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GENETICS OF ANTERIOR SEGMENT DYSGENESIS DISORDERS

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Abstract

Purpose of review—Anterior segment dysgenesis (ASD) disorders encompass a spectrum of developmental conditions affecting the cornea, iris, and lens and are generally associated with an approximate 50% risk for glaucoma. These conditions are characterized by both autosomal dominant and recessive patterns of inheritance often with incomplete penetrance/variable expressivity. This article summarizes what is known about the genetics of ASD disorders and reviews recent developments.

Recent findings—Mutations in *Collagen 4A1 (COL4A1)* and *Beta-1,3-glucosyltransferase (B3GALT1)* have been reported in ASD patients. Novel findings in other well-known ocular genes are also presented, among which regulatory region deletions in *PAX6* and *PITX2* are most notable.

Summary—Although a number of genetic causes have been identified, many ASD conditions are still awaiting genetic elucidation. The majority of characterized ASD genes encode transcription factors, several factors represent extracellular matrix related proteins. All of the involved genes play active roles in ocular development and demonstrate conserved functions across species. The use of novel technologies, such as whole genome sequencing/comparative genomic hybridization, is likely to broaden the mutation spectrums in known genes and assist in the identification of novel causative genes as well as modifiers explaining the phenotypic variability of ASD conditions.

Keywords

Axenfeld-Rieger anomaly; Peters anomaly; anterior segment dysgenesis; inheritance; gene

INTRODUCTION

Anterior segment dysgenesis (ASD) disorders encompass a wide variety of developmental conditions affecting the cornea, iris, and lens. Congenital anomalies typically include, alone or in combination, corneal opacity, posterior embryotoxon, iris hypoplasia, corectopia or polycoria, and adhesions between the iris and cornea or lens and cornea. Some specific combinations have been recognized as separate diagnostic entities: Axenfeld-Rieger anomaly (ARA) is the term given to the combination of iris hypoplasia, posterior embryotoxon, iris hypoplasia, corectopia/polycoria, and/or irido-corneal adhesions while

Peters anomaly is used to refer to the triad of corneal opacity, defects in the posterior layers of the cornea, and lenticulo-corneal and/or irido-corneal adhesions.

Anterior segment dysgenesis can be an isolated ocular anomaly or accompanied by systemic defects. As a whole, anterior segment anomalies are associated with an approximate 50% risk of glaucoma [1, 2]. The most common syndromes associated with ASDs are Axenfeld-Rieger syndrome (ARS), characterized by ARA of the eye and systemic anomalies (typically hypo/microdontia, redundant periumbilical skin/umbilical hernia, and craniofacial dysmorphism; Figure 1); Peters Plus syndrome (PPS) that comprises anterior chamber eye defects (primarily Peters anomaly; Figure 2) along with short stature, brachydactyly and/or rhizomelic shortening and variable other systemic anomalies; Alagille syndrome, characterized by the presence of posterior embryotoxon in the eye as well as characteristic facial appearance and abnormalities of the liver, heart, skeleton, and kidneys; SHORT syndrome (Short stature, Hyperextensibility of joints or inguinal Hernia, Ocular depression, Rieger eye anomaly, and delay in dental eruption (Teeth); Figure 3); and Pierson syndrome, also called microcoria-congenital nephrosis syndrome. Our review will focus on genes with new reports published within the past two years.

AUTOSOMAL DOMINANT ANTERIOR SEGMENT DYSGENESES

Thus far, the majority of genes associated with ASD have demonstrated autosomal dominant inheritance. Please see Table 1 for details of identified genes and associated phenotypes [3-18].

PAX6

The first gene discovered to play a role in human anterior segment disorders was *PAX6* [3, 4]. The spectrum of *PAX6* mutations and associated phenotypes has been extensively reviewed in several previous publications ([19-21*]. The majority of *PAX6* mutations are nonsense, splicing, insertions, and deletions, and the most common associated phenotype is aniridia, with or without other ocular anomalies ([19-21*]. A few missense mutations have been reported that typically result in milder ocular phenotypes without aniridia including Peters anomaly, uveal ectropion, ectopia pupillae, cataracts, vascularized cornea (autosomal dominant keratitis), elliptical anterior iris stromal defects and iris hypoplasia [22-25]. While *PAX6* deletion was reported in one case of Axenfeld-Rieger syndrome with ocular and systemic anomalies [26], this association was recently rescinded. The authors reported subsequent testing showed normal *PAX6* copy number and identification of a *PITX2* mutation (c.253-11A>G) in the original patient [27**].

Interestingly, several groups have reported deletions of the downstream regulatory region of *PAX6* which leave the coding region intact yet result in an aniridia phenotype [28-31]. Array-based comparative genomic hybridization (aCGH) has recently identified deletions downstream of *PAX6* in three additional families and multiplex ligation-dependent probe amplification (MLPA) analysis identified a fourth. These deletions resulted in aniridia in three families [32*,33*,34*] and atypical aniridia which was initially diagnosed as Axenfeld-Rieger anomaly in the other [35**]. These new reports confirm the importance of the 3' regulatory region and provide further evidence of disease causing mutations outside the coding region of a gene.

Several recent publications have focused on the role of *PAX6* in the developing brain, reporting mutations associated with absence of the pineal gland and interhemispheric brain anomalies [36*], autism [37*], and developmental delay [38*]. A number of other papers published in the past year report novel *PAX6* mutations with expected phenotypes or new occurrences of previously reported mutations [39*,40*,41*,42*].

JAG1

Alagille syndrome, a highly variable developmental disorder involving liver, heart, ocular, and vertebral anomalies along with characteristic facial features, is associated with mutations in or deletions of the *JAG1* gene [5, 6]. Bile duct paucity, chronic cholestasis, heart murmur due to pulmonary stenosis or structural intracardiac disease, and characteristic facial features are seen in almost all affected individuals [43]. Butterfly vertebrae and kidney disease also commonly seen [43]. Ocular anomalies are seen in 78-95% of patients, primarily posterior embryotoxon, although other ASDs such as iris hypoplasia and small corneal diameters are also common and irido-corneal synechiae and corectopia have been occasionally reported [43-45]. Abnormalities affecting the posterior segment of the eye are also seen in most patients, including pigmentary retinopathy, abnormal retinal vessels, and optic disc anomalies, particularly optic disc drusen [44-45].

PITX2 and *FOXC1*

Both *PITX2* [7] and *FOXC1* [8, 9] disruption via intragenic mutation or deletion are associated with Axenfeld-Rieger anomaly with or without systemic anomalies. The spectrum of phenotypes associated with mutations in these genes was recently reviewed [46**]. While other phenotypes including Peters anomaly (*PITX2* and *FOXC1*), isolated iris hypoplasia/iridogoniodysgenesis (*PITX2* and *FOXC1*), ring dermoid of the cornea (*PITX2*), primary congenital glaucoma (*FOXC1*), and aniridia (*FOXC1*) have been associated with mutations in these genes, *PITX2* disruption is primarily associated with ARS with typical ocular anomaly accompanied by dental and umbilical defects and *FOXC1* disruption primarily results in ARS with heart or hearing defects or an isolated ocular phenotype [46]. Duplication of *FOXC1* also results in ASD including iris hypoplasia with glaucoma [47, 48], microcornea [49], Peters anomaly [50], and iridogoniodysgenesis [51].

A recent screening of 80 probands with ASD with or without systemic anomalies provided the first thorough screening of *PITX2* and *FOXC1* for both nucleotide mutations and copy number changes. Intragenic mutations or deletions were detected in 32 (40%) [52**]. Eleven of the 13 probands with *PITX2* disruption had ocular, dental and umbilical anomalies, one had ocular and dental anomalies with umbilicus not examined, and no details were available for the final case [52**]. Details regarding systemic features was provided for 14 of the 19 probands with *FOXC1* disruption: six had isolated ocular (with minor craniofacial features in three), six had ocular and hearing loss (with dental anomalies in four), and two had ocular and dental anomalies with normal hearing [52**].

Similar to *PAX6*, aCGH identified deletion of an upstream regulatory region of *PITX2* in a patient with ARS (Figure 1) [53**]. Array CGH also identified a deletion of *FOXC1* in an infant with partial aniridia, congenital glaucoma, heart defect, and bilateral club feet [35]. Two additional papers presented new cases of intragenic *PITX2* mutations: a novel missense mutation was reported in a patient with Peters anomaly, persistent ocular fetal vasculature, and unilateral microphthalmia [54*]. A previously reported missense mutation was identified in a three-generation pedigree with dental and craniofacial features in affected family members [55*]. These reports further highlight the variable expressivity of *PITX2* mutations, including both ocular and craniofacial features.

FOXC2

Ocular examination of patients with lymphedema-distichiasis syndrome and mutations in *FOXC2*, another member of the forkhead family, identified mild ASD, including partial iris hypoplasia, corectopia, reduced corneal diameter, and localized corneal opacification, in those with mutations within the forkhead domain [10]. No subsequent studies have investigated the role of *FOXC2* in anterior segment dysgenesis.

PITX3

Heterozygous mutations in *PITX3*, another member of the PITX family, have been reported in 11 families with congenital posterior polar cataract with ASD in some individuals [11, 56-60]. The most common mutation is a recurrent 17-bp insertion (c.657_673dup17) in the C-terminal region seen in all but three families. In one family, two individuals inherited homozygous *PITX3* mutations resulting in bilateral microphthalmia, corneal opacification, and severe developmental delay [59]. The paucity of reported cases as well as two recent studies reporting a lack of mutation in 27 probands with isolated congenital cataract [41] and a large family with autosomal recessive history of cataract and mental retardation [61*] suggests that mutations in *PITX3* do not seem to be a major cause of congenital cataract. A recent review summarized what is known about the Pitx3 molecule and the role of *PITX3* in human disease [62*]. New investigations suggest that *PITX3* may play a role in Parkinson's disease as well [63, 64*].

FOXE3

While homozygous/compound heterozygous mutations in *FOXE3* result in microphthalmia with primary aphakia/sclerocornea, heterozygous mutations have been reported in six families with ASD with or without cataract [12, 41, 65-67*]. The first mutation identified and three subsequent heterozygous mutations disrupt the distal part of the gene (three in stop codon 320 and one in residue 315) and result in extension of the FOXE3 protein with the addition of 72-117 erroneous amino acids [12, 41, 66, 67**]. These mutations primarily resulted in anterior segment dysgenesis with cataract, one proband demonstrated colobomatous microphthalmia in addition to ASD, and one had isolated congenital cataract. The first missense mutation, p.R90L in the DNA-binding domain, resulted in familial Peters anomaly with or without cataract [65]. A second missense mutation, p.G49A, was reported in a proband with microphthalmia/coloboma and family members with cataract [66]; although, a more recent study suggested that p.G49A may be a polymorphic variant as it was seen in 3% of African American controls [68]. Interestingly, carrier relatives of individuals with homozygous/compound heterozygous *FOXE3* mutations are almost universally unaffected [66, 68-71], suggesting an alternate mechanism for mutations which result in dominant versus recessive disease. The possibility of a dominant-negative mechanism for heterozygous mutations has been raised, but one group recently challenged this hypothesis [67**].

BMP4 and BMP7

Disruption of *BMP4* by deletion or mutation is associated with ocular, digit (polydactyly), brain/neurological (abnormal structure, hypotonia/delay) and craniofacial (dysmorphic facial features, macrocephaly) anomalies as well as poor growth [72**]. While most individuals with *BMP4* disruption exhibit clinical anophthalmia/microphthalmia with or without ASD [13, 72**], anterior segment anomalies with normal eye size has also been reported [73]. Most recently, a patient with SHORT syndrome was found to have a 2.3-Mb deletion of *BMP4* and 13 other genes [72**]; ocular features included ARA, congenital glaucoma and microcornea (Figure 3).

Another member of the BMP family, *BMP7*, has been recently evaluated in patients with anophthalmia, microphthalmia, and coloboma with mutations not seen in controls (but inherited from unaffected or mildly affected mothers) identified in two patients with anophthalmia and systemic defects [74*]. Screening of patients with ASD phenotypes is indicated to determine whether or not this gene plays a role in other ocular disorders since, similar to *Bmp4*, *Bmp7* has also been implicated in the development of anterior segment structures in mice [75].

COL4A1

One of the most recently reported genes associated with ASD is *COL4A1*, which encodes a collagen chain important in the formation of basement membranes. Mouse *Col4a1* is expressed in the anterior segment of the eye [76]. Mutations in *COL4A1* were initially identified as a cause of porencephaly and brain small vessel disease with stroke and retinal arteriolar tortuosity in some individuals [14, 15] and then also found to be associated with anterior segment ocular anomalies (Table 2) including early-onset cataract [77-79], ARA, corneal opacities, congenital cataract, microcornea, elevated intraocular pressure, and/or glaucoma [80, 81**]. The range of neurological features was recently reviewed [82*]. Brain MRI often reveals anomalies in mutation carriers even in the absence of neurological symptoms.

AUTOSOMAL RECESSIVE ANTERIOR SEGMENT DYSGENESES

Other identified loci are mainly associated with autosomal recessive inheritance of ocular disease (Table 1).

CYP1B1

Homozygous/compound heterozygous mutations in *CYP1B1* are typically associated with primary congenital glaucoma [16]. Several reports have identified mutations in patients with isolated Peters or Axenfeld-Rieger anomaly, typically in association with glaucoma [83-86]. Three out of 11 patients with anterior segment defects had only a single heterozygous mutation identified, suggesting that there may be a second mutation in a *CYP1B1* regulatory region that is yet to be identified, or a mutation in a second gene which contributes to the phenotype, as has been reported for *CYP1B1* and *MYOC* in primary congenital and juvenile onset glaucoma [87-89].

Two novel anterior segment phenotypes were recently linked to *CYP1B1* mutations. Compound heterozygous *CYP1B1* mutations were identified in a patient with Axenfeld-Rieger syndrome including protruding umbilicus and malaligned teeth [90**]. This is the first association of *CYP1B1* with the systemic features of ARS. Homozygous or compound heterozygous mutations were identified in eight probands with mild ectropion uveae, partial aniridia, and congenital glaucoma [91*], further expanding the ocular phenotype associated with *CYP1B1* mutations.

LAMB2

Mutations in *LAMB2* result in Pierson syndrome, characterized by congenital nephrotic syndrome and ocular defects along with neurologic anomalies in some [17]. The primary ocular feature is miosis. Other eye defects that are occasionally observed include iris hypoplasia, ectropion uveae, microcornea, glaucoma, cataract, posterior embryotoxon, microphthalmia, posterior lenticonus, microspherophakia, cloudy or enlarged corneas, and generalized anterior segment dysgenesis [92]. The full spectrum of mutations and associated phenotypes was recently reviewed [93**]. The majority of mutations are truncating; while missense mutations are typically associated with later onset of renal disease and lack of neurologic abnormalities, phenotypic variability is not perfectly correlated to *LAMB2* genotype. Recently, the first two Asian patients with two truncation mutations have been reported with typical ocular findings but milder renal involvement, suggesting that race may play a role in phenotypic variability [94*, 95]. Finally, a novel homozygous missense mutation was seen in nine members of a Mennonite family affected with a variant phenotype consisting of infantile nephrotic syndrome, chorioretinal pigmentary changes, and retinal detachments in some individuals, but no microcoria or neurologic anomalies [96*]. Results

from a screening of 30 patients suggested that *LAMB2* mutations explain all cases of typical Pierson syndrome [93**].

B3GALT

Peters Plus syndrome (PPS) is a rare congenital disorder characterized by anterior chamber eye defects (primarily Peters anomaly) and variable systemic anomalies primarily including short stature, brachydactyly and/or rhizomelic shortening, developmental delay, dysmorphic facial features, cleft lip and/or palate, and heart, genitourinary, or ear anomalies [97]. The role of *B3GALT* in PPS was recently identified with splicing mutations/deletions identified in 20 of 20 patients [18], including a recurrent c.660+1G>A mutation. Subsequent screens revealed mutations/deletions in nine additional patients with typical PPS [98-101*, 102*]; splicing mutations are the most commonly seen. Review of these previous reports suggests that the presence of ASD, short stature, brachydactyly, and characteristic facial features is predictive of *B3GALT* mutations while no mutations in *B3GALT* were identified in eight patients with atypical PPS (some but not all of these typical features) (Table 3) [99, 101*, 104*]. However, recent screening of *B3GALT* in two siblings whose phenotype closely matched PPS failed to identify mutations: the siblings were affected with bilateral corneal opacity, small hands/feet, short stature, and similar facial features along with growth hormone deficiency and hypoplastic pituitary gland in one (Table 3) [103**].

CONDITIONS AND GENES OCCASIONALLY ASSOCIATED WITH ANTERIOR SEGMENT DYSGENESIS

Oculo-dental-digital dysplasia, affecting the eye, dentition, digits of the hands and toes, with facial features, and neurological and hearing deficits, is caused by mutations in the *GJA1* gene [105]. While microphthalmia and microcornea are the primary ocular phenotype, increased risk of glaucoma is also seen and a proportion of patients have iris anomalies [106]. Mutations in *SOX2* are primarily associated with SOX2 Anophthalmia syndrome characterized by clinical anophthalmia/microphthalmia and variable brain, pituitary, genitourinary, and gastroesophageal defects [107, 108]. One individual with isolated iris hypoplasia and a family member with isolated microcornea were reported with a missense mutation in *SOX2* [109*]. Subsequent screening of 28 probands with various ASDs failed to identify any mutations in *SOX2* [110*].

Anterior segment anomalies were first reported with mutations in *FGFR2* in three patients with Pfeiffer or Crouzon syndrome (craniosynostosis syndromes), including two with Peters anomaly [111]. In another family, the proband was affected with ARA and right microcornea along with premature fusion of the sagittal suture. His mother carried the same *FGFR2* mutation and was found to have mild iris hypoplasia and posterior embryotoxon with mild exorbitism but no craniosynostosis [112]. Most recently, corectopia, limbal scleralization, microcornea, and glaucoma were reported in a patient with Pfeiffer syndrome [113*].

NOVEL GENOMIC REGIONS ASSOCIATED WITH ANTERIOR SEGMENT DYSGENESIS

Several new cases of chromosomal anomalies associated with ASD have been reported. Linkage to chromosome 2 was identified in a large family affected with microcornea, atypical iris coloboma, congenital cataract, and microphthalmia [114]. A proband with ARA, global delay, dysmorphic features, and retinoblastoma was found to have del(13)(q12;q22) including the *RBI* gene at 13q14 [115*] and overlapping the 13q deletions reported in two previous cases of ARA, one of whom also exhibited retinoblastoma and

severe developmental delay [116, 117]. A complex chromosomal rearrangement, inv(2)(p22.3q12.1)t(2;16)(q12.1;q12.2), was detected in another patient with aniridia, aphakia, corneal anomalies, and congenital glaucoma. The authors hypothesized that the separation of the *IRXB* gene cluster from its regulatory region at 16q12.2 is the cause of the observed anterior segment dysgenesis [118*]. Finally, aCGH identified a 326-kb deletion at 9p22.31 in a patient with an atypical PPS phenotype consisting of unilateral Peters anomaly and microphthalmia, intrauterine growth retardation, clinodactyly, dysmorphic facial features, agenesis of the right lung, and heart, gastrointestinal, and genitourinary defects [119]. This deletion encompasses 8 of the 9 exons of the *ROR2* gene, previously associated with an autosomal recessive form of Robinow syndrome, a condition that sometimes involves infantile glaucoma (Dr. Alex Levin, personal communication).

CONCLUSION

Identification of the genetic etiology of ASDs has revealed multiple genetic loci. While the primary phenotype associated with ASD genes is typically distinct, most genes are involved in multiple related ASD phenotypes with a high degree of inter- and intrafamilial variable phenotypic expressivity. Novel technologies including whole genome/exome sequencing and aCGH have greatly facilitated identification of the genetic etiology of these conditions [120*] and are likely to broaden the spectrum of mutations associated with known ASD genes as well as to assist in identification of new causative and modifier loci. Array CGH has identified several deletions of regulatory regions in ASDs, highlighting a novel disease mechanism. Genetic interactions between known factors are beginning to be elucidated and are likely to provide insight into the basis of the extreme variability of what are currently known as single-gene conditions.

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Abbreviations

(ASD)	Anterior segment dysgenesis
(ARS)	Axenfeld-Rieger syndrome
(ARA)	Axenfeld-Rieger anomaly
(PPS)	Peters Plus syndrome
(aCGH)	Array-based comparative genomic hybridization

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KEY POINTS

- Anterior segment dysgeneses demonstrate different modes of inheritance and a high degree of inter- and intrafamilial phenotypic variability. Molecular genetic analysis and examination of family members can assist in providing genetic counseling.
- A significant overlap among phenotypes attributed to mutations in different ASD genes is well recognized. Functional studies have suggested that several of the ASD causative genes may function within a common pathway.
- Identification of deletions downstream of *PAX6* and upstream of *PITX2* highlight the importance of regulatory region mutations in human ocular disease and suggest that aCGH data should be analyzed for possible deletions of upstream and downstream regions of other genes.

Fig 1. Photographs of Patient with *PITX2* regulatory region deletion and Axenfeld-Rieger syndrome

Previously Published

Legend: A. Facial photograph showing maxillary hypoplasia, thin upper lip, and broad nasal bridge. B. Left eye corectopia. C. Right eye posterior embryotoxon. D. Dental anomalies, including maxillary hypodontia. E. Redundant periumbilical skin.

Source: Figure 5 from Volkmann BA, Zinkevich NS, Mustonen A, et al. Potential novel mechanism for Axenfeld-Rieger syndrome: deletion of a distant region containing regulatory elements of *PITX2*. *Invest Ophthalmol Vis Sci* 2011, 52(3):1450-1459.

Fig. 2. Photograph of an eye affected with Peters anomaly (courtesy of Dr. Alex Levin)

Fig 3. Photographs of Patient with *BMP4* deletion and SHORT syndrome

Previously Published

Legend: **A.** Patient displays short stature, macrocephaly, decreased subcutaneous fat in upper trunk and head, prominent forehead, sunken eyes, small chin, and hypoplastic nares. **B,C.** Ocular anomalies include Axenfeld-Rieger anomaly, congenital glaucoma, and microcornea.

Source: Figure 1A-C from Reis LM, Tyler RC, Schilter KF, et al. *BMP4* loss-of-function mutations in developmental eye disorders including SHORT syndrome. *Hum Genet* 2011. Epub ahead of print.

Table 1

Summary of Major Genes Associated with Anterior Segment Dysgeneses

Gene	OMIM	Locus	Phenotypes	Mode of inheritance	Reference
<i>PAX6</i>	607108	11p13	Aniridia, Peters anomaly, keratitis, foveal hypoplasia, congenital cataract	AD	[3,4]
<i>JAG1</i>	601920	20p12	Alagille syndrome with posterior embryotoxon, iris hypoplasia, small corneal diameter, iridocorneal synechiae and corectopia	AD	[5,6]
<i>PTX2</i>	601542	4q25-q26	Axenfeld-Rieger syndrome, Peters anomaly, iris hypoplasia	AD	[7]
<i>FOXC1</i>	601090	6p25	Axenfeld-Rieger syndrome, Peters anomaly, iris hypoplasia, primary congenital glaucoma, aniridia	AD	[8,9]
<i>FOXC2</i>	602402	16q24.3	Lymphedema-distichiasis syndrome, ASD	AD	[10]
<i>PTX3</i>	602669	10q25	Congenital posterior polar cataract with or without ASD	AD	[11]
<i>FOXE3</i>	601094	1p32	ASD with cataract, Peters anomaly, microphthalmia	AD or AR	[12]
<i>BMP4</i>	112262	14q22-q23	ASD with or without A/M, systemic anomalies	AD	[13]
<i>COL4A1</i>	120130	13q34	Porencephaly/ small vessel brain disease with early-onset cataract or ASD in some	AD	[14,15]
<i>CYP11B1</i>	601771	2p22-p21	Primary congenital glaucoma, Peters anomaly, other ASD, aniridia	AR	[16]
<i>LAMB2</i>	150325	3p21	Pierson syndrome with microcoria or other ASD	AR	[17]
<i>B3GALT1</i>	610308	13q12.3	Peters Plus syndrome	AR	[18]

AD, Autosomal Dominant; AR, Autosomal Recessive; A/M, anophthalmia/microphthalmia; ASD, anterior segment dysgenesis

Table 2Anterior Segment Anomalies Described in Patients with *COL4A1* mutations

<i>COL4A1</i> mutation	Patient identifier	Age	Anterior segment anomalies ^a	Other ocular features ^a	Neurological symptoms	Brain anomalies	Reference
p.G1236R	Patient 1	54	cataract (age 52)	exotropia, mild retinal arteriolar tortuosity	Yes	Yes	[77]
p.G1236R	Patient 2	33	“polar” cataract (age 33)	mild esotropia	Yes	Yes	[77]
p.G1236R	Patient 3	30	nuclear cataract (age 30)	mild exotropia	Yes	Yes	[77]
p.G755R	Proband	14	dot-like cataracts (age 9)		Yes	Yes	[78]
p.G755R	Mother	NR	cataracts (age mid-30s)		Yes	Yes	[78]
p.G755R (presumed)	Maternal grandmother	NR	cataracts (age 9)		Yes	Yes	[78]
p.G755R	Case	21	unilateral posterior “capsular” cataract (age 21)	infantile strabismus	No	Yes	[79]
p.G720D	Case II.2	58	iridogoniodysgenesis, iris hypoplasia, microcornea, congenital cataract, elevated IOP (age 55)	high myopia	Yes	Yes	[80]
p.G720D	Case III.2	37	congenital cataracts, congenital glaucoma, microcornea, peripheral opacities	unilateral retinal detachment	Yes	Yes	[80]
p.G720D	Case III.3	32	congenital cataract, juvenile glaucoma, unilateral polycoria,	high myopia	No	Yes	[80]
p.G720D	Case III.4	29	microcornea, cataract		No	Yes	[80]
p.G720D	Case IV.1	8	congenital cataract, iris hypoplasia, microcornea		Yes	Yes	[80]
p.G2159A	A.I.1	58	Iridogoniodysgenesis, iridocorneal synchia, iris hypoplasia, microcornea, congenital cataract, elevated IOP	high myopia, macular hemorrhages	No	Yes	[81**]
p.G2159A	A.II.1	38	congenital cataract, iris hypoplasia, high IOP (age 23), microcornea, peripheral corneal opacities, corectopia	myopia, severe amblyopia, unilateral retinal detachment	Yes	Yes	[81**]
p.G2159A	A.II.2	35	microcornea, congenital cataract, juvenile glaucoma (age 32), corneal opacities, corneal neovascularization, iridocorneal synchia, unilateral corectopia and polycoria	high myopia, unilateral retinal detachment	No	Yes	[81**]

<i>COL4A1</i> mutation	Patient identifier	Age	Anterior segment anomalies ^a	Other ocular features ^a	Neurological symptoms	Brain anomalies	Reference
p.G2159A	A.II.3	29	microcornea, cataract	strabismus	No	Yes	[81**]
p.G2159A	A.III.1	8	congenital cataract, iris hypoplasia, microcornea	strabismus	Yes	Yes	[81**]
p.G755R	B.I.1	47	lens opacities	severe hyperopia	Yes	Yes	[81**]
p.G755R	B.II.1	10	congenital cataract, posterior embryotoxon, microcornea		No	Yes	[81**]

^aBilateral unless specified; IOP = intraocular pressure

Table 3

Comparison of Patients with and without mutations in B3GALTL

Publication	B3GALTL mutations	Peters Anomaly	Anterior Chamber Anomaly	Short Stature (<=3 rd)	Brachydactyly	Developmental Delay	Cleft Lip/Palate	Heart Anomaly	Genitourinary anomaly	Ear Anomaly	Brain anomaly
Lesnik Oberstein, et al. (2006) [18]	20/20	15/19	20/20	20/20	NR	15/19	9/20	5/19	renal 5/20	NR	NR
Kapoor et al. (2008) [98]	1/1	1/1	1/1	1/1	1/1	1/1	0/1	0/1	0/1	1/1	0/1
Reis, et al. (2008) [99]	4/4	4/4	4/4	4/4	4/4	3/3	4/4	3/4	2/4	3/4	2/3 hypoplasia of corpus callosum and enlarged ventricles (2)
Halderman-Englert et al. (2009) [100]	1/1	NR	1/1	1/1	1/1	NR	0/1	1/1	1/1	1/1	1/1 -hypoplasia of corpus callosum and enlarged ventricles
Dassie-Ajdid et al. (2009) [101*]	2/2	2/2	2/2	2/2	2/2	2/2	0/2	2/2	0/2	0/2	NR
Aliferis et al. (2010) [102*]	1/1	1/1	1/1	1/1	1/1	1/1	0/1	0/1	1/1	1/1	1/1 hypoplasia of corpus callosum and enlarged ventricles
Total Mutation Positive	29/29 (100%)	21/27 (78%)	29/29 (100%)	29/29 (100%)	9/9 (100%)	22/26 (85%)	13/29 (45%)	11/29 (38%)	9/29 (31%)	6/9 (67%)	4/6 (67%)
Reis et al. (2008) [99*]	0/4	3/4	4/4	1/4	1/3	2/3	2/4	1/4	3/4	4/4	3/4
Dassie-Ajdid et al. (2009) [101*]	0/2	2/2	2/2	0/2	0/2	2/2	0/2	0/2	0/2	0/2	NR
Al-Gazali et al. (2009) [103**]	0/2	2/2	2/2	2/2	1/2	2/2	0/2	1/2	0/2	0/2	2/2 hypoplasia of corpus callosum (1), hypoplastic pituitary gland (1)
Shimizu et al. (2010) [104*]	0/1	0/1	1/1	0/1	1/1	NR	1/1	1/1	0/1	1/1	NR
Total Mutation Negative	0/9	7/9 (78%)	9/9 (100%)	3/9 (33%)	3/8 (38%)	6/7 (86%)	3/9 (33%)	3/9 (33%)	3/9 (33%)	5/9 (56%)	5/6 (83%)

NR= Not Reported