically unexplained (Reis et al. 2013; Shiels and Hejtmancik 2017). Further study of candidate genes and pathways identified through animal models of cataracts (Zeiss 2013), databases such as iSyte which analyze the expression of various genes at different stages of lens development (Kakrana et al. 2018), and genetic analysis of human patients, including exome sequencing, genome sequencing, and microRNA analysis (Yu et al. 2017), is likely to continue to identify new factors involved in hereditary pediatric cataract. These studies will explain additional pediatric cataract cases and extend/connect pathways involved in lens development.

Compliance with ethical standards

Conflict of interest Authors report no conflict of interest.

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