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REVIEW

Candidate Genes for Non-Syndromic Pediatric Cataracts

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Introduction: Pediatric cataracts are a significant cause of vision loss in children and may present in isolation or in association with other ocular or systemic diseases. Despite advances in molecular diagnostics, the underlying etiology of cataracts in most patients remains unknown, even in the setting of a positive family history. Genetic testing for pediatric cataracts is neither standardized nor widely utilized. Lack of standardization is multifold, including limited published clinical and experimental reports and the absence of a comprehensive list of candidate genes with grading of the strength of gene-disease relationships.

Areas Covered: The purpose of this review is to provide a comprehensive list of the 81 candidate genes potentially associated with non-syndromic pediatric cataracts and the accompanying case-based and experimental literature support in order to start the process of developing a standardized approach to genetic testing. Inheritance patterns, other associated ocular findings, and proposed mechanisms of pathogenesis will be described for the candidate genes. Genes that are associated with two distinct phenotypes, one syndromic and one characterized by non-syndromic cataracts, will also be presented. The types of cataracts and age of onset are often highly variable at both the gene and variant level, so they will not be the focus of this review, but are of interest for future studies.

Future Work: Future work is needed to formalize a standardized list of established and candidate genes for non-syndromic pediatric cataracts and to systematically grade our confidence in the gene-disease relationships through the ClinGen framework. An improvement in genetic testing for pediatric cataracts will improve clinical care of these patients and their families regarding prognostication, personalized medical management, and clarification of recurrence risk for reproductive decision making. Further, a better understanding of the pathogenesis of pediatric cataracts can lead to targets for novel treatment development.

Keywords: congenital cataracts, pediatric cataracts, ocular genetics, isolated cataracts, inherited eye diseases

Introduction

Pediatric cataracts have been reported to cause 5–20% of low vision or blindness in children, with an estimated 314,000 new cases worldwide every year.[1] There are many potential etiologies of cataracts in children such as congenital infections, trauma, medication/treatment-related, inflammation, and genetic.[2] It has been reported that 22–50% of pediatric cataracts are inherited, however due to the low rate of genetic testing for pediatric cataracts, the true rate is likely underreported.[3,4] Additionally, genetic testing practices for pediatric cataracts, including gene panel content, are not standardized across laboratories. Consequently, the specific genes analyzed vary substantially between laboratories. Without a standardized list of candidate genes, there is significant variability in which genes are analyzed for individuals undergoing genetic testing for pediatric cataracts. Notably, among seven major commercial laboratories, pediatric cataract gene panels range in size from 66 to 171 genes each and collectively encompass 227 unique genes with only modest overlap across panels (Figure 1). Moreover, 55% (125/227) of these genes are included on only one panel, and only one laboratory's panel includes analysis of mitochondrial DNA genes. The emergence of broad genomic sequencing

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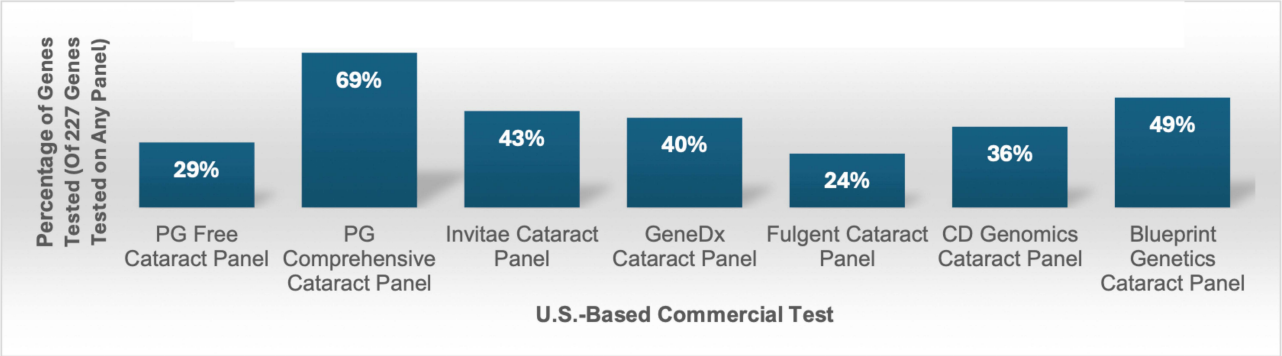

Figure 1 Percentage of Genes Tested on Each U.S.-Based Commercial Test.
Abbreviation: PG, Prevention Genetics.

such as whole exome sequencing (WES) and whole genome sequencing (WGS) exacerbates this issue; data filtration of these assays is highly dependent on an established gene-disease relationship. The absence of a known relationship of a gene to manifestation of cataracts may preclude thorough analysis, leaving potentially causative variants as unrecognized and unreported. Adding to the difficulty in establishing or clarifying these gene-disease associations, the type of cataract and other ocular and systemic findings often differ for patients with pathogenic variants in the same gene, including intrafamilial phenotypic variability.

A standardized list of genes with formalized grading of the strength of the gene-disease relationships is needed to improve genetic testing for patients with pediatric cataracts. The Clinical Genome Resource (ClinGen) is an NIH-funded organization developed in 2013 to standardize genetic testing analysis through expert panels, such as gene curation expert panels (GCEPs). The GCEPs follow a rigorous protocol to grade the strength of gene-disease relationships, known as gene curation. The majority of candidate genes for pediatric cataracts have not yet been addressed in current GCEPs. In order to prepare for gene curation of pediatric cataracts, a thorough examination of the literature is required. The purpose of this review is to provide a summary of the case-based and experimental literature support for the 81 identified candidate genes associated with non-syndromic pediatric cataracts as we prepare for future gene-disease validation work. The genes associated with syndromic pediatric cataracts will be the focus of another review.

Methods

The genes tested in these seven commercial panels, the National Health Service (NHS) panel in England, and an online reference database[5] identified over 500 established and candidate genes for pediatric cataracts. A literature review was completed by utilizing the The Human Gene Mutation Database (HGMD) to identify reports of gene variants and querying PubMed for each gene. Reports on case-based human data and in vitro and in vivo non-human studies that described a possible gene-disease relationship with non-syndromic pediatric cataracts were included. Around 300 of the genes had at least one literature report of an association with pediatric cataracts. The 81 candidate genes that were reported to have a potential association with non-syndromic pediatric cataracts were included in this paper. Genes were included if they were reported to have a possible association with isolated pediatric cataracts and non-syndromic pediatric cataracts with other anterior segment and retinal diseases. Genes that are associated with non-syndromic cataracts in some reports and in association with other systemic diseases in other reports were also included. The remainder of the genes associated with syndromic pediatric cataracts will be reported in a subsequent review paper.

Crystallin Genes

Previous reports predict that about half of isolated cataracts are due to variants in one of the 13 crystallin genes (Table 1).[6–8] Crystallins, of which there are three subtypes (α, β, and γ), occupy about 90% of the protein content of the human lens. While pediatric cataracts associated with pathogenic variants in the crystallin genes are predominantly associated with an autosomal dominant inheritance pattern, some forms are autosomal recessive. Additionally,

Table 1 Crystallin Genes

α-Crystallins	β-Crystallins	γ-Crystallins
CRYAA (AD/AR)	*CRYBA1* (AD/AR)	*CRYGA (AD)*
CRYAB (AD/AR)	*CRYBA2* (AD)	*CRYGB (AD)*
	CRYBA4 (AD/AR)	*CRYGC (AD)*
	CRYBB1 (AD/AR)	*CRYGD (AD)*
	CRYBB2 (AD)	*CRYGS (AD)*
	CRYBB3 (AD)	

Note: Crystallin genes with reported inheritance patterns in parentheses.
Abbreviations: AD, autosomal dominant; AR, autosomal recessive.

pathogenic variants in crystallin genes are generally associated with isolated cataracts, though some have also been linked to other systemic manifestations. Most notably *CRYAB* is associated with cardiac and musculoskeletal abnormalities in addition to cataracts.

α-Crystallins

There are two α-Crystallin subunits, αA and αB, encoded by *CRYAA* and *CRYAB*, respectively.[6,9,10] The α-Crystallins are heat shock proteins that act as molecular chaperones to maintain lens clarity by preventing other proteins from aggregating.[9,11] Heterozygous pathogenic variants in *CRYAA* have been associated with variable types of bilateral cataracts presenting from birth to adulthood.[6,12–35] Many of the pediatric cataracts are also associated with other ocular abnormalities/diseases including microcornea, microphthalmia, and secondary glaucoma.[13–17] Notably, missense variants replacing an arginine appear to be enriched in individuals with cataracts; substitutions of arginine by an amino acid of a different charge may alter heat shock protein structure, decreasing solubility as well as impacting protein expression.[6,13,14,17–25] Patients with heterozygous protein-elongating (eg, stop-loss) variants appear to have more severe ocular abnormalities, including congenital aphakia and retinal and optic nerve anomalies.[26] Biallelic pathogenic variants in *CRYAA* have also been reported in association with pediatric cataracts, with some heterozygous "carriers" also having subtle lens changes.[27,28] Functional in vitro and in vivo mouse and zebrafish studies support this gene-disease relationship.[15,22,29–35]

CRYAB is the crystallin gene with the strongest and best characterized link to non-cataract phenotypes, particularly cardiac and skeletal muscle abnormalities.[6] Heterozygous *CRYAB* pathogenic variants, mostly missense, have been linked to pediatric cataracts occurring either in isolation[14,36–43] or in conjunction with cardiac and/or muscular defects.[44–46] Like *CRYAA*, biallelic pathogenic variants in *CRYAB* have also been reported in individuals with isolated pediatric cataracts.[47,48] However, many reports of individuals with *CRYAB* variants focus predominantly on cardiac disease and do not describe pediatric cataracts as part of the phenotype.[49–71] Functional studies with in vitro assays and in vivo zebrafish and mouse models have validated the pathogenesis of *CRYAB* variants and elucidated the role of αB-Crystallin as a heat shock protein in the lens.[49,50,72–77]

β-Crystallins

Six β-Crystallin genes – 3 acidic (*CRYBA1, CRYBA2*, and *CRYBA4*) and 3 basic (*CRYBB1, CRYBB2*, and *CRYBB3*) – encode proteins that are not heat shock proteins, but rather function to maintain the refractive index of the lens.[50,51] Of the β-Crystallin genes, *CRYBA1, CRYBB1*, and *CRYBB2* are the most well studied and supported with respect to their involvement in cataracts. Heterozygous pathogenic variants in *CRYBA1*, encoding both the βA1-Crystallin and βA3-Crystallin proteins, have been reported in many individuals and families with isolated bilateral pediatric cataracts of various types, with considerable intra-familial variability.[30,31,78–89] However, one group identified a potential association between *CRYBA1* variation and cardiomyopathy or learning disabilities,[52] warranting further studies on phenotypic associations. Whereas missense variants make up the majority of variants identified in the isolated cataract-associated

CRYAA and *CRYAB* variants, the *CRYBA1* mutational spectrum comprises mainly nonsense, frameshift, and splicing variants predicted to result in protein truncation or loss of protein expression, with missense variants reported much more rarely.[24,53–65] Similar to *CRYAA* and *CRYAB*, biallelic pathogenic variants in *CRYBA1* have been reported in association with cataracts, with one group reporting a homozygous frameshift pathogenic variant in association with isolated cataracts in a family.[66] Functional studies, including mouse models and in vitro assays, have strengthened the association of *CRYBA1* with pediatric cataracts.[65,67–71] Heterozygous missense variants in *CRYBA2* have been associated with pediatric cataracts of variable types in individuals, with incomplete penetrance demonstrated in at least one family.[54,90–93] Compared to *CRYBA2*, there have been more reports of heterozygous missense variants in *CRYBA4* associated with pediatric cataracts of various types (often nuclear/lamellar when described) and frequently associated with microcornea/microphthalmia.[54,64,78–81,94–98] Homozygous *CRYBA4* missense variants have also been reported in two families with pediatric cataracts.[82,83]

There are numerous reports of *CRYBB1* heterozygous missense, nonsense, frameshift, and start-loss variants associated with pediatric cataracts of various types; these cataracts often require surgery at a young age, and sometimes present with microcornea/microphthalmia and glaucoma, and, rarely, posterior scleral staphylomas and colobomas.[6,27,32,88,99–113] There have also been five reports of patients with *CRYBB1* biallelic variants associated with cataracts.[84–87,97] In vitro and in vivo mouse studies have also supported the association of *CRYBB1* variants with cataracts.[88,89,114,115] Similarly, *CRYBB2* also has significant clinical evidence supporting the role of heterozygous missense and nonsense variants in development of pediatric cataracts; additionally, some individuals presented with microcornea/microphthalmia, and one individual each with coloboma and microphthalmia.[14,15,27,31,81,108,116–127] Of interest, several variants have been determined to be the result of pseudogene conversions with the pseudogene *CRYBB2P1*.[128–130] Overall, there is less published support for an association between *CRYBB3* and cataracts; the majority of studies report heterozygous missense variants in individuals with various types of cataracts[14,79,90–92,99,131,132] and the same homozygous variant in several families with isolated cataracts.[14,133]

γ-Crystallins

The five γ-Crystallins are encoded by genes mainly clustered on the long arm of chromosome 2 (*CRYGC, CRYGD, CRYGA,* and *CRYGB* are located at 2q33.3 and *CRYGS* is located at 3q27.3) and, like the β-Crystallins, maintain the refractive index of the lens.[11] Of the γ-Crystallin-encoding genes, *CRYGC* and *CRYGD* are the best described and most well supported in their association with pediatric cataracts, whereas *CRYGA, CRYGB*, and *CRYGS* have very limited data available. There are a few reports of heterozygous missense *CRYGA* variants associated with pediatric cataracts[18,134–136] with in vitro and in vivo mouse models reported.[116,137,138] While two studies report a possible association of heterozygous *CRYGB* variants with pediatric cataracts, their causal relationship remains inconclusive;[139,140] however, in vitro and in vivo mouse studies have provided more support by showing abnormal protein development and cataract formation due to the *Crygbnop* variant.[116,138] *CRYGC* has substantial evidence linking heterozygous variants to pediatric cataracts, often with microcornea or microphthalmia.[6,28,88,99,108,114,135,141–155] Similarly, *CRYGD* heterozygous variants have been reported frequently in the literature in association with pediatric cataracts, also sometimes with microcornea or microphthalmia.[6,12,19,27,46,100,114,144,148,151,156–174] Heterozygous *CRYGS* variants have also been reported with progressive congenital cataracts in multiple families[18,39,41,54,56,93,100,175–178] and the role of the gene and variants in cataract formation have been supported by in vitro and in vivo mouse studies.[100–103,178]

Additional Non-Syndromic Cataract Genes

In addition to the crystallin genes, there are 22 genes associated with isolated cataracts in the literature, many of which encode proteins vital to lens development and maintaining clarity (Table 2). The amount of literature support is variable, ranging from one case report to several identified pathogenic variants.

EPHA2 encodes a membrane bound tyrosine kinase receptor expressed in lens epithelial cells.[104] Heterozygous variants in *EPHA2* have been identified with pediatric cataracts in many patients and are suspected to account for 5% of inherited cataracts in South-Eastern Australia.[105,106] Multiple in vivo and in vitro studies have suggested that the absence of EphA2 disrupts cell–cell junctions, thereby disrupting communication and ultimately lens homeostasis.[105,107]

Table 2 Non-Crystallin Genes Associated with Non-Syndromic Pediatric Cataracts

Autosomal Dominant Inheritance	Autosomal Dominant or Recessive Inheritance	Autosomal Recessive Inheritance
EPHA2	*HSF4*	*DNMBP*
CHMP4B	*GJA3*	*FYCO1*
GJA8	*LIM2*	*AKR1E2*
MIP	*BFSP1*	*RNLS*
BFSP2	*SIPA1L3*	*SLC7A8*
CCNP		*WDR87*
LRP5L		
PANK4		
RRAGA		
TSR1		
VIM		

CHMP4B encodes a key protein with multivesicular bodies that regulates membrane remodeling within the lens epithelial cells.[108] Shiels et al (2007) first reported on the association of *CHMP4B* heterozygous variants with pediatric cataracts with further in vitro studies showing the importance of this gene's expression in maintaining lens clarity.[109] Other groups have also reported heterozygous variants in *CHMP4B* in association with pediatric cataracts and our institution has identified two unrelated families with isolated cataracts due to heterozygous variants in *CHMP4B*.[110,111] Additionally, a conditional *Chmp4b*-knockdown mouse deficient in lens CHMP4B results in variable lens changes,[108] providing functional data supporting the role of deficient CHMP4B protein in cataract development.

HSF4 encodes a heat-shock transcription factor required for lens cell growth and differentiation.[112] At least 16 heterozygous or biallelic *HSF4* variants have been reported in association with pediatric cataracts across geographical and ethnic populations; the heterozygous variants reside in the α-helical DNA-binding-domain, whereas the biallelic variants are outside of it.[112] *Hsf4* knockout mice develop cataracts due to abnormal lens development[113] and zebrafish models also support this gene's importance for lens development.[179]

Variants in two connexin genes, *GJA3* (Cx46) and *GJA8* (Cx50) have been linked to pediatric cataracts due to their disruption of hemichannel formation and function, leading to disordered crystallin proteins and cataract development.[180,181] Hassan et al (2021) reviewed the literature and identified 48 variants present in the heterozygous state in individuals with isolated pediatric cataracts, and two instances caused by a homozygous *GJA3* variant.[180] To date, more than 30 heterozygous variants in *GJA8* have been reported in association with pediatric cataracts.[182]

Genes encoding membrane proteins within the lens have also been associated with cataracts. *LIM2* encodes the protein MP20, which colocalizes with Cx46 and is expressed in lens fiber cells as the second most prevalent membrane protein in the lens.[117] Both heterozygous and biallelic variants in *LIM2* have been reported in association with pediatric cataracts.[117–120] *MIP* encodes MIP, an intrinsic membrane protein that comprises 45% of the membrane protein in lens fiber cells.[121] At least 22 heterozygous *MIP* variants have been reported in association with pediatric cataracts and functional in vitro studies support their role in disease pathogenesis.[121]

The lens-specific beaded filament structural proteins (BFSPs) within the cytoskeleton are essential for lens clarity and homeostasis; both *BFSP1* (filesin) and *BFSP2* (phakinin) have been associated with pediatric cataracts.[122] There has been one report of a homozygous *BFSP1* variant and one heterozygous *BFSP1* variant in individuals with pediatric cataracts with supporting in vitro studies.[122–124] A few groups have also identified heterozygous *BFSP2* variants associated with pediatric cataracts.[125–127] Knockout *Bfsp1* and *Bfsp2* mouse models support their importance in preserving lens clarity, but not always cataract formation.[141,183,184]

Pediatric cataracts, sometimes also with microphthalmia and anterior segment dysgenesis, have been reported to be associated with both heterozygous and biallelic variants in *SIPA1L3*, which encodes a GTPase activating protein.[185,186]

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Pathogenicity has been suggested to be due to the role of the encoded protein in Rap1 signaling of the regulation of lens epithelial cell polarity and morphogenesis, as shown in mouse studies.[185,186]

Ansar et al (2018) identified homozygous *DNMBP* frameshift variants in three consanguineous families with bilateral pediatric cataracts; functional studies in *Drosophila* examined the role of the *DNMBP*-encoded dynamic binding protein in tight junctions and regulation of E-cadherin in lens vesicle separation and lens epithelial cell survival.[187]

Iqbal et al (2020) reported that homozygous variants in *FYCO1*, a gene involved with transport of microtubule vesicles, were found in 15% of a cohort of patients with inherited cataracts in Pakistan.[188] The group also reviewed the literature and identified many additional individuals with biallelic *FYCO1* variants (mostly frameshift, nonsense, or affecting splicing) identified with pediatric cataracts worldwide.[188]

Some candidate genes have only one or two cases reported in the literature of heterozygous variants identified in individuals with pediatric cataracts, including *CCNP, LRP5L, PANK4, RRAGA, TSR1*, and *VIM*, and therefore less strong support for their gene-disease relationship. Khaliq et al (2002) reported on a *CCNP* heterozygous variant that segregated with cataracts in members of a four-generation family.[189] Sun et al (2020) identified a heterozygous variant in *LRP5L* associated with a membranous congenital cataract in a four-generation family.[190] Functional studies of the variant supported pathogenicity and proposed that inhibition of laminin γ1 and c-MAF resulted in cataract formation.[190] Sun et al (2019) identified an intronic heterozygous *PANK4* variant in a four-generation family with pediatric cataracts.[191] Furthermore, the authors developed a *Pank4*-mutant mouse that also developed cataracts and demonstrated that this variant affects crystallin expression, suggesting a possible mechanism for disease.[191] Chen et al (2016) identified three heterozygous variants in *RRAGA* associated with pediatric cataracts and performed functional in vitro studies that suggested that their pathogenicity may be due to effects on mTORC1 signaling.[192] Yu et al (2020) reported a *TSR1* heterozygous variant in a family with pediatric cataracts and performed studies in mice and fetal lens tissue to characterize *TSR1* expression.[193] An association of *VIM*, which encodes vimentin, an intermediate filament expressed in the lens, with pediatric cataracts has been suggested based on identification of heterozygous *VIM* variants in two patients.[14,142]

There are also candidate genes with limited case reports in the literature of biallelic variants associated with pediatric cataracts, including *AKR1E2, RNLS, SLC7A8*, and *WDR87*, and like the genes described in the paragraph above, have less strong support for gene-disease association. Aldahamesh et al (2012) reported a homozygous canonical splice site variant in *AKR1E2* that segregated with pediatric cataracts in one family.[143] *AKR1E2* has been shown to have lens-enriched gene expression in mice,[144] and the authors suggest that the variant results in 1,5-anhydro-D-fructose accumulation, which increases osmotic pressure in the lens and leads to cataract development.[143] The same group reported a homozygous truncating variant in *RNLS* associated with pediatric cataracts in a family, yet the mechanism of pathogenesis is unclear.[143] Knopfel et al (2019) identified a homozygous variant in *SLC7A8*, which encodes LAT2 that is highly expressed in the lens, in a family with pediatric cataracts and conducted in vivo mouse studies to support pathogenesis.[145] Khan et al (2017) reported a homozygous *WDR87* variant in a family with pediatric cataracts with associated mouse studies.[66,146] Importantly, the heterozygous parents in the aforementioned families were not reported to have any ocular manifestations, supporting a true autosomal recessive inheritance pattern for these genes, at least with respect to the specific identified variants.

Genes Associated with Non-Syndromic Pediatric Cataracts and Other Anterior Segment Diseases

Pediatric cataracts may also be one component of a more severe anterior segment dysgenesis (ASD) phenotype. While microcornea/microphthalmia is considered a standard feature associated with many pediatric cataracts, other anterior segment disorders such as posterior embryotoxon, iris hypoplasia, congenital corneal opacities, and glaucoma may also be seen in association with 10 genes (Table 3).

There are several genes associated with either anterior segment or global ocular anomalies and pediatric cataracts, including *FOXD3, PITX3, PXDN*, and *SOX2*. Heterozygous variants in *FOXD3*, which encodes a forkhead transcription factor that is an early marker for neural crest cell specification, have been shown to be associated with various forms of

Table 3 Genes Associated with Non-Syndromic Pediatric Cataracts and Other Anterior Segment Diseases

Autosomal Dominant Inheritance		Autosomal Recessive Inheritance	
Gene	**Other Ocular Anomalies**	**Gene**	**Other Ocular Anomalies**
FOXD3	Anterior segment dysgenesis: aniridia, Peters anomaly, anophthalmia	*PXDN*	Anterior segment dysgenesis: microcornea, other corneal abnormalities, glaucoma
PITX3	Anterior segment dysgenesis		
SOX2	Anophthalmia, microphthalmia, and coloboma		
MYOC	Adult and juvenile open angle glaucoma		
WDR36	Glaucoma	*CPAMD8*	Iris hypoplasia, ectopia lentis, corectopia, ectropion uveae
MIR184	Keratoconus		
PIKFYVE	Fleck corneal dystrophy		
TMCO3	Cornea guttata		

anterior segment dysgenesis, including aniridia, Peters anomaly, anophthalmia, and at least one case of isolated congenital cataracts.[147] *PITX3* heterozygous variants have been reported in several reports of patients with pediatric cataracts with or without anterior segment dysgenesis, and functional in vitro studies have shown expression within the early lens vesicle and regulation of lens epithelial cell differentiation.[148] Biallelic variants in *PXDN*, which is in the same signaling pathway as *PITX3* and *FOXE3*, have also been reported in individuals with various ASD phenotypes, including congenital cataract-microcornea, corneal abnormalities, and glaucoma.[149] Although the mechanism is not fully known, it has been suggested that the lack of PXDN protein in the cornea and lens allows for the buildup of reactive oxygen intermediates that leads to clouding of the cornea and lens.[150] *SOX2* pathogenic heterozygous variants can result in multiple ocular anomalies including anophthalmia, microphthalmia, and coloboma, with the latter two commonly found in association with pediatric cataracts.[151]

Several genes traditionally associated with glaucoma have also been reported with pediatric cataracts in a few instances, including *CPAMD8, MYOC*, and *WDR36*. Cheong et al (2016) reported on three unrelated families with biallelic variants in *CPAMD8* associated with iris hypoplasia, ectopia lentis, corectopia, ectropion uveae and pediatric cataracts; in vitro and in vivo (zebrafish and mice) functional studies support the role of *CPAMD8* in anterior segment development.[152] Siggs et al (2020) identified 11 patients with either childhood or juvenile glaucoma and biallelic variants in *CPAMD8*, the majority of whom also had iris abnormalities and cataracts, further supporting its role in anterior segment development.[153] *MYOC* is a gene with a well-known association with adult and juvenile onset open-angle glaucoma.[154] In the Li et al (2016) evaluation of patients with non-familial sporadic pediatric cataracts, they identified one pediatric patient with bilateral cataracts and a heterozygous *MYOC* variant, though it is unclear whether this patient also had glaucoma.[91] The same group identified heterozygous *WDR36* variants in two patients with pediatric cataracts, another gene previously implicated in glaucoma only.[91,155]

Additionally, variants in genes associated with corneal diseases have also been rarely identified in patients with pediatric cataracts. These genes include *MIR184, PIKFYVE*, and *TMCO3*. Hughes et al (2011) evaluated a large family with autosomal dominant keratoconus and early onset anterior polar cataract, identifying a heterozygous *MIR184* variant; functional studies conducted support the pathogenicity of this variant.[156] *PIKFYVE*, previously implicated in fleck corneal dystrophy, is also associated with pediatric cataracts; Mei et al (2022) identified a heterozygous variant segregating with pediatric cataracts in a four-generation family and demonstrated lens defects in a zebrafish model.[157] Chen et al (2016) identified a heterozygous variant in *TMCO3* segregating with cornea guttata and anterior polar cataract, sometimes presenting at birth, in 17 members of a family.[158]

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Genes Associated with Non-Syndromic Pediatric Cataracts and Retinal Dystrophies

Pediatric patients with inherited retinal dystrophies may also have cataracts as an ocular manifestation of their disease as has been previously reported for 14 genes, although the literature support is sparse and mainly include one or two cases (Table 4). For example, a few genes associated with early onset Leber Congenital Amaurosis (LCA) also contain variants associated with pediatric cataracts. Biallelic *AIPL1* variants are associated with LCA and the development of cataracts in teen years or early adulthood in addition to the retinal findings.[159] Biallelic *GUCY2D* variants are also well known to be associated with LCA and have been shown to cause pediatric cataracts as well.[160] Ahmad et al (2011) also reported on a family with LCA due to a homozygous variant in *LCA5* that led to the typical retinal findings in addition to cataract development during the teen years.[161]

*M*icrocornea, *R*od-cone dystrophy, *C*ataract and posterior *S*taphyloma *(MRCS)*, an autosomal dominant ocular disease characterized by reduced visual acuity, congenital cataract, microcornea, posterior staphyloma, and reduced scotopic and photopic responses on electroretinography, is thought to be due to variation in one of at least two genes. Cai et al (2019) reported a heterozygous variant in *ARL2* that segregated within a family with MRCS. *ARL2* encodes a GTP-binding protein belonging to the RAS superfamily; in vitro functional studies demonstrated that abnormal ARL2 resulted in mitochondrial dysfunction and a mouse model largely recapitulated the ocular findings seen in humans.[162] While variation in *BEST1* is most commonly known to be associated with Best vitelliform macular dystrophy, heterozygous variants in *BEST1* have also been linked to MRCS.[163]

There are several other genes associated with retinal and vitreoretinal disorders as well as pediatric cataracts. Biallelic pathogenic variants in *ADAM9* can cause cone-rod dystrophy in addition to pediatric cataracts; in vitro studies have shown *ADAM9* to be downregulated in anterior polar cataracts.[164–166] Khan et al (2012) reported 2 different homozygous variants in *ATOH7* in families with a variety of findings, including vitreoretinal dysplasia, optic nerve hypoplasia, persistent fetal vasculature, microphthalmia, congenital cataracts, microcornea, and corneal opacities.[167] Although mice models do not directly mirror human clinical data, they show some ocular anomalies and *PAX6*, gene known to be key in ocular dysgenesis, is an upstream regular of *ATOH7*.[167] Khan et al (2015) also reported two unrelated patients with a congenital vitreo-retinal dystrophy and pediatric or early-onset cataracts who were identified to have the same homozygous variant in *KCNJ13*.[168] Additionally, Tang et al (2021) reported on a heterozygous missense variant in *AQP5* that segregated with congenital cataracts in a 4-generation family also presenting with opaque vitreous bodies and sometimes posterior staphylomas.[169] They further supported this association through development of an *Aqp5* knockout mouse that recapitulated the early-onset cataract phenotype seen in humans.[169] The group showed that *AQP5* helps

Table 4 Genes Associated with Non-Syndromic Pediatric Cataracts and Retinal Dystrophies

Autosomal Dominant Inheritance		Autosomal Recessive Inheritance	
Gene	**Other Ocular Anomalies**	**Gene**	**Other Ocular Anomalies**
ARL2	MRCS	*AIPL1*	LCA
BEST1	MRCS	*GUCY2D*	LCA
AQP5	Opaque vitreous bodies, posterior staphyoma	*LCA5*	LCA
VCAN	Wagner vitreoretinopathy (myopia, chorioretinal degeneration/atrophy, uveitis, glaucoma)	*ADAM9*	Cone-rod dystrophy
TSPAN12	FEVR, myopia, heterochromia	*ATOH7*	Vitreoretinal dysplasia, optic nerve hypoplasia, PFV, microphthalmia, microcornea, corneal opacities
MIR204	Retinal dystrophy, coloboma	*KCNJ13*	Congenital vitreo-retinal dystrophy
ABCB6	Coloboma	*P3H2*	High myopia (axial), lens subluxation

Abbreviations: FEVR, familial exudative vitreoretinopathy; LCA, Leber Congenital Amaurosis; MRCS, *M*icrocornea, *R*od-cone dystrophy, *C*ataract and posterior *S*taphyloma; PFV, persistent fetal vasculature.

maintain lens clarity and protects against cataract formation, with the suggestion that *AQP5* may regulate vimentin expression via miR-124-3p.1.[169] Wagner vitreoretinopathy, due to heterozygous variants in *VCAN*, may also present with cataract, myopia, chorioretinal degeneration/atrophy, uveitis or glaucoma.[170] Elhusseiny et al (2022) described a child with familial exudative vitreoretinopathy (FEVR), myopia, pediatric cataract, and heterochromia who was found to have a heterozygous in *TSPAN12*, a gene most closely linked to FEVR.[171,172]

Patients with inherited colobomas may also have cataracts as described in a couple families. Conte et al (2015) reported a heterozygous *MIR204* variant that segregated in a large 5-generation family with autosomal dominant retinal dystrophy and coloboma; some individuals in this family also developed pediatric cataracts.[173] *ABCB6*, associated with autosomal dominant coloboma, was also implicated in a family with pediatric cataracts.[132,174]

Homozygous truncating variants in *P3H2 (*previously *LEPREL1*, which encodes prolyl 3-hydroxylase 2, an enzyme involved in hydroxylation of collagens, were identified in multiple families with various ocular features including lens subluxation, lens opacities and axial high myopia.[194,195]

Genes Associated with Non-Syndromic Cataracts and/or Systemic Diseases

In addition to *CRYAB*, as discussed above, 22 genes have been reported in association with isolated cataracts with or without other ocular findings in some patients, syndromic cataracts in others, and systemic manifestations without cataracts in yet others (Table 5).

Table 5 Genes Associated with Non-Syndromic Cataracts and/or Systemic Diseases

Gene	Inheritance of Non-Syndromic Cataracts	Systemic Diseases	Other Ocular Anomalies
PRX	AD	Charcot-Marie-Tooth disease type 4F or Dejerine-Sottas disease (AR inheritance)	
SLC16A12	AD	Renal glucosuria	
TDRD7	AR	Azoospermia	
COL4A1	AD	Porencephaly, diabetes, sporadic intracerebral hemorrhage, and glomerulopathy	
IARS2	AR	Leigh and West syndromes	
PGRMC1	X-linked	Intellectual disability, dental abnormalities, dysmorphic features	
TRPM3	AD	TRPM3-related neurodevelopmental disorder	Glaucoma
SMO	AR	Pallister-Hall-like syndrome	Anterior segment dysgenesis, morning glory disc
LSS	AR	Hypotrichosis, alopecia, intellectual disability, and growth delay	
MAF	AD	Ayme-Gripp syndrome	
UNC45B	AD	Congenital myopathy (AR inheritance)	
ABCA3	AD	Surfactant metabolism dysfunction (AR inheritance)	Microcornea
CYP21A2	AD	Congenital adrenal hyperplasia (AR inheritance)	
PAX6	AD	Variable	Highly variable (eg aniridia, foveal hypoplasia)
ELP4	AD	Variable	Aniridia
FOXE3	AD/AR	Variable	Anterior segment dysgenesis, microphthalmia

(*Continued*)

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Table 5 (Continued).

Gene	Inheritance of Non-Syndromic Cataracts	Systemic Diseases	Other Ocular Anomalies
SHH	AD	Midline abnormalities	FEVR, myopic astigmatism, primary open angle glaucoma, colobomatous microphthalmia
OAT	AR	Neurodevelopmental issues	Retinal degeneration
ADAMTS18	AR	Craniofacial abnormalities	Cone-rod dystrophy, ectopic pupil, ectopia lentis
ADAMTSL4	AR	Dysmorphic facial features, neurodevelopmental and musculoskeletal abnormalities	Ectopia lentis, glaucoma, anterior segment abnormalities
WFS1	AD	Diabetes mellitus, hearing loss (often AR inheritance)	Optic atrophy (often AR inheritance)
OPA3	AD	3-methylglutaconic aciduria type III/Optic atrophy plus syndrome (AR inheritance)	Optic atrophy (AD or AR inheritance)

Abbreviations: AD, autosomal dominant; AR, autosomal recessive.

Several genes have been reported to be associated with either isolated or syndromic cataracts. For example, Yuan et al (2016) identified a heterozygous *PRX* variant in a 4-generation family with pediatric cataracts and incomplete penetrance[196] but did not have systemic findings of Charcot-Marie-Tooth disease type 4F or Dejerine-Sottas disease, which have been associated with biallelic *PRX* variants.[196] *Prx* knockout mice have abnormal lenses, suggesting an importance of this gene in lens development.[197] *SLC16A12* heterozygous variants have been associated with pediatric cataracts, sometimes in isolation and others with renal glucosuria with pathogenicity supported by rat studies.[91,198] Biallelic *TDRD7* variants have been associated with pediatric cataracts in isolation or in combination with azoospermia, with supportive functional in vitro and in vivo studies completed.[83,132,199–201] Patients with *COL4A1* heterozygous variants often have syndromic cataracts in addition to porencephaly, diabetes, sporadic intracerebral hemorrhage, and glomerulopathy, yet non-syndromic pediatric cataracts have been identified in a few families.[93,202] Biallelic variants in *IARS2* have been associated with severe conditions like Leigh and West syndromes, though more rarely with isolated cataracts.[64,203] Hemizygous variants in *PGRMC1* can result in non-syndromic pediatric cataracts or with syndromic features such as intellectual disability, dental abnormalities and dysmorphic features; notably, *pgrmc1* knockdown zebrafish develop cataracts.[204] The role of *TRPM3* in human disease is not well understood but thought to be related to a neurodevelopmental disorder; however, Bennett et al (2014) reported on a family with pediatric cataracts and glaucoma and a heterozygous variant in *TRPM3*.[205] *Trpm3* is co-expressed with *Mir204* in mice ocular tissues, and *Pax6* has been shown to regulate both.[205] In addition to its known association with Pallister-Hall-like syndrome, *SMO* and its encoded smoothened protein are known to be an important regulator of eye development, and biallelic variants were identified in an individual with pediatric cataracts, anterior segment dysgenesis and morning glory disc, comparable to findings in mouse models.[206]

In some instances, the location of the variant determines whether systemic manifestations accompany the cataracts. Biallelic variants in *LSS* have been associated with cataracts in isolation or with systemic manifestations including hypotrichosis, alopecia, intellectual disability, and growth delay; missense variants and those on the N-terminus tend to lead to hair loss, whereas those in the C-terminus usually are associated with cataracts.[207] For variants in *MAF*, at least 17 heterozygous variants in the C-terminus region of the encoded transcription factor have been identified in individuals with isolated cataracts compared to those in the N-terminus, which lead to cataracts as a manifestation of Ayme-Gripp syndrome.[208]

For some genes, biallelic variants are associated with systemic diseases but monoallelic/heterozygous variants have been linked to isolated cataracts. A heterozygous *UNC45B* variant has been linked to autosomal dominant cataracts in one patient, while a homozygous *UNC45B* variant was suggested as the cause of congenital myopathy in another, with in vivo models supporting both phenotypes.[209,210] Though biallelic *ABCA3* variants have been associated with surfactant metabolism dysfunction, multiple different heterozygous *ABCA3* variants were reported by Chen et al (2014) in

individuals with pediatric cataract and microcornea.[211] Similarly, biallelic pathogenic variants in *CYP21A2* cause congenital adrenal hyperplasia, while heterozygous variants have been linked to isolated cataracts.[212]

Some genes associated with anterior segment dysgenesis are also associated with cataracts and variably with systemic diseases. Heterozygous *PAX6* variants are associated with a wide spectrum of disease, ranging from pediatric cataracts in several cases to aniridia, foveal hypoplasia, amongst other ocular findings with or without systemic manifestations (even in absence of subsequent deletion of *WT1*).[213,214] Heterozygous variants in *ELP4*, which is downstream of *PAX6* and involved in PAX6 regulation, can lead to aniridia and pediatric cataracts.[215,216] Variation in *FOXE3* is linked to ocular phenotypes including an array of anterior segment dysgenesis, microphthalmia, and pediatric cataracts, with both autosomal dominant and recessive inheritance, sometimes with ocular only phenotypes and other times with variable systemic manifestations.[217]

Genes associated with vitreoretinal abnormalities may also be associated with cataracts, sometimes with systemic findings. Young et al (2022) reported on a large family with multiple variable ocular manifestations, including pediatric cataracts in most, as well as FEVR, myopic astigmatism, and primary open-angle glaucoma; a heterozygous intronic variant in *SHH* was found to segregate with these phenotypes.[218] SHH plays an important role in eye development through well-characterized pathways involving *PTCH1* and *PAX6*, amongst others.[218] *SHH* variants have also been reported in association with non-syndromic colobobomatous microphthalmia[219] in addition to other more well-described midline abnormalities.[218] In vivo studies have similarly confirmed the importance of *SHH* in ocular development along with allowing for better understanding of its mechanism of pathogenesis.[218,220] Gyrate atrophy is caused by biallelic variants in *OAT*, leading to retinal degeneration and childhood cataracts, with or without neurodevelopmental issues.[221] Biallelic *ADAMTS18* variants have been associated with various ocular abnormalities, including cone-rod dystrophy, ectopic pupils, pediatric cataracts, and ectopia lentis in multiple families with or without craniofacial abnormalities.[222,223] Patients with biallelic *ADAMTSL4* variants have ocular findings such as ectopia lentis, early-onset cataracts, glaucoma and other anterior segment abnormalities; though the majority of individuals with *ADAMTSL4*-related disease do not have systemic involvement, dysmorphic facial features as well as neurodevelopmental and musculoskeletal abnormalities have been reported in some.[224]

Additionally, two genes associated with optic atrophy may also be associated with cataracts and variable systemic manifestations. Wolfram syndrome, associated with pathogenic variants in *WFS1* and characterized clinically by diabetes mellitus, hearing loss, and optic atrophy, can be inherited in either autosomal dominant or recessive manners.[78,93,225] Pediatric cataracts are more common in the autosomal dominant form and a heterozygous *WFS1* variant was identified in a family with cataracts only.[78,93,225] Biallelic variants in *OPA3* are associated with 3-methylglutaconic aciduria type III, also referred to as "optic atrophy plus syndrome", while heterozygous pathogenic variants lead to a less severe form of disease with optic atrophy and cataract, and rarely with neurologic features.[226]

Discussion

At least81 genes have been reported to be associated with pediatric cataracts without systemic manifestations, though the amount of literature support varies widely. Some genes have only one variant identified, while others have dozens with accompanying functional studies. Additionally, not all have known pathogenic mechanisms for how variation leads to disease. Accordingly, clinicians and laboratories should be cautious in assigning pathogenicity to variants associated with genes described within this manuscript with only minimal literature support. In order to have greater confidence in providing genetic diagnoses for patients with pediatric cataracts, ClinGen gene curations are needed to formally grade the strength of each gene-disease relationship. This work is particularly critical given the number of cataract-associated genes potentially presenting with multiple inheritance patterns and with syndromic and non-syndromic phenotypes. Variant interpretation is also inherently tied to a thorough understanding of the gene, as numerous criteria that are directly influenced by the gene curation process (eg mechanism of disease, minor allele frequency thresholds, mutational hotspots).

However, the quality of gene-disease curation is only as good as the literature available. The limited support for many of the genes included in this paper may not be due to lack of pathogenicity, but due to the sparsity of clinical testing and reporting on potential genetic associations with pediatric cataracts. In order to better understand the strength and scope of

gene-disease relationships as well as to the development of genotype-phenotype correlations, more reports on genetic testing results of patients with pediatric cataracts with detailed ocular phenotypes are needed. With improved knowledge, we can begin developing more individualized screening and treatment guidelines for patients and families based on their specific molecular etiology. In addition to increasing our clinical and medical genetic knowledgebase, a better understanding of the pathogenesis of pediatric cataracts through functional studies to help elucidate gene-disease relationships, as well as the impact of individual variants, can lead to advances in treatment.

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