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ORIGINAL INVESTIGATION

An update on the genetics of ocular coloboma

Aisha S. ALSomiry[1] · Cheryl Y. Gregory-Evans[1] · Kevin Gregory-Evans[1]

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Abstract
Ocular coloboma is an uncommon, but often severe, sight-threatening condition that can be identified from birth. This congenital anomaly is thought to be caused by maldevelopment of optic fissure closure during early eye morphogenesis. It has been causally linked to both inherited (genetic) and environmental influences. In particular, as a consequence of work to identify genetic causes of coloboma, new molecular pathways that control optic fissure closure have now been identified. Many more regulatory mechanisms still await better understanding to inform on the development of potential therapies for patients with this malformation. This review provides an update of known coloboma genes, the pathways they influence and how best to manage the condition. In the age of precision medicine, determining the underlying genetic cause in any given patient is of high importance.

Introduction

Ocular coloboma (from the Greek word *Koloboma*) is a congenital malformation resulting in a 'defect' or 'hole' in various structures of the eye. It is caused by a failure of the embryonic fissure to close during development. Ocular colobomata are characteristically variable in appearance—affecting to varying degrees the iris, choroid and/or optic nerve (Fig. 1). In general, both eyes will be affected to the same degree; however, asymmetry between eyes can occur. The condition is often associated with other, systemic anomalies in particular of the central nervous system (Table 1). The prevalence of ocular coloboma is estimated to be from 2 to 14 per 100,000 (Shah et al. 2011). In recent times, a number of animal models of ocular coloboma have been recorded (Table 2) providing evidence that gene mutations are causative.

✉ Kevin Gregory-Evans
kge30@mail.ubc.ca

[1] Department of Ophthalmology and Visual Sciences, University of British Columbia, 2550 Willow Street, Vancouver, BC V5Z 3N9, Canada

Embryology and prevalence of coloboma defects

Normal human ocular morphogenesis begins with the bilateral evagination of the optic vesicles from the neuroectoderm of the developing brain from 21 to 25 days of gestation (Ozanics and Jacobiec 1982) (Fig. 2). The equivalent stage in mouse is embryonic (E) day 8.5 and at six somites (~ 12 h post-fertilization [hpf]) in zebrafish. As the optic vesicle reaches the surface ectoderm, the ventral surface of the optic vesicle and optic stalk begin to invaginate at about day 30 (E9.5 in mouse; 18–20 somites [~ 18.5 hpf] in zebrafish). This forms a double-layered optic cup where the inner layer of the optic cup becomes the retina and the outer layer forms the retinal pigment epithelium (Onwochei et al. 2000). At the same time, a groove is formed along the length of the ventral aspect of the optic vesicle and optic stalk, referred to as the optic fissure which is fully formed at day 32 (E10.5 in mouse; 24 hpf in zebrafish). Concurrently, the surface ectoderm thickens to form the lens placode which itself invaginates to form the lens vesicle. This complex tissue remodeling is required to allow the hyaloid vessels from the vascular mesoderm to enter the eye, and to allow the optic nerve fibers from the retinal ganglion cells to exit the eye and connect to the brain. By the 5th week of gestation (E11.5 in mouse; ~ 36 hpf in zebrafish), the margins of the optic fissure displace the periocular mesenchyme to fuse in the central region of the fissure and proceeds proximally along the optic stalk and distally toward the optic cup rim. Recent evidence

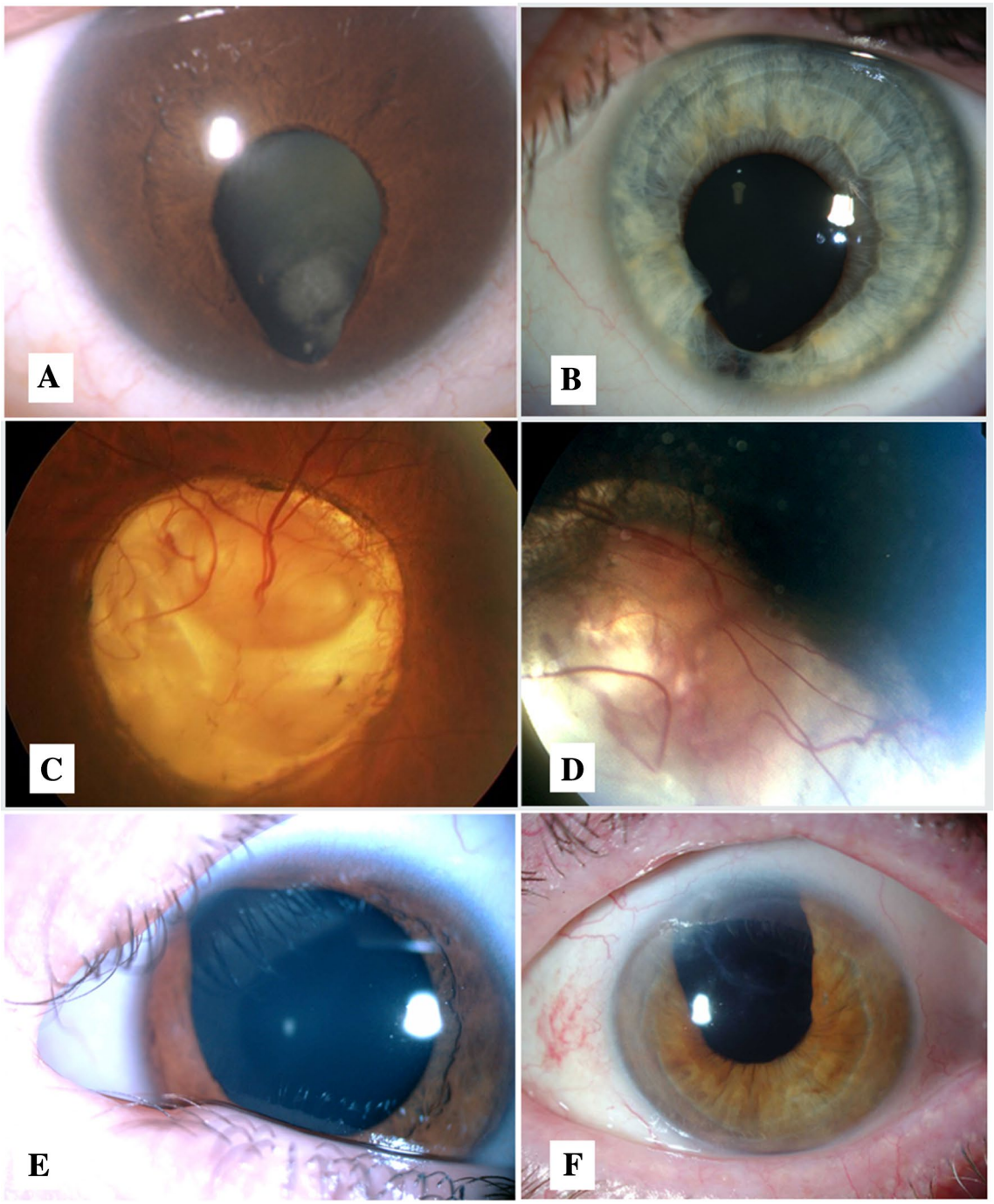

Fig. 1 Clinical images of ocular coloboma. **a** Complete iris coloboma (with lens opacity); **b** partial iris coloboma; **c** optic nerve coloboma; **d** choroidal plus optic nerve coloboma; **e** phenocopy coloboma, superior coloboma; **f** phenocopy coloboma, surgical coloboma. All images are from Caucasian patients, except in D who is of Afro-Caribbean decent

from chick studies suggests there is a second mechanism of closure termed 'intercalation' characterized by migration of $SOX2^{+}/PAX2^{+}$ positive astrocytes into the fissure and outgoing optic nerve fibers (Bernstein et al. 2018). Fissure closure is complete by 7 weeks of gestation (E12.5 in mouse; 48 hpf in zebrafish). Although these morphogenetic events have been well characterized, the molecular mechanisms driving these processes are yet to be fully described. Since the timing of optic fissure morphogenesis is very early in humans, little tissue is available for study; thus, the majority of our understanding to date has come from mouse and zebrafish models of the disease phenotype.

Table 1 Human uveal coloboma genes

OMIM number	Disease	Type of coloboma	Gene or locus	Point mutations	Syndromic (S) or isolated (I)	Inheritance pattern
614497	Microphthalmia with coloboma 7	I, R, Ch	ABCB6	3 (100% C)	I	AD
243310	Baraitser–Winter syndrome 1	I, R	ACTB	68 (25% C)	S	AD
614583	Baraitser–Winter syndrome 2	I, R	ACTG1	33 (35% C)	S	AD
102560	**Ocular coloboma**	**I, Ch**	**ACTG1**	**2 (100% C)**	**I**	**AD**
615113	Microphthalmia, isolated 8	R, I, Ch	ALDH1A3	10 (40% C)	I	AR
601110	CDG syndrome type Id	I	ALG3	25 (10% C)	S	AR
136760	Frontonasal dysplasia	I	ALX3	8 (< 10% C)	S	AR
300166	Microphthalmia, syndromic 2	I, M	BCOR	102 (60% C)	S	XLD
112267	Eye, brain, ENT, skeletal defects	Ch, ON	BMP7	11 (< 10% C)	S	AD
218340	Temtamy syndrome	I, R, Ch, O	C12orf57	20 (80% C)	S	AR
216360	Coach syndrome	O, Ch	CC2D2A	99 (80% C)	S	AR
610188	Joubert syndrome 5	R	CEP290	108 (17% C)	S	AR
214800	CHARGE syndrome	O, I, R	CHD7	270 (80% C)	S	AD
602499	Colobomatous macrophthalmia	I, ON, ch	CRIM1	11 (< 5% C)	S	AD
180849	Rubinstein–Taybi syndrome 1	I, R, Ch, O, M	CREBBP	97 (19% C)	S	AD
604219	Cataract 9	I	CRYAA	18 (3% C)	S	AD, AR
274270	DPD deficiency	I, Ch, M	DPYD	19 (2% C)	S	AR
166750	Ocular–oto-dental syndrome	I, R	FADD	5 (20% C)	S	AD
300244	Terminal osseous dysplasia	I, L	FLNA	137 (< 1% C)	S	XLD
610256	Anterior segment dysgenesis 2	I, R	FOXE3	19 (40% C)	S	AR
601723	Microphthalmic coloboma	R, Ch	FZD5	16 (< 10% C)	I	AD
613702	Klippel–Feil syndrome 3	I, R, ON	GDF3	9 (10% C)	S	AD
118100	Klippel–Feil syndrome 1	I, Ch	GDF6	17 (< 5% C)	S	AD
613842	Joint laxity, short stature, myopia	I, R, Ch	GZF1	19 (20% C)	S	AR
300915	Microphthalmia, syndromic 13	I, R, Ch, O	HMGB3	2 (50% C)	S	XL
612109	Oculoauricular syndrome	I, M, R, Ch	HMX1	2 (100% C)	S	AR
300472	Corpus callosum agenesis	I, O	IGBP1	3 (30% C)	S	XLR
213300	Joubert syndrome 1	R, O, Ch	INPP5E	55 (28% C)	S	AR
181270	Scalp–ear–nipple syndrome	I, L	KCTD1	11 (< 10% C)	S	AD
609460	Goldberg–Shprintzen syndrome	I	KIAA1279	5 (20% C)	S	AR
147920	Kabuki syndrome 1	R, I, Ch, O	KMT2D	148 (< 5% C)	S	AD
222448	Donnai-Barrow syndrome	I	LRP2	27 (< 10% C)	S	AR
153430	**Ocular coloboma**	**I, Ch**	**LCP1**	**1 (100% C)**	**I**	**AD**
615877	Coloboma ± skeletal dysplasia	I, R, Ch	MAB21L2	7 (100% C)	S/I	AD, AR
610202	Cataract 21 ± microcornea	I, M	MAF	44 (30% C)	S	AD
616722	Retinal dystrophy with coloboma	I	MIR204	1 (100% C)	I	AD
617306	COMMAD syndrome	I	MITF	4 (100% C)	S	AR
249000	Meckel syndrome 1	I	MKS1	45 (< 10% C)	S	AR
309800	Syndromic microphthalmia 1	O, Ch, I, M	NAA10	22 (90% C)	S	XL
163200	SFM (nevus) syndrome	I, Ch	NRAS/HRAS/KRAS	77 (< 5% C)	S	Mosaic

Table 1 (continued)

OMIM number	Disease	Type of coloboma	Gene or locus	Point mutations	Syndromic (S) or isolated (I)	Inheritance pattern
610125	Microphthalmia syndromic 5	I, R	OTX2	26 (3% C)	S	AD
120200	**Ocular coloboma**	**I, Ch, R, O**	**PAX6**	**162 (< 1% C)**	**I**	**AD**
120330	Papillorenal syndrome	R, O, M	PAX2	34 (100% C)	S	AD
615665	Joubert syndrome 22	M, O	PDE6D	22 (25% C)	S	AR
280000	CHIME syndrome	R	PIGL	19 (100% C)	S	AR
180500	Axenfeld–Rieger syndrome type	I, M	PITX2	31 (< 5% C)	S	AD
236670	Walker–Warburg syndrome	M, O	POMT1	16 (< 20% C)	S	AR
305600	Focal dermal hypoplasia	I, Ch, M, R, O	PORCN	20 (40% C)	S	XLD
309500	Renpenning syndrome	Ch, I	PQBP1	29 (< 10% C)	S	XLR
109400	Basal cell nevus syndrome	I	PTCH1/2	205 (< 1% C)	S	AD
163950	Noonan syndrome 1	R, O, I	PTPN11	125 (< 5% C)	S	AD
615583	Verheij syndrome	I, R, ON	PUF60	26 (20% C)	S	AD
600118	Warburg micro syndrome 1	R, M	RAB3GAP1	33 (< 1% C)	S	AR
611038	Microphthalmia, isolated 3	O	RAX	12 (< 10%)	I	AR
616428	Microphthalmic coloboma 10	M, I, Ch, R	RBP4	12 (80% C)	I	AD, AR
216360	COACH syndrome	Ch	RPGRIP1L	45 (< 5% C)	S	AR
107480	Townes–Brocks syndrome 1	R, Ch	SALL1	48 (< 1% C)	S	AD
216820	**Ocular coloboma**	**R, I, Ch, O**	**SALL2**	**1 (100% C)**	**I**	**AR**
607323	Duane-radial ray syndrome	I, Ch, M, O	SALL4	31 (50% C)	S	AD
214800	CHARGE syndrome	O, I, R	SEMA3E	11 (< 10% C)	S	AD
611638	Microphthalmic coloboma 5	R, Ch, I, O	SHH	58 (< 5% C)	I	AD
157170	Holoprosencephaly 2	M, Ch, I, R	SIX3	27 (< 10% C)	S	AD
212550	Optic disc anomalies	I, Ch, ON	SIX6	7 (< 10% C)	I	AR
603457	Bosma arhinia syndrome	R, I, Ch	SMCHD1	143 (30% C)	S	AD
601707	Curry–Jones syndrome	I, Ch, O, M	SMOH	4 (50% C)	S	Mosaic
206900	Microphthalmia, syndromic 3	R, O, M, Ch	SOX2	28 (8% C)	S	AD
612713	Kahrizi/CDG1Q syndrome	I	SRD5A3	18 (30% C)	S	AR
601186	Microphthalmia with coloboma 8	I, R, ON	STRA6	42 (< 5% C)	I	AR
192430	Velocardiofacial syndrome	M, Ch, R, I	TBX1	37 (< 1% C)	S	AD
302905	Abruzzo–Erickson syndrome	R	TBX22	11 (< 5% C)	S	AR
615145	Microphthalmia with coloboma 9	O, I, Ch	TENM3	4 (100% C)	I	AR
113620	Branchiooculofacial syndrome	I, O	TFAP2A	23 (40% C)	S	AD
610688	Joubert syndrome 6	Ch	TMEM67	88 (< 3% C)	S	AR
608091	Joubert syndrome 2	R, Ch	TMEM216	11 (< 3% C)	S	AR
614424	Joubert syndrome 14	R	TMEM237	26 (15% C)	S	AR
610932	**Ocular coloboma**	**I, Ch**	**TWF1**	**1 (100% C)**	**I**	**AD**
610093	Microphthalmia, isolated 2	I	VSX2/CHX10	24 (20% C)	I	AR
606417	10q26 deletion syndrome	I, ON	WDR11	10 (< 5% C)	S	AD
220210	Ritscher–Schinzel syndrome 1	I, R	WSHC5	6 (60% C)	S	AR
120433	Coloboma syndrome (COB1)	I, R, Ch	YAP1	2 (100%)	S	AD
235730	Mowat–Wilson syndrome	I, R	ZEB2	158 (< 1% C)	S	AD
609637	Holoprosencephaly 5	Ch	ZIC2	17 (< 5% C)	S	AD
218650	Craniosynostosis	R, C, O	2q24–2q31	–	S	–
147791	Jacobsen syndrome	I, Ch, R	11q23	–	S	–

Table 1 (continued)

OMIM number	Disease	Type of coloboma	Gene or locus	Point mutations	Syndromic (S) or isolated (I)	Inheritance pattern
194190	Wolf–Hirschhorn syndrome	I	4p16.3	–	S	–
609408	Holoprosencephaly 8	I, R	14q13	–	S	–
605738	Microphthalmia with coloboma 2	I, R	15q12-q15	–	I	–
115470	Cat eye syndrome	I, Ch, O	22q11	–	S	AD
107550	Aortic arch anomalies	R	Unknown	–	S	–
304050	Aicardi syndrome	M, I, O	Unknown	–	S	XLD
601427	Anterior chamber cleavage	I	Unknown	–	S	AR
210350	Biemond syndrome 2	I, R, M	Unknown	–	S	AD, AR
215105	Chondrodysplasia punctate	R	Unknown	–	S	AR
218650	Craniosynostosis	I, R, Ch, O	Unknown	–	S	–
223370	Dubowitz syndrome	I, M	Unknown	–	S	AR
229400	Frontofacionasal dysostosis	I, O	Unknown	–	S	AR
234100	Hallermann–Streiff syndrome	I, C, O, M	Unknown	–	S	–
164210	Hemifacial macrosomia	I, O, R, Ch, M	Unknown	–	S	AD
142500	Heterochromia iridis	I	Unknown	–	I	AD
274205	Hypoplastic thumb, coloboma	Ch	Unknown	–	S	AR
300337	Hypomelanosis of Ito	I, R, M	Unknown	–	S	Mosaic
244300	Kapur–Toriello syndrome	I, Ch, R, O	Unknown	–	S	AR
600628	Loose anagen hair syndrome	I, Ch, M	Unknown	–	S	–
602499	Macrophthalmia + microcornea	I, R, O, M, Ch	Unknown	–	I	AD
251505	Microphthalmia	R, Ch	Unknown	–	I	AR
605738	Microphthalmia with coloboma 2	M, I, R	Unknown	–	I	–
157980	MOMO syndrome	R, Ch, O	Unknown	–	S	AD
258865	Oral–facial–digital syndrome 9	R, Ch	Unknown	–	S	AR
155145	Pai syndrome	I	Unknown	–	S	AD
606519	PHACE association	I	Unknown	–	S	XLD
184705	Steinfeld syndrome	I, R	Unknown	–	S	AD
600122	Verloes syndrome	Ch	Unknown	–	S	AR, XL
601706	Yemenite deaf–blind syndrome	I, Ch	Unknown	–	S	AR

OMIM lists 315 entries under the search term 'coloboma'. In the table, we list 110 uveal-derived coloboma caused by optic fissure closure defects. The other entries in OMIM describe coloboma in animals, only affect the eyelid, referred to as a macular coloboma, only occur in one eye, are described as not having coloboma, or has the word 'coloboma' in the related reference list. Reported number of pathogenic point mutations [and approximate % that have coloboma (C) in that disease] in the genes listed in ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/) and from literature review

Entries in bold are isolated coloboma genes

O optic nerve, *I* iris, *Ch* choroid, *R* retina, *M* microphthalmia, *AD* autosomal dominant, *AR* autosomal recessive, *XL* X-linked, *XLD* X-linked dominant, *XLR* X-linked recessive

Partial or complete failure of optic fissure closure results in the clinical entity recognized as ocular coloboma (Fig. 1). Typically, this is seen as a ventral gap in the iris; however, it can also affect the retina, choroid and optic nerve. The extent of the coloboma depends on when in development the fissure fails to close, thus if late in the closure process then only an iris defect is seen. The effect on visual impairment can range from complete loss of vision to being asymptomatic. In blind children of European descent, 5–10% suffer from ocular coloboma, making this an important contributor to visual impairment. The prevalence is variable affecting 2.6 per 10,000 births in the USA (Porges et al. 1992) and

Table 2 Animal models of ocular coloboma

Gene	Genotype	Phenotype	Species	References
Abcb6	*Abcb6*$^{-/-}$	C	Zebrafish	Wang et al. (2012)
Aldh1a3	*Aldh1a3*$^{-/-}$	C	Mouse, zebrafish	Fares-Taie et al. (2013) Yahyavi et al. (2013)
Aldh7a1	*Adlh7a1*$^{-/-}$	C	Zebrafish	Babcock et al. (2014)
Axin2	*Axin2*$^{-/-}$	I	Mouse	Alldredge and Fuhrmann (2016)
Adamts16	*Adamts16*$^{-/-}$	C	Zebrafish	Cao et al. (2018)
Cdh2	*Cdh2*$^{-/-}$	C	Mouse, zebrafish	Masai et al. (2003) Chen et al. (2012)
Cdo	*Cdo*$^{-/-}$	C	Mouse	Zhang et al. (2009)
Dkk	*Dkk*$^{+/-}$	C	Mouse	Lieven and Rüther (2011)
Fbn2	*Fbn2*$^{-/-}$	I	Mouse	Shi et al. (2013)
Foxg1	*Fox1*$^{-/-}$	I, C, O	Mouse	Smith et al. (2017)
Fzd5	*Fzd5* $^{-/-}$	I, C	Mouse, zebrafish	Burns et al. (2008) Liu et al. (2016)
Ipo13	*Ipo13*$^{-/-}$	C	Zebrafish	Huang et al. (2018)
Jag1	*Jag1 +/dDSL*	I	Mouse	Xue et al. (1999)
Lamb1	*Lamb1*$^{-/-}$	C, O	Zebrafish	Lee and Gross (2007)
Lmo2	*Lmo2*$^{-/-}$	C, O	Zebrafish	Weiss et al. (2012)
Lrp6	*Lrp6*$^{-/-}$	I, C	Mouse	Kelly et al. (2004)
Nlz1/2	*Nlz1*$^{-/-}$ *Nlz2*$^{-/-}$	C	Zebrafish	Brown et al. (2009)
Pax2	*Pax2*	I, C, O	Mouse	Favor et al. (1996) Schwarz et al. (2000)
Pitx2	*Pitx2*$^{-/-}$	O	Mouse	Gage et al. (1999)
sfrp1a/sfrp5	*sfrp1a/5*$^{-/-}$	C	Zebrafish	Holly et al. (2014)
Sall2	*Sall2* $^{-/-}$	C	Mouse	Kelberman et al. (2014)
Smad7	*Smad7*$^{-/-}$	I, C	Mouse	Zhang et al. (2013)
Stra6	*Stra6*$^{-/-}$	C	Zebrafish	Casey et al. (2012)
Sox11	*Sox11*$^{-/-}$	C	Zebrafish	Pillai-Kastoori et al. (2014)
Sox4	*Sox4*$^{-/-}$	C	Zebrafish	Wen et al. (2015)
Tbx2	*Tbx2* $^{-/-}$	C	Mouse	Behesti et al. (2006)
Vax1	*Vax1*$^{-/-}$	I, C, O	Mouse	Hallonet et al. (1999)
Vax2	*Vax2*$^{-/-}$	I, C, O	Mouse, zebrafish	Take-uchi et al. (2003) Hagglund et al. (2013)
Zic 2	*Zic2*$^{-/-}$	R	Zebrafish	Sedykh et al. (2017)

C chorioretinal coloboma, *I* iris coloboma, *O* optic nerve coloboma, *R* retina

7.5 per 10,000 births in China (Hornby et al. 2000). Since posterior segment coloboma can be asymptomatic, the rates may be higher than reported. This is an important consideration when a patient is seen in the clinic, thus relatives of an affected patient should be examined to inform on inheritance patterns and prevalence. It has been suggested that variability across different populations could be attributed to environmental factors such as maternal vitamin A deficiency (Hornby et al. 2003), drug use (Miller and Stromland 1999) and alcohol abuse during pregnancy (Stromland and Pinazo-Duran 2002). However, based on evidence of recurrent risk in siblings (Morrison et al. 2002) and coloboma being present at birth, the major cause of ocular coloboma is genetic (Gregory-Evans et al. 2004).

Clinical features of ocular coloboma

Ocular coloboma can affect the cornea, iris, lens, choroid, retina and optic nerve. This often occurs in isolation (without systemic association) and there can be marked asymmetry between the left and right eyes (Morrison et al. 2002). Ocular coloboma was first described in the iris in 1673 (Bartholin the Younger 1673) and the iris is still the most frequently observed site for ocular coloboma. It is typically located in the inferonasal quadrant of the eye. Iris colobomas are wedge-shaped transillumination defects of the iris that can be complete (involving all layers of the iris) or incomplete (involving the stroma only or the pigment epithelium only) (Fig. 1). Corneal coloboma usually manifests as a marked

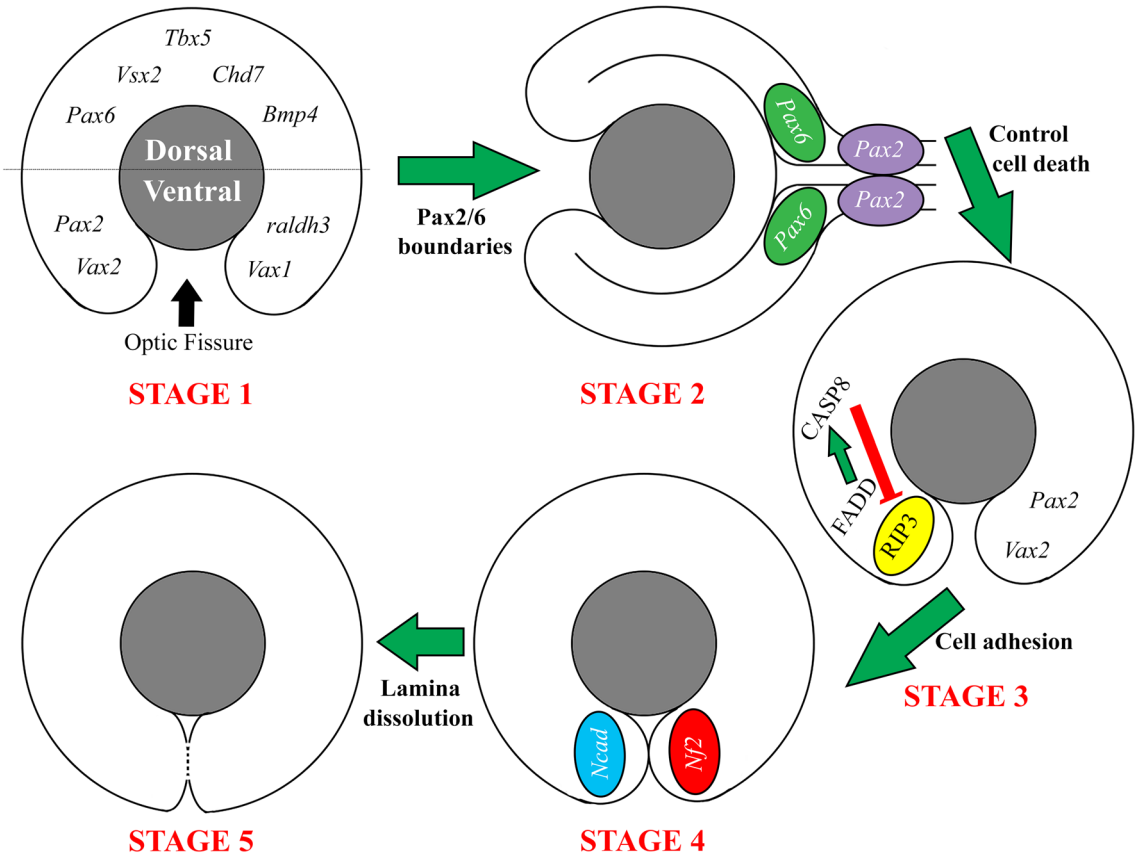

Fig. 2 Discrete stages of optic fissure morphogenesis and closure. *Stage 1* Establishment and maintenance of dorsal–ventral identity in the optic cup. *Stage 2* Maintenance of the *Pax6* optic cup/*Pax2* optic stalk boundary. Here, *Pax2* is located in both dorsal and ventral regions of the optic stalk. *Stage 3* Balanced cell death and proliferation in the edges of the optic fissure epithelium. Casp8 normally inhibits RIP3 activity as shown by red line. *Stage 4* Cell adhesion of the opposing optic fissure edges. *Stage 5* Dissolution of the basal lamina membrane

astigmatic refractive error in association with either iris and/or lens coloboma. Lens coloboma is a congenital anomaly of the capsular bag due to congenital absence of zonules in a quadrant of the eye (Singh et al. 2018). Such lens colobomas are often associated with a defect in the corresponding ciliary body.

Chorioretinal colobomas occur almost exclusively in the inferior-nasal quadrant. Such defects in other quadrants will relate to non-developmental diseases (such as toxoplasmosis scarring). Chorioretinal colobomas usually have the appearance of a bare, white quadrant devoid of choroid, but with atrophic, scarred retina overlying the defect. This quadrant can be complete, extending from the ora serrata and involving the optic nerve or incomplete as a well-circumscribed area in the peripheral retina. Approximately, 8–43% of cases can be associated with retinal detachment (Daufenbach et al. 1998).

Ocular coloboma is often associated with microphthalmos (small eye). A large number of systemic congenital defects can also be associated with coloboma, in particular defects of the central nervous system, craniofacial anomalies such as cleft lip, skeletal defects and genitourinary anomalies (Table 1).

Visual defects resulting from ocular coloboma can be present at birth and can range from insignificant to severe. Isolated coloboma affecting only the iris often exhibits minimal visual loss, whereas hard to identify corneal and lens defects can significantly affect visual acuity. Chorioretinal colobomas are always associated with overlying retinal abnormalities and visual field defects. Coloboma of the optic disk is often associated with significant, stationary visual field defects.

Phenocopies of ocular coloboma

The term ‘coloboma’ has also been used to describe ocular malformations not due to abnormalities of embryonic fissure closure. Perhaps, the commonest phenocopy of ocular coloboma is as a consequence of anterior segment surgery or trauma (Fig. 1). Another important example is eyelid

coloboma. This rare congenital anomaly can affect both the upper and lower eyelids. Congenital colobomas of the upper eyelid are particularly problematic since they can be associated with corneal exposure and subsequent corneal opacification (Tawfik et al. 2015).

Macular coloboma is also a rare phenocopy of ocular coloboma occurring in 0.5–0.7/10,000 live births (Hornby et al. 2000). Macular coloboma affects the posterior pole of the eye and is characterized by a well-demarcated, atrophic area inclusive of the macula. Macular coloboma has been linked to intrauterine ocular inflammation (Yamaguchi and Tamai 1990), although other reports have suggested an incomplete differentiation of the arcuate bundles along the horizontal raphe during development when macular coloboma is associated with excavation under the area of chorioretinal atrophy (Sattore et al. 1990).

There have been cases of ocular coloboma that are present in the upper hemisphere of the iris (Abouzeid et al. 2009). Most recently, eight patients with such 'superior coloboma' were identified and studied using exome sequencing (Hocking et al. 2018). These defects were correlated to abnormalities in development of the transient superior groove in the dorsal optic cup that has been associated with entry of the dorsal radial vessels of the superficial vasculature into the superior eye (Hocking et al. 2018).

Clinical management of ocular coloboma

Most chorioretinal coloboma patients present without symptoms and are usually discovered by the patient's physician or optometrist. Consequent clinical examination involves a comprehensive ocular examination to document the extent of colobomatous damage and other ocular anomalies (such as microphthalmos). In addition, an orthoptic assessment and cycloplegic refraction are carried out since squint and refractive error are common associations with ocular coloboma. Glare symptoms can occur in some patients in whom a conservative approach to management is recommended. This would involve recommending a brimmed hat, sunglasses or in some cases colored contact lens to control symptoms. Very rarely is surgical correction of an iris coloboma indicated. Such opportunities usually arise during surgery for other ocular problems such as cataract extraction. In such circumstances, a McCannel suture technique can be used (http://www.aao.org/image/mccannel-technique). Furthermore, systemic assessment for non-ocular associations should probably be undertaken by a general pediatrician. Moreover, examination of first degree relatives might help to establish a genetic (rather than environmental) cause for the condition. Molecular genetic assessment should be considered if available. In particular, molecular genetics should be considered if there is a family history of ocular defects or if systemic associations are found.

The risk of retinal detachment in chorioretinal coloboma of the posterior segment is estimated to be 8–43%. Importantly, since these patients often have limited vision, symptoms of retinal detachment may go unnoticed leading to treatment delay. Retinal detachment can be repaired using various techniques including vitrectomy with silicone oil tamponade (Hussain et al. 2017). Subretinal neovascularization at the edge of a colobomatous region can also occur and is usually managed with a course of anti-VEGF intraocular injections (Hussain et al. 2017).

Molecular basis of ocular coloboma

Environmental associations

Environmental causes have been implicated in ocular coloboma. Prominent examples include vitamin A deficiency, thalidomide exposure and fetal alcohol syndrome. Less certain associations include exposure to methimazole, carbamazepine, hydantoin and lysergic acid diethylamide (LSD). A more detailed review of these associations has been previously published (Moosajee and Gregory-Evans 2006).

Genetic associations

In cases of ocular coloboma where the cause is known, the majority are due to a molecular genetic abnormality. In most cases of isolated ocular coloboma, only one or two mutations in a gene have been identified in different individuals or families, e.g., one *SALL2* mutation, two *YAP1* mutations, and one *PAX6* mutation have been identified as disease causing (Kelberman et al. 2014; Oatts et al. 2017; Holt et al. 2017; Guo et al. 2013). A recent study revealed that in cases of non-syndromic ocular coloboma, more than 70% of individuals have no identified genetic cause (Williamson et al. 2014). Estimation of diagnostic hit rate for syndromic ocular coloboma is much higher. For example, *CDH7* mutations are identified in 67–90% of CHARGE syndrome cases (Legendre et al. 2017). In renal coloboma syndrome, about 50% of cases are caused by mutations in *PAX2* (Schimmenti 2011). According to the PAX2 mutation database (Bower et al. 2012), 92 mutations have been identified in the *PAX2* gene and one mutation (Val26Glyfs*28) is a common defect being reported 57 times (https://grenada.lumc.nl/LOVD2/PAX2/home.php).

Due to the phenotypic and genetic heterogeneity observed in ocular coloboma, deciphering the molecular mechanisms controlling the morphogenetic events remains a challenge. In a previous review, we proposed a coloboma gene network model based on early eye development studies in human and animal models (Gregory-Evans et al. 2004). This network provided a framework to inform on direct gene interactions

that regulate cell proliferation, differentiation, connection to neural networks and cell death processes associated with optic fissure closure (Jean et al. 1998). Since then with the emergence of high-throughput sequencing technologies, many new genes have been identified improving our understanding of the causes of the optic fissure closure defects. Here, we focus on grouping coloboma genes using a signaling pathway analysis and recognize that there is cross talk between pathways.

Optic fissure morphogenesis can be divided into five distinct events (Fig. 2). In Stage 1, the dorsoventral boundary is defined. In Stage 2, the Pax2/Pax6 boundary appears. In Stage 3, there are controlled cell death processes. In Stage 4, cell adhesion begins to close the fissure and in Stage 5 there is dissolution of the basal lamina. In the optic vesicle and optic cup, key transcription factors (TFs) include Pax2, Pax6, Vax1, Vax2, Mitf and Vsx2, and three T-box proteins (Nornes et al. 1990; Walther and Gruss 1991; Hallonet et al. 1998; Barbieri et al. 1999; Takabatake et al. 2002; Fuhrmann 2010), whereas in the periocular mesenchyme Foxc1 and Pitx2 are critical proteins (Acharya et al. 2011). The interaction of these TFs characterized in mouse or zebrafish models in specific pathways is described below, along with corresponding gene defects that have been observed in humans.

Hh/Pax/Vax pathway

Pax6 is one of the earliest determinants of the eye field in the developing embryo and its expression is inhibited by sonic hedgehog (Shh) which divides the eye field into two, driving the formation of the optic vesicles (Chiang et al. 1996). In addition, Shh promotes *Pax2* expression in the optic stalk and optic fissure, and at the same time restricts *Pax6* to the optic cup. A boundary between the retinal pigment epithelium (RPE) and optic nerve is then established by mutual inhibition between Pax2 and Pax6 (Macdonald et al. 1995). Shh signaling also upregulates *Vax1* and *Vax2* in the ventral optic cup (Hallonet et al. 1999; Mui et al. 2005). These Vax TFs promote *Pax2* expression and repress *Pax6* expression (Mui et al. 2005). Most recently, it has been shown that limiting Hedgehog signaling during ocular morphogenesis is regulated via *Sox11* and *Sox4* expression (Wen et al. 2015).

Homozygous mutations in *Pax2* in both mice and zebrafish cause ocular coloboma and kidney defects (Torres et al. 1996; Macdonald et al. 1997). Homozygous *pax6b* zebrafish and heterozygous *Pax6* mice exhibit microphthalmia, but not coloboma (Kleinjan et al. 2008; Hill et al. 1991). In contrast, *Shh* mutations in mice and zebrafish do not have colobomatous defects (Chiang et al. 1996; Schuaerte et al. 1998). Mutations have been identified in the *PAX2*, *PAX6* and *SHH* genes in patients with isolated ocular coloboma (Eccles and Schimmenti 1999; Azuma et al. 2003; Schimmenti et al. 2003). In addition, mutations in zebrafish *sox11*/*sox4*, mouse *Sox11* and human *SOX11* cause ocular coloboma (Wurm et al. 2008; Pillai-Kastoori et al. 2014; Wen et al. 2015). Although mutations have been found in both *Vax1* and *Vax2* in mouse and zebrafish mutants (Takeuchi et al. 2003) resulting in a coloboma phenotype, to date no mutations have been identified in coloboma patients.

BMP/Tgfβ pathway

The bone morphogenetic proteins Bmp4 and Bmp7 are involved in optic fissure morphogenesis (Adler and Belecky-Adams 2002). The expression of *Bmp4* is restricted to the dorsal optic vesicle by Shh signaling (Zhao et al. 2010). In this region Bmp4 induces the expression of the *Tbx2*, *Tbx3* and *Tbx5* and concomitantly restricts *Vax2* expression to the optic fissure margins in the ventral region (Behesti et al. 2006). Bmp7 is required for the initiation of optic fissure formation and controls the early expression of *Pax2* before *Shh* promotes its expression in the optic stalk (Morcillo et al. 2006). Bmp signaling is also required to maintain *Vsx2 (Chx10)* expression (Macdonald et al. 1995), a gene that establishes the boundary between the neural retina and RPE at the optic fissure margins (Cai et al. 2013). Most recently, it has been established that Tgfβ2 is required for optic fissure closure and that inhibition of this gene by BMP signaling prevents optic fissure fusion (Knickmeyer et al. 2018).

A heterozygous *Bmp4*^{tm1Blh} mutation in the mouse results in microphthalmia, kidney, skeletal and craniofacial defects (Dunn et al. 1997), whereas the *Bmp4*^{tm1} mutation causes optic nerve coloboma (Chang et al. 2001). Mutations in mouse *Bmp7* causes microphthalmia/anophthalmia, failure of optic fissure formation (absent hyaloid artery and agenesis of the optic nerve), kidney and skeletal defects (Jena et al. 1997; Morcillo et al. 2006). Null mutations in mouse *Vsx2* result in microphthalmia and hypopigmentation of the retina (Zou and Levine 2012). In both mouse and zebrafish *Tgfβ2* mutants, the margins of the optic fissure meet; however, localized remodeling of the extracellular matrix through induction of BMP4 antagonists does not occur, preventing basement membrane dissolution and subsequent fusion (Knickmeyer et al. 2018). The ClinVar public archive of human variation and phenotypes (https://www.ncbi.nlm.nih.gov/clinvar/) lists rare heterozygous mutations that have been identified in the *BMP4* gene in microphthalmia syndrome that includes iris and/or chorioretinal coloboma (Bakrania et al. 2008). In contrast, a single heterozygous missense mutation has been identified in *BMP7* in a patient with unilateral chorioretinal and optic nerve coloboma (Wyatt et al. 2010); however, the significance of this incomplete penetrance (affecting only one eye) awaits further investigation. Mutations in *VSX2* (*CHX10*) have also been found in families with microphthalmia and iris coloboma (Ferda-Percin et al. 2000; Bar-Yosef et al.

2004). Thus far, no mutations have been identified in *TBX2*, *TBX3*, *TBX5* and *TGFβ2* genes in patients with ocular coloboma. A very recent report has identified a mutation in *TBX2* and a mutation in the *BMPR1A* gene associated with a superior coloboma defect that were consistent with dorsal retina defects in corresponding zebrafish mutants (Hocking et al. 2018). However, transmissions of these defects are yet to be demonstrated and in most cases of superior coloboma only one eye is affected.

FGF signaling pathway

During development, FGF signaling regulates eye field formation (Moore et al. 2004) and specification of the neural retina (Hyer et al. 1998). Most *Fgf* mutants in mice do not manifest an eye phenotype, most likely because of functional redundancy as there are 22 different *Fgf* genes. Thus, several studies have focused on the receptors for Fgf proteins. For example, *Fgfr1/Fgfr2* conditional mutants display coloboma defects, which are thought to be due to loss of Pax2 expression (Chen et al. 2013). Binding of ligands to FGF receptors results in tyrosine phosphorylation of FRS2, which creates a docking site for the protein tyrosine phosphatase SHP2, important for activating the Ras-ERK signaling. The double *Frs2a/Shp2* mutant has an ocular coloboma phenotype lacking *Pax2* expression in the margins of the optic fissure and inducing instead the ectopic expression of Mitf (Cai et al. 2013). Ocular coloboma defects are observed in *Mitf* mutant mice (Hero 1989).

Several human diseases have been associated with mutations in the FGF signaling pathway. Iris and optic disc colobomas have been described in some individuals with Noonan syndrome (previously known as LEOPARD syndrome), who have gain-of-functions mutations in Ras-MAPK signaling (Kleanthous et al. 1987; Rudolph et al. 2001). Iris coloboma is a rare feature of Crouzon craniofacial dysostosis caused by *FGFR2* mutation (Graul-Neumann et al. 2017). Mutations in human *MITF* have been identified in two families with COMMAD syndrome which includes an ocular coloboma phenotype (George et al. 2016).

Retinoic acid and Hippo-YAP pathways

Retinoic acid signaling acts synergistically with the Hippo–YAP pathway in promoting migration of neural crest cells (Hindley et al. 2016). Both these signaling pathways independently are associated with optic vesicle and/or optic fissure morphogenesis. Retinoic acid is required for establishment of the dorsoventral retinal axis (Sasagawa et al. 2002). It also upregulates *Rbp4* and *Vax2*, whereas it inhibits *Shh* and *Ptch* (Helms et al. 2005; Busch et al. 2014). Furthermore, it has a paracrine role in upregulating the expression of *Foxc1* and *Pitx2* in the periocular mesenchyme (Lupo et al. 2011). In the eye, the Hippo–YAP signaling pathway functions to limit cell growth by promoting cell cycle exit and terminal differentiation of retinal progenitor stem cells (Jiang et al. 2009). Recently, Hippo–YAP signaling has been shown to direct RPE cell fate in the optic cup of zebrafish (Miesfeld et al. 2015) and *YAP1* has been shown to be expressed in the developing human retina (Holt et al. 2017).

Mutations in *RBP4* have been found in patients with iris and chorioretinal coloboma (Chou et al. 2015; Cukras et al. 2012; Khan et al. 2017) and *PTCH1* mutations are associated with iris coloboma (Hahn et al. 1996). Additionally, mutations in genes involved in retinoic acid synthesis such as *STRA6* (Casey et al. 2012) and ALDH1A3 (Yahyavi et al. 2013) are also a cause of colobomatous defects. In *yap* $^{nl13/nl13}$ zebrafish mutants there is loss of RPE associated with an ocular coloboma phenotype (Miesfeld et al. 2015), suggesting that defects in the ventral RPE could affect the movement of cells lining the optic fissure during closure. This is supported by data in *yap* medaka fish mutants where it regulates actinomycin contractions (Porazinski et al. 2015). Several reports now describe mutations in YAP1 causing optic fissure closure defects in humans (Williamson et al. 2014; Holt et al. 2017; Oatts et al. 2017).

FOXC1/PITX2 pathway and the POM

The periocular mesenchyme (POM) originating from the neural crest has a major role to play in optic cup morphogenesis as it gives rise to the hyaloid vasculature (Gage et al. 2005). *Pitx2* is expressed in the POM, and knockdown in mice causes optic nerve coloboma and microphthalmia (Gage et al. 1999). *Lmx1b* is also a POM expressed gene and when mutated in zebrafish causes optic fissure closure defects (McMahon et al. 2009). The *lmo2* gene is required for vascular development, and in zebrafish mutants the hyaloid vessels are abnormal causing failure of optic fissure closure (Weiss et al. 2012). In *foxc1* zebrafish mutants, the hyaloid vasculature is disrupted, but there is no coloboma phenotype (Skarie and Link 2009).

In patients with Axenfeld–Reiger's syndrome type 1, a *PITX2* mutation was identified in a patient who had iris coloboma in one eye and iris hypoplasia in the other; however, this is a rare finding (Ozeki et al. 1999). Two patients have been identified with *FOXC1* mutations and ocular coloboma (Kaur et al. 2009). Typically though, mutations in *PITX2* and *FOXC1* cause anterior segment dysgenesis phenotypes with iris anomalies mirroring the phenotypes in corresponding mouse and mutants (Kume et al. 1998; Gage et al. 1999). Mutations in *LMX1B* cause nail–patella syndrome with optic nerve defects and loss of retinal tissue, but coloboma was not reported (Romero et al. 2011). It should be noted that the hyaloid vascular system in mammals is transient and regresses prior to birth, whereas in zebrafish the hyaloid

does not regress, but grows with the retina to nourish it (Alvarez et al. 2007). This may explain why only rare mutations in these genes are associated with ocular coloboma in humans.

WNT/β-catenin pathway

The Wnt/β-catenin signaling pathway also contributes to the cellular mechanisms underlying optic fissure morphogenesis. In one study, Foxg1 was found to limit Wnt8b signaling in the optic stalk (Smith et al. 2017), and in *Foxg1* knockout mice a large ventral coloboma is present (Huh et al. 1999). In the absence of Foxg1 (and therefore upregulated Wnt signaling), *Pax2* expression is reduced in the optic fissure margins which may explain the coloboma defect. However, there was also a reduction in apoptotic cell death in the fissure margins. Previous studies have shown that both increased and decreased cell death contributes to ocular coloboma phenotypes in mice (Cai et al. 2013; Noh et al. 2016; Ozeki et al. 2000). In other studies, mutations in the mouse Wnt receptor gene *Fzd5* resulted in the opposite effect of reduced Wnt signaling, upregulated Pax2 expression and increased apoptosis (Liu and Nathans 2008). Yet, other studies show that in *Dkk1* and *Axin2* mouse mutants, there is increased Wnt signaling associated with coloboma defects (Lieven and Rüther 2011; Alldredge and Fuhrmann 2016). Additionally, Lrp6 is a Wnt co-receptor and in *Lrp6* knockout mice there is a decrease in ventral *Vax2* expression, and a reduction in BMP and retinoic acid signaling in the dorsal optic cup associated with a coloboma defect (Zhou et al. 2008). These studies suggest that Wnt signaling needs to be tightly regulated for proper optic fissure closure.

A frameshift mutation has been identified in *FZD5* in a large autosomal dominant family with isolated ocular coloboma (Liu et al. 2016). It was suggested that loss of Wnt signaling resulted in effects on the actin cytoskeleton associated with optic fissure closure. No other mutations have been identified in Wnt signaling pathway genes associated with coloboma, suggesting they are very rare mutations in humans.

Cell proliferation/migration pathway genes

Other factors contributing to optic fissure formation and closure include cell migration, cell proliferation, cell adhesion and basement membrane delamination. Movement of cells and tissue due to the action of the actin-myosin cytoskeleton are needed for optic cup formation (Sidhaye and Norden 2017). The optic cup changes shape as it develops because cells migrate into the optic cup. Live imaging has revealed that flow of cells into the optic fissure margin relies on BMP signaling (Heermann et al. 2015) and another study has suggested that cells from the distal optic stalk line the optic fissure (Holt 1980). Cell proliferation is also implicated in optic fissure closure. A mutation in Phactr4, which encodes a negative regulator of cell proliferation, leads to a coloboma phenotype (Kim et al. 2007) and ephrin mutants also exhibit cell proliferation and coloboma defects (Noh et al. 2016). Disruption of *Mab21l2* gene expression at the stage of optic cup formation leads to decreased retinal cell proliferation and microphthalmic coloboma (Sghari and Gunhaga 2018). Cadherin-mediated cell adhesion is required for optic fissure closure in mice and zebrafish (Chen et al. 2012; Masai et al. 2003). During fissure closure, the basement membrane of the two apposing fissure margins delaminates. A persistent basement membrane has been observed in some animal models (Masai et al. 2003; See and Clagett-Dame 2009). Disruption of *talin1* prevents breakdown of the basement membrane in the fissure margins (James et al. 2016) showing it is an active process.

Although a number of animal models display coloboma defects associated with cell proliferation, migration and adhesion abnormalities, very few gene mutations have been reported in humans. Mutations in the actin genes *ATCG1* and *ATCB* have been identified in isolated coloboma and in Baraitser–Winter syndrome which includes a coloboma phenotype (Rainger et al. 2017; Riviere et al. 2012). Iris and retinal coloboma has been identified in patients with *MAB21L2* mutations (Rainger et al. 2014; Deml et al. 2015).

Cell death pathway signaling genes

As previously mentioned, precise control of cell death is necessary for optic fissure closure (Ozeki et al. 2000). Further evidence supporting this notion comes from a number of different reports. Mutations in *Chd7* cause retinal coloboma in mice (Gage et al. 2015). Chd7 regulates p53, thereby controlling apoptosis in affected tissues (Van Nostrand et al. 2014). In addition, zebrafish studies have shown that bcl6 acts downstream of vax2 to inhibit p53 and reduce apoptosis leading to closure of the optic fissure (Lee et al. 2013). Furthermore, *ephA5* and *ephB2* mutant mice exhibit optic fissure closure defects associated with a reduction in apoptosis (Noh et al. 2016). Interestingly, in *Sall2*-deficient mice optic closure defects are observed (Kelberman et al. 2014). Given that SALL2 has pro-apoptotic properties, it is possible that perturbation of cell death may explain the open fissure defects. Finally, a direct downstream target of Pax2 is the *Fadd* gene that inhibits Rip3-mediated necroptosis in the optic fissure margins (Viringipurampeer et al. 2012). In the absence of Pax2 and therefore decreased Fadd activity, too much cell deaths occur preventing optic fissure closure.

A number of different cell death gene mutations have been identified in coloboma patients. Hemizygous deletion of *FADD* in humans causes oculo-oto-dental syndrome with a coloboma phenotype (Gregory-Evans et al. 2007).

Mutations in *CHD7* cause CHARGE syndrome that has a coloboma phenotype (Janssen et al. 2012). Finally, patients with recessive mutations in *SALL2* exhibit ocular coloboma (Kelberman et al. 2014).

Conclusions

Ocular coloboma defects are a common cause of ocular morbidity in childhood and can result in significant visual impairment. Most advances in the subject in recent years have been in the identification of a large number of genetic mutations causally linked to the condition and the unraveling of numerous molecular pathways improving our understanding of not only of the causes of ocular coloboma, but also advancing our understanding of how the normal eye develops. A large proportion of isolated ocular coloboma, however, remains idiopathic, without a confirmed genetic or environmental cause.

There are still some aspects to optic fissure morphogenesis and closure that remain to be answered. (1) Little is understood regarding the basement membrane breakdown between the apposing fissure margins and how continuity is achieved after fusion. (2) Information regarding the contribution of the RPE to tissue fusion process is also lacking. (3) Sometimes, mutations in animal models show a different phenotype to that seen in humans. For instance, heterozygous mutations of *Shh* in mice and zebrafish have no ocular phenotype (Chiang et al. 1996; Schauerte et al. 1998), whereas heterozygous mutations of human *SHH* causes ocular coloboma with or without holoprosencephaly (Schimmenti et al. 2003). In another example, the heterozygous $Bmp4^{tm1Blh}$ mutation causes microphthalmia (Dunn et al. 1997), whereas as a different targeted mutation ($Bmp4^{tm1}$) causes optic nerve coloboma (Chang et al. 2001). This phenotypic difference is most likely related to genetic background and the interactions of modifying genes or environmental factors that cause local stochastic variations in active BMP4 protein levels. Thus, considering evidence of the effect of genetic mutations in different species and for different types of mutations may be necessary to corroborate that the coloboma defect is caused by the specific gene mutation. (4) Why patients in the same family exhibit different phenotypes is unclear. For instance, we described a patient with iris coloboma whose niece had chorioretinal coloboma (Gregory-Evans et al. 2007). In other studies, patients within families exhibited either bilateral coloboma, coloboma in just one eye, or coloboma involving different ocular regions (Morrison et al. 2002). This suggests that there is incomplete penetrance for some of the mutations and suggests that genetic background or environment contributes to these differences in phenotype.

With the advent of induced pluripotent stem cell-derived ocular organoid culture (Eiraku et al. 2011), it is now possible to study aspects of optic fissure morphogenesis in real time. For example, in mouse embryonic stem cell-derived retinal organoids, dorsal–ventral polarity specification prior to fissure formation requires sequential Wnt and Bmp signaling (Hasegawa et al. 2016). These organoids also develop a cleft structure similar to the optic fissure that expresses Vax2 in the fissure margins with Tbx5 expression in the dorsal region of the optic cup. It is therefore possible to obtain cells from patients with ocular coloboma and grow retinal organoids to study the cellular and molecular defects in vitro, with the potential of testing novel therapeutics. In addition, this might be a way to identify new genes or pathways causing ocular coloboma where the underlying genetic defect is not known, and to test how environmental factors influence optic fissure closure.

Compliance with ethical standards

Conflict of interest On behalf of all the authors, the corresponding author states that there is no conflict of interest.

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