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REVIEW

Genetic architecture of retinoic-acid signaling-associated ocular developmental defects

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Abstract

Ocular developmental anomalies are among the most common causes of severe visual impairment in newborns (combined incidence 1–2:10,000). They comprise a wide range of inborn errors of eye development with a spectrum of overlapping phenotypes and they are frequently associated with extraocular malformations, neuropsychomotor developmental delay and/or intellectual disabilities. Many studies from model organisms have demonstrated the role of retinoic acid (RA) during organogenesis, including eye development, and have revealed the wide spectrum of malformations that can arise from defective RA signaling. However, genes coding for homeobox proteins and morphogenetic factors were implicated in anomalies of ocular development long before genes coding for RA-signaling proteins. The purpose of this review is to discuss current knowledge about the highly complex genetic architecture of RA-signaling-associated ocular developmental anomalies in humans. Despite less than a dozen genes identified thus far, all steps of RA-signaling, from vitamin A transport to target cells to transcriptional activation of RA targets, have been implicated. Furthermore, the majority of these genetic disorders are associated with both dominant and recessive inheritance patterns and a wide spectrum of ocular malformations, which can dominate the phenotype or represent one of many features. Although some genotype–phenotype correlations are described, in many cases, the variability of clinical expression cannot be accounted for by the genotype alone. This observation and the large number of unsolved cases suggest that the relationship between RA signaling and eye development deserves further investigation.

Introduction

Vitamin A has long been recognized as being critically important for day-to-day vision and eye development by virtue of two of its principal metabolites, 11-cis retinaldehyde, and all-trans retinoic acid (RA) (Sahu and Maeda 2016). The relation of 11-cis retinaldehyde to retinal diseases has been well reviewed (Perusek and Maeda 2013; Travis et al. 2007; Tsin et al. 2018) and will not be discussed here. The development of the eye involves the coordinated development of the neuroectoderm, surface ectoderm, and neural crest cell (NCC)-derived mesenchyme (Heavner and Pevny 2012; Williams and Bohnsack 2015). Retinoic-acid signaling has revealed a pivotal role in initiating and coordinating the morphogenetic movements involving these embryonic cell lineages. These cell types will produce the neural ectoderm-derived neuroretina, the retinal-pigmented epithelium and the surface ectoderm- and perioptic mesenchyme (POM)-derived anterior segment structures of the eye, from the lens to the cornea and sclera (Cvekl and Tamm 2004; Graw 2010; Williams and Bohnsack 2015). At the earliest stages of organogenesis, RA synthesis occurs in the optic vesicle, the adjacent mesenchyme and the lens placode to allow reciprocal invagination of the optic cup and lens pit that will generate an RA gradient along the dorsoventral axis of the developing eye (Duester 2009; Cvekl and Wang 2009; Heavner and Pevny 2012). This gradient, which results from the balance between RA synthesis and degradation, controls the growth of the ventral retina and regulates the closure of the choroid fissure. It is also essential to allow a proper development of the POM-derived eye structures. Neural crest cells of the POM do not produce the

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RA necessary for anterior segment development, but express RA receptors required for morphogenetic movements. RA signaling induces *EYA2*-dependent apoptosis necessary for POM remodeling and *PITX2*- and *FOXC1*-mediated anterior segment morphogenesis (Matt 2005), which involves the migration of NCC in three successive waves that will colonize the territories involved in the formation of some cornea and iris layers (Fig. 1) (Williams and Bohnsack 2015). Consistently, mutations in *PITX2* and *FOXC1* have been reported to cause a range of anterior segment anomalies, described as Axenfeld–Rieger syndrome, Rieger anomaly, Axenfeld anomaly, iridogoniodysgenesis or iris hypoplasia.

Establishing and controlling the dorso-ventral RA gradient in time and space involve a large number of transport proteins and enzymes (Cvekl and Wang 2009; Duester 2009; Rhinn and Dollé 2012). So far, less than a dozen of them have been involved in congenital eye anomalies, manifesting as anophthalmia, microphthalmia, and/or colobomas. Although small in number, they involve all stages of RA signaling, from vitamin A transport to cellular uptake, retinoic-acid synthesis and gene transactivation, and their mutations display variable modes of inheritance (Table 1). This review focuses on these genes, their mutations and associated ocular and extraocular malformations. Ocular anomalies downstream of RA signaling will be briefly discussed.

Retinoic-acid signaling and eye development

Vitamin A supply

In mammalian embryos, RA comes from maternal circulating retinol and retinyl esters (RE) delivered from liver stores, bound to the retinol-binding protein (RBP4, MIM#180250), and lipoproteins of dietary origin. Retinol bound to RBP4 is the main contributor to fetal development (Quadro et al. 2005). RBP4 is the specific transport protein for retinol in serum (Wang et al. 2018). It is produced in the liver and to some extent in adipose tissues (Makover et al. 1989; Motani et al. 2009) as a monomeric protein of 21 kDa (Folli et al. 2005; Maher 2013). To avoid glomerular filtration and subsequent excretion through the kidney, RBP4 circulates bound to vitamin A and the high molecular weight transthyretin (TTR, MIM#173300) protein as a 1:1:1 molar complex (Berry et al. 2012a; Frey et al. 2008). Maternal RBP4 cannot cross the placenta (Chou et al. 2015; Quadro et al. 2004). Maternal retinol diffuses across the yolk sac and placenta and reaches the fetal circulation to bind RBP4 delivered from the fetal liver (Rhinn and Dollé 2012), where the gene is expressed from E11.5 onwards in the mouse, i.e., when the lens vesicle becomes completely closed and

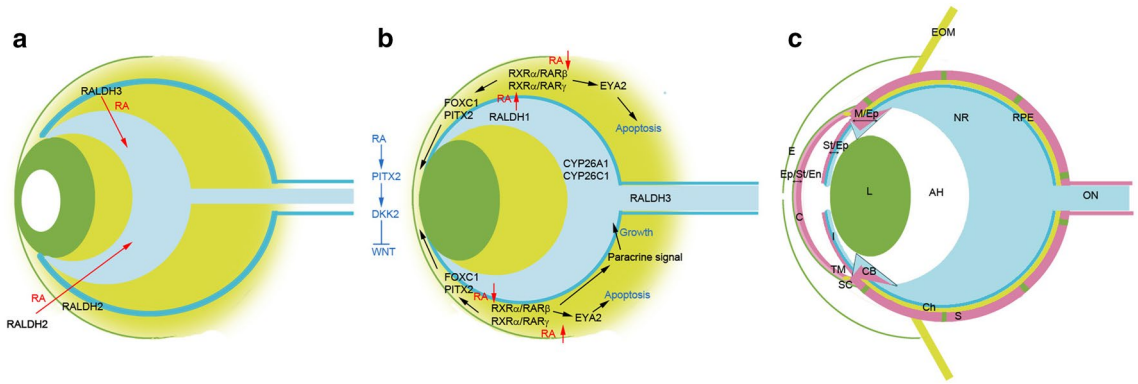

Fig. 1 Retinoic-acid signaling during the development of the mouse eye. **a** Transient expression of Aldh2 in the optic vesicle and the periocular mesenchyme (POM) between E8.5 and E10 and that of *Aldh1a3* in the surface ectoderm over the eye field between E8.75 and E10.5 allows the reciprocal invagination of the optic cup and lens vesicle. Aldh1a3 expression in the dorsal RPE between E9.5 and E10. 5 and by E10.5 in ventral neural retina contributes to ventral invagination of the optic cup and to the development of the cornea and eyelids (Duester 2008). **b** Balance between RA synthesis and RA degradation by Cyp26 enzymes generates a RA gradient along the dorso-ventral axis of the developing retina. RA synthesized in the neural retina, the retinal-pigmented epithelium and the corneal ectoderm by Aldh1a1 and Aldh1a3 diffuses towards the POM which expresses Rxrα/Rarβ and Rxrα/Rarγ heterodimers. Upon binding of RA to its nuclear receptors the apoptotic *Eya2* gene is activated leading to POM remodeling. Pitx2 and Foxc1 are also activated in the POM. Pitx2 controls both Foxc1 transactivation and expression of *Dkk2,* whose activation locally suppresses the canonical Wnt/β-catenin-signaling pathways in POM and thus controls eye morphogenesis (Matt 2005). **c** Embryological origin of mature eye structures: neural ectoderm (NE in blue) which forms the optic cup, retina, optic nerve, iris and ciliary body, the surface ectoderm (SE in green) giving rise to the lens and corneal epithelium, the neural crest contributes to corneal endothelium, choroid, and sclera (NC in pink) and finally the mesoderm (M in yellow) forming the extraocular muscle and corneal stroma. *L* lens, *E* eyelid, *RPE* retinal-pigmented epithelium, *NR* neural retina, *C-Ep* corneal epithelium, *C-St* corneal stroma, *C-En* corneal endothelium, *AH* aqueous humor, *I* iris, *I-St* iris stroma, *I-Ep* iris epithelium (pigmented and non-pigmented), *TM* trabecular meshwork, *SC* Schlemm's canal *CB* ciliary body, *M* muscle, *EOM* extraocular muscle, *S* sclera, *Ch* choroid, *ON* optic nerve, *RA* retinoic acid (Sowden 2007)

Table 1 Summary of clinical findings associated with genes involved in retinoic-acid signaling

	ALDH1A3	RARB		RBP4		STRA6
	Recessive	Dominant	Recessive	Dominant	Recessive	Recessive
Families/patient	25/67	12/13	1/4	4/16	3/5	31/51
Sex ratio (M/F)	1.54	0.4	3	2.2	0.25	1.6
Consanguinity	93%	0%	0%	0%	60%	53%
M/A	100%	100%	100%	81%	20%	100%
Iris anomalies	18%	–	–	25%	80%	–
Retinal dystrophy	–	–	–	–	100%	–
Chorioretinal coloboma	7.50%	–	–	25%	20%	–
Optic nerve anomalies	33%	–	–	18%	20%	–
Optic chiasm	10%	–	–	6%	–	–
Sclerocornea/corneal opacity	3%	91%		–	–	–
Cyst	27%	–	–	12.5%	–	–
Extraocular muscle anomalies	16%	–	–	6%	–	–
Other ocular anomalies	24%	–	–	–	–	–
Sensorineural hearing loss	–	8%	–	–	–	–
Intellectual disability/autism	31%	62%	–	–	–	84%[a]
CNS	1.5%	15%	–	–	–	13%
Language disorder	–	54%	–	–	–	–
Cardiac	1.5%	–	–	12.5%	20%	57%
Pulmonary	1.5%	–	–	–	–	43%
Diaphragm	–	–	–	–	–	24%
Renal	1.5%	–	–	–	–	22%
Genital/urinary	–	15%	25%	–	–	16%
Gastrointestinal	–	46%	25%	–	–	8%
Spleen	–	–	25%	–	–	12%
Skeletal	–	8%	–	–	–	13%
Craniofacial anomalies	–	8%	25%	–	–	11%
Growth defects	–	8%	–	–	–	–
Skin defects	3.0%	–	–	–	80%	–

[a]5/6 individuals examined with age ≥ 10 years

detached from the ectoderm and when the peripheral margins of the eye become well defined (Table 2). However, mouse embryos from *Rbp4*± and −/− mothers develop normally unless on a vitamin A-depleted diet, which causes anomalies of organogenesis including microphthalmia and anophthalmia in both *Rbp4*+/- and −/− embryos, the severity of which is correlated with the stage and level of vitamin A depletion (Chou et al. 2015). This is consistent with the view that dietary vitamin A from lipoprotein-associated retinyl esters (chylomicrons) contribute largely to fetal retinoid stores and can support normal development, independent of *Rbp4* expression. *Rbp4*−/− mice born to *Rbp4*−/− mothers on a sufficient vitamin A diet develop normally (Quadro et al. 2005), but they are unable to mobilize stored retinol from liver and develop retinal-specific dysfunction in the first month of life, suggesting that in peripheral tissues other than the eye, vitamin A can be delivered independent of *Rbp4*, likely through dietary vitamin A from chylomicrons (Kaukonen et al. 2018).

Vitamin A uptake

The uptake of retinol required for RA synthesis involves *STRA6*, an RA-responsive gene encoding the stimulated by retinoic acid 6 receptor (Bouillet et al. 1997). STRA6 is a 74 kDa integral multi-transmembrane cell-surface receptor comprising nine transmembrane (TM), five extracellular (EC), and four intracellular (IC) domains (Kawaguchi et al. 2008). It acts as a retinoid channel to facilitate the bidirectional flux of vitamin A between extracellular and intracellular compartments independent of ATP (Amengual et al. 2014a, b; Kawaguchi et al. 2011, 2012) (Fig. 2).

STRA6 associates with cellular RBPs, in particular the major intracellular isoform CRBP1 (MIM#180260) (CRBP2 (MIM#180280) and CRBP3 (MIM#611866), also known as RBP5, are the intestinal mucosa and adipose tissue-specific isoforms, respectively), and lecithin retinol acyltransferase (LRAT, MIM#604863) for vitamin A uptake (Napoli 2016). Neither CRBP1 nor LRAT is absolutely

Table 2 Summary of genes expression patterns in the eye of the mouse

Gene	Ocular expression pattern
crabp1	Preferentially expressed in the vitreous body and weakly in perioptic mesenchyme at E11.5 (Molotkov et al. 2006)
crabp2	Dorsal and ventral perioptic mesenchyme at E11.5 (Molotkov et al. 2006)
crb1	Retina (Luhmann et al. 2015)
crbp2	Not reported
crbp3	No eyes expression (Vogel et al. 2001)
cyp26a1	Neural retina and RPE (E14.5 to P14) (Abu-Abed et al. 2002; Sakai et al. 2004)
cyp26b1	RPE (E14.5) (Abu-Abed et al. 2002)
cyp26c1	Retina (E14.5 to P14) (Sakai et al. 2004; Luo et al. 2006)
lrat	RPE (Ruiz et al. 2007; Sears and Palczewski 2016)
aldh1a1	Dorsal neural retina (10.5-birth) and temporal side of the ventral retina (E11.5 and E13.5)(Matt 2005; Duester 2009)
aldh1a2	Optic vesicle (E8.5–E9) and perioptic mesenchyme (E9–E10). Developing muscles present around the eye (E11.5 and E13.5) (Matt 2005; Duester 2009)
aldh1a3	Ventral retina (E10.5-birth), peripheral portion of the dorsal retina, in the optic nerve anlage and in the corneal ectoderm (E10.5 and E11.5 and 13.5) and the RPE (E10.5 and E11.5) (Matt 2005; Cvekl and Wang 2009)
rarα	Neuroretina (E10.5 to adulthood), RPE(detected at all the stages from E10.5 with decrease at post-natal stages), lens (detected at all the stages), periocular, mesenchyme, iris/ciliary body (E14.5 to adult) choroid, sclera (broadly distributed prenatally and diminished post-natally) cornea conjunctiva (E14.5 to adulthood). (Mori et al. 2001; Dollé et al. 2009; Cvekl and Wang 2009)
rarβ	Periocular mesenchyme and body sclera (E10.5 to P4) iris/ciliary (E14.5 to adult) and RPE (weakly detected from E14.5 to P7) choroid, sclera (E10.5 to P4) (Mori et al. 2001; Cvekl and Wang 2009)
rarγ	Periocular mesenchyme, choroids, sclera (E10.5 to adulthood),cornea, conjunctiva (E14.5 to adulthood) (Mori et al. 2001; Dollé et al. 2009; Cvekl and Wang 2009)
rbp4	Retinal pigment epithelium (Herbert 1991; Shen et al. 2016)
rdh5	Dorsal part of the optic vesicle (9.5) and presumptive RPE of the optic cup at E10.5 and E12.5 as well as in the RPE in adults mice (Driessen et al. 2000; Wen et al. 2016)
rdh10	Dorsal portion of the optic vesicle neuroepithelium (E9.5), in the prospective pigmented epithelium and neural retina (E10.5),ventral and dorsal margins of the neural retina E12.5, margin of the neural retina, from which the ciliary body will develop (E16.5) and inner ciliary body (E18.5), RPE and Muller cells (remain strongly expressed throughout life) (Wu et al. 2004; Sandell et al. 2007; Romand et al. 2008)
rdh12	Photoreceptor inner segments and the outer nuclear layer (low expression level at birth, with expression increasing after P3 and throughout post-natal development) (Kurth et al. 2007; Kanan 2008)
Rere	Not reported
rxrα	Neuroretina (E10.5 and E12.5), RPE (E10.5 to E17.5), lens (detected only at E10.5 and E12.5) iris/ciliary body (broadly distributed prenatally and diminished post-natally) and cornea, conjunctiva (E14.5 to adulthood) (Mori et al. 2001; Cvekl and Wang 2009))
rxrβ	Ubiquitous distribution in developing and adult eyes (Mori et al. 2001)
rxrγ	Specific retinal cell layers (E14.5 to P7) and RPE (E10.5) and lens (detected only at E10.5 and E12.5) (Mori et al. 2001)
stra6	Optic vesicle (E9.5), RPE, inner nuclear layer of the neural retina, anterior most part of the lens, meninges of the optic nerve and the periocular mesenchyme at E10.5. At E16.5 and E17.5 is expressed in the epithelium lining the conjunctival sac and in the adult eye, Stra6 remained expressed only in the RPE and the meninges surrounding the optic nerve (Bouillet et al. 1997)
pitx2	During early eye development *pitx2* is expressed throughout the periocular mesenchyme, including the structures of the anterior segment, the sclera, ocular vasculature and extraocular muscles. At E15 is localized at rhe corneal stroma (Evans and Gage 2005; Ittner et al. 2005)
foxc1	Expressed in the periocular mesenchyme during early development. E15 is expressed at the corneal endothelium and structures of the forming trabecular meshwork (Ittner et al. 2005)

required for STRA6 activity; transfer of retinol from holo-RBP4 to apo-CRBPs increases internalization. In the cell, retinol is converted into all-trans RE by LRAT, increasing the amount of available apo-CRBP and hence enhancing the uptake (Berry et al. 2012a, b; Kawaguchi et al. 2012, 2013). Remarkably, STRA6 can also catalyze retinol efflux from holo-CRBP when presented with apo-RBP4, thus acting as a hub for retinol exchange between retinol-binding proteins (Napoli 2016). The spatiotemporal expression, the consequences of complete ablation of *Stra6*, *Crbp1,* and *Lrat* and rescue from the loss of these genes by dietary supplementation of vitamin A, have been extensively analyzed in the mouse (Amengual et al. 2012; Ghyselinck 1999; Kelly et al. 2016; Liu and Gudas 2005; Napoli 2016) (Table 2). *Stra6−/−* newborns present with congenital atrophy of the choroid and the RPE and their retina rapidly degenerates.

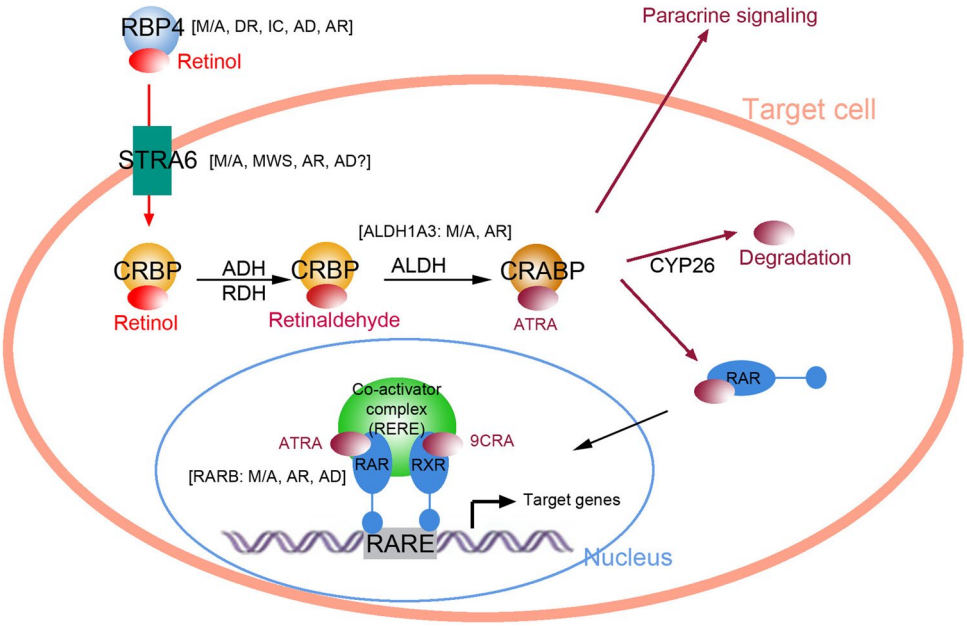

Fig. 2 RA-signaling pathway and associated ocular malformations in humans. Retinol is transported in the serum by retinol-binding protein (RBP4) secreted from the liver. Retinol enters into cells through the specific receptor STRA6, and binds to the cellular retinol-binding proteins (CRBPs) to be converted into retinyl esters for storage or to be oxidized to retinaldehyde by either alcohol dehydrogenase (ADH) or retinol dehydrogenase (RDH). Retinaldehyde is again oxidized to RA by retinaldehyde dehydrogenase (RALDH). The abundant form of RA known as all-trans-RA (ATRA) can (1) be secreted and act in a paracrine manner and provide insight into the cell–cell signaling networks that control differentiation of pluripotent cells, (2) enter the nucleus directly or bind to the cellular RA-binding protein (CRABP), which greatly facilitates cellular uptake of RA and transfer to the nucleus or (3) be degraded by three cytochrome P450 enzymes (CYP26A1, CYP26B1, and CYP26C1). RA serves as a ligand for two families of nuclear receptors that bind DNA and directly regulate transcription: (1) the RA receptors (RARα, RARβ, and RARγ) which bind ATRA and (2) the retinoid X receptors (RXRα, RXRβ, and RXRγ) which bind an isomer known as 9-cis-RA. The ternary complex of ligand bound-RAR with RXR and a retinoic-acid response element (RARE) regulates transcription of RA target genes by altering the binding of corepressors and coactivators. In eyes, nuclear receptors control the expression of Pitx2 and Foxc1, which are required for normal morphogenesis of the eye anterior segment. In addition, genes described in this review are shown in the RA-signaling pathway with their phenotype and mode of inheritance associated. *M/A* microphthalmia, *MWS* Matthew-Wood syndrome, *RD* retinal dystrophy, *IC* iris coloboma, *AR* autosomal recessive, *AD* autosomal dominant

Profuse vitamin A diet during pregnancy does not alleviate the developmental defect, but post-natal supplementation does protect the retina from degenerating, suggesting that RPE cells can use dietary vitamin A from chylomicrons, as perhaps is also the case in peripheral organs, where retinoid levels are maintained despite *Stra6* ablation (Amengual et al. 2014a, b; Ruiz et al. 2012). *Lrat*−/− mice develop normally, but present with an early onset severe retinal dystrophy that resists vitamin A supplementation (Maeda and Palczewski 2013; O'Byrne et al. 2005). This suggests that RE arising from acyl-CoA:retinol acyltransferase (arat) activity, in particular upon profuse dietary vitamin A supplementation, can maintain retinoid levels in most tissues, but not the retina (Liu et al. 2008; Napoli 2016; O'Byrne et al. 2005). *Crbp1*−/− mice display no ocular phenotype, but increased adiposity, glucose tolerance and insulin sensitivity upon diet-induced obesity (Maeda and Palczewski 2013; Saari et al. 2002; Zizola et al. 2010). This metabolic phenotype has been ascribed to elevated pancreatic content of 9-cis-RA arising from a compensatory increase in Crbp2 and cellular retinoic-acid-binding protein 2 (Crabp2) expression (Kane et al. 2011), which likely provides RA necessary for embryonic development and the visual cycle.

Retinoic-acid synthesis

Most RA signaling relies on intracellular RA synthesis, which involves a two-step enzymatic cascade (Duester 2001). The first step consists of oxidation of retinol to retinaldehyde by cytosolic alcohol dehydrogenases (ADHs) and microsomal retinol dehydrogenases (RDHs) of the medium- and short-chain dehydrogenase/reductase families, respectively (Parés et al. 2008; Rhinn and Dollé 2012). ADHs and RDHs are broadly expressed and display overlapping patterns of expression during development (Duester 2008; Sandell et al. 2007) (Table 2). Gene knockouts and vitamin A supplementation in animal models have suggested that ADHs have no specific role in eye development and might

control the removal of excess retinol instead of participating in RA synthesis (Rhinn and Dollé 2012). In contrast, similar studies and genetic analysis in patients and naturally occurring animal models have revealed the pivotal role of RDH5 and RDH12 in the visual cycle (Parker and Crouch 2010; Rhinn and Dollé 2012). In addition, *Rdh10−/−* mice, which die between E10.5 and E14.5, have been reported to display small optic vesicles (Cunningham et al. 2011; Sandell et al. 2007).

The second step of RA synthesis is NAD^+-dependent oxidation of RAL to RA. Nineteen aldehyde dehydrogenases (*ALDHs*) have been identified in the human genome, encoding enzymes with broad substrate specificities (Marchitti et al. 2008). ALDHs cluster into nine families (ALDH1-9) and many subfamilies. The ALDH1A1, 1A2, and 1A3 members of the ALDH1A subfamily are cytosolic and mitochondrial isoenzymes involved in the synthesis of RA from RAL. They function as homotetramers made up of 55 kDa monomers, and are organized into three structural domains: a catalytic domain, a cofactor-binding domain, and an oligomerization domain (Totah and Rettie 2007) (Fig. 2). ALDH1A isotypes share more than 70% sequence identity, but studies in mice have demonstrated that they have variable substrate specificities, catalytic efficiencies, and expression profiles. ALDH1A1 preferentially catalyzes oxidation of aldehydes produced by lipid peroxidation, whereas free and CRBP-bound retinal are the preferred substrates of ALDH1A2 and ALDH1A3 and this latter isotype has a tenfold higher catalytic efficiency than the other two (Makia et al. 2011; Maly et al. 2003; Moretti et al. 2016; Sima et al. 2009). ALDH1A isotypes are expressed with non-overlapping spatiotemporal patterns, leading to tissue- and time-restricted retinoic-acid synthesis during development (Duester 2008, 2009) (Table 2). *Aldh1a2* displays the earliest and shortest period of expression. It is detected in the optic vesicle between E8.5 and E9 and in the POM in the temporal side of optic cup between E9 and E10. The gene is undetectable by E10.5. *Aldh1a2* invalidation in mice causes embryonic mortality at E9.5 due to cardiac defects. The optic vesicle of *Aldh1a2−/−* embryos that receive no RA fails to invaginate ventrally (Heavner and Pevny 2012; Molotkov et al. 2006) and to initiate optic cup formation (Heavner and Pevny 2012; Mic et al. 2004). *Aldh1a3* can be detected in the surface ectoderm over the eye field between E8.75 and E10.5, playing a role in the reciprocal invagination that generates the optic cup and lens vesicle. It is expressed in the dorsal RPE between E9.5 and E10. 5 and by E10.5 in ventral neural retina, where it contributes to ventral invagination of the optic cup and to the development of the cornea and eyelids (Cvekl and Wang 2009). *Aldh1a3*$^{-/-}$ mice begin the process of optic cup formation, but experience shortening of the ventral retina with abnormal projections of retinal cells into the brain. Knock-out animals display associated ocular anomalies including ventral rotation of the lens, thickening of the central neural retina and ventral POM, loss of the vitreous body and persistence, and hyperplasia of the primary vitreous (PHPV). These mice die from choanal atresia at 1 day of post-natal life. Eye defects and viability can be rescued by maternal dietary RA supplementation (Dupé et al. 2003; Niederreither et al. 2000). *Aldh1a1* is expressed in the lens, corneal ectoderm, dorsal neural retina and to some extent the temporal side of the ventral retina from E10.5 to birth. However, *Aldh1a1−/− mice* display no noticeable defects at birth and survive to adulthood, suggesting that ALDH1A3 is the most functionally active isotype producing RA required for development (Duester 2008, 2009). *Aldh1a1−/−* mice, however, develop cataracts at 6–9 months of age, in particular when exposed to UV light (Chen et al. 2012; Lassen et al. 2007). By catalyzing oxidation of aldehydes produced by lipid peroxidation (Makia et al. 2011), *Aldh1a1* could serve to protect ocular tissues from oxidative damage instead of having a role in development (Chen et al. 2012).

Retinoic-acid degradation

Cells can absorb RA released from neighboring cells (Cvekl and Wang 2009). The mechanisms are unknown, but it is recognized that RA is both an effective morphogen and teratogen. Expression of RA in regions, where it should not signal can interfere with embryonic patterning (Pijnappel et al. 1993; Rhinn and Dollé 2012). Preventing inappropriate signaling is achieved by oxidation of RA bound to CRABP1 (Pennimpede et al. 2010; Rhinn and Dollé 2012). Oxidation is completed by three cytochrome P450 (CYP) enzymes known as CYP26A1 (Abu-Abed et al. 2001; Duester 2008), CYP26B1 (Duester 2008; Yashiro et al. 2004), and CYP26C1 (Duester 2008; Uehara et al. 2007). Genes encoding CYP26 enzymes contain functional RA-response elements (RAREs) (Loudig et al. 2005; Rhinn and Dollé 2012). Binding of RA to *CYP26* RAREs induces their expression, thus regulating RA concentration through a negative-feedback loop (Rhinn and Dollé 2012; White et al. 2007). Consistent with a regulatory role, CYP26 enzymes display unique tissue-specific patterns of expression during mouse embryogenesis, which are complementary to that of ALDH1A enzymes (Table 2). This generates specific territories along the dorso-ventral axis of the developing retina with or without RA (Matt 2005; Cvekl and Wang 2009). Unlike *Aldh1a−/−* mice, *Cyp26a1−/−*, *Cyp26b1−/−*, *Cyp26c1−/−*, and *Cyp26a1/Cyp26c1* double null animals do not present ocular anomalies. *Cyp26-null* phenotypes range from normal (*Cyp26c1−/−*) to severe multiorgan anomalies leading to mortality in the neonatal (*Cyp26a1−/−*, *Cyp26b1−/−*) or embryonic (*Cyp26a1/Cyp26c1* double null) periods (Abu-Abed et al. 2001; Bowles et al. 2006;

Maclean et al. 2007; Maclean et al. 2009; Sakai et al. 2001; Yashiro et al. 2004). Regarding *Crabp1*, ocular expression analysis has been restricted to embryos at E11.5, showing preferential expression in the vitreous body and weak expression in the POM at E11.5 (Molotkov et al. 2006) (Table 2), and to our knowledge, there are no data regarding the consequence of its invalidation on eye development.

Retinoic-acid-mediated transcriptional response

CRABP2 is thought to favor nuclear import and delivery of RA to its receptors by direct protein–protein interactions (Duester 2008), contrasting with CRABP1 which presents newly synthesized RA to metabolizing CYP26 enzymes (Nelson et al. 2016). Upon RA binding, a conformational change occurs on CRABP2 which exposes an internal nuclear localization motif for nuclear translocation (Majumdar et al. 2011). In the nucleus, free RA can interact with ligand-regulated transcription factors, namely, nuclear RA receptors (RAR) and retinoid X receptors (RXR). Three RAR and three RXR isoforms, referred to as RARα/β/γ and RXRα/β/γ, have been described and form active heterodimers.

In the mouse, information regarding *Crabp2* in the eye is limited to expression in dorsal and ventral POM at E11.5 (Molotkov et al. 2006) (Table 2). In contrast, the pattern of expression of *Rar* and *Rxr* isotypes during eye development and the consequences of their invalidation have been extensively analyzed. *Rar* and *Rxr* receptors are expressed with some spatial variations throughout the course of prenatal and post-natal stages of eye organogenesis and display ubiquitous distribution in adult eyes with the exception of *Rxrβ* which displays ubiquitous expression without significant spatiotemporal variations from the earliest developmental stages to adulthood (Kastner et al. 1997; Mark et al. 2009; Mori et al. 2001) (Table 2). Single invalidation of any *Rar* or *Rxr* isotype causes variable phenotypes from minor behavioral and metabolic (*Rxrγ*) or reproductive (*Rxrβ*) anomalies, to growth retardation with some malformations (*rarβ*) or multiorgan anomalies (*Rarα*, *Rarγ*), and to embryonic mortality (*Rxrα*) (for review, see Mark et al. 2009). Although all *Rar* and *Rxr* isotypes are expressed in the eye (Table 2), *Rarβ−/−* and *Rxrα−/−* mice are the only single mutants to display eye anomalies. *Rarβ−/−* mice present with PHPV. The ocular phenotype is far more complex in *Rxrα−/−* mice, including PHPV, agenesis of the anterior chamber with ventral rotation of the lens, and thicker cornea. In addition, these mice display shorter ventral retina and coloboma of the optic nerve, further demonstrating a paracrine RA-mediated signaling process (Kastner et al. 1994; Molotkov et al. 2006). Double *Rar*-null mutants do not survive embryonic life or the perinatal period and display varying multiorgan malformations, many of which are reminiscent of vitamin A deficiency syndromes. Ocular anomalies are either absent (*Rarα*/*Rarβ*) or resemble that of *Rxrα−/−* mutants [eyelid anomalies, thickening of the corneal stroma with lens agenesis (*Rarα*/*Rarγ*) or with lens malposition (*Rarβ*/*Rarγ*); PHPV, optic disk coloboma with retinal coloboma (*Rarα*/*Rarγ*), or ventral retina shortening (*Rarβ*/*Rarγ*)]. Interestingly, ocular symptoms are aggravated and/or more prevalent in *rxrα*/*rarγ* and to some extent in *Rxrα/Rarβ* double mutants, suggesting that *Rxrα*/*Rarγ* (and *Rxrα*/*Rarβ*) heterodimers are instrumental for eyelid, anterior segment, and retina development (Kastner et al. 1997; Mark et al. 2009).

Retinoic-acid signaling in the POM

In the mouse by E10, a stage which marks the arrest of *Aldh1a2* expression (Duester 2008), there is no further RA synthesis in the POM. NCCs in the POM are, however, capable of absorbing RA released from neighboring cells (Cvekl and Wang 2009). These NCCs express both the RA-binding protein CRABP2 and nuclear RA receptors to sense RA synthetized in the neural retina, the RPE, and the corneal ectoderm by *Aldh1a1* and *Aldh1a3*. RA from these sources diffuses towards the POM to contribute to invagination of the optic cup and closure of the choroid fissure as well as to mesenchymal remodeling and NCC migration/proliferation required for the development of the cornea, iris structures and eyelids (Matt 2005). These morphogenetic movements are coordinated by a complex network of RA targets, including *PITX2* [MIM#601542] and *FOXC1* [MIM#601090] (Fig. 1). *PITX2* encodes the paired-like homeodomain 2, a bicoid-like homeodomain transcription factor, which is expressed in mesenchyme surrounding the optic eminence as early as E8.5 in the mouse. By E11.5, *Pitx2* is highly expressed in migrating NCCs of the POM as well as in POM derivatives. By E18.5 and to adulthood, *Pitx2* expression is restricted to the irido-corneal angle, including the trabecular meshwork and Schlemm's canal. *Pitx2−/−* mice fail to close the ventral body wall and thorax, leading to embryonic lethality. The eyes of these embryos have been reported to display absent or defective closure of the choroid fissure (Gage et al. 1999), while conditional knockout in the neural crest causes absence of corneal endothelium and stroma and thick and short optic stalks (Evans and Gage 2005). Heterozygous *Pitx2* ± animals are viable and display diminished central corneal thickness, ciliary body atrophy, and iris hypoplasia with occasional pupil enlargement and extensive irido-corneal synechiae that compromise aqueous humor draining lead to elevated intraocular pressure (IOP)-mediated glaucoma and optic nerve fiber loss (Chen and Gage 2016). The very early *Pitx2* expression, before the formation of the optic cup and lens vesicle, highlights the role played by NCCs in both optic cup formation and anterior

segment morphogenesis. *Pitx2* is an essential integration point between RA and canonical Wnt/β-catenin-signaling pathways during eye development. This involves a critical downstream target of *Pitx2* in NCCs, the Dickkopf family member *Dkk2,* encoding an extracellular antagonist of canonical Wnt/β-catenin signaling. *Dkk2* expression in the developing eye of the mouse is nearly identical to that of *Pitx2,* but slightly staggered in time, consistent with it being a downstream effector (Table 2) (Gage et al. 2008; Zacharias and Gage 2010). *Dkk2* invalidation in mice provokes an elevation of canonical Wnt/β-catenin signaling in the POM, leading to ectopic vascularization of the developing corneal stroma and from the iris to the corneal endothelium in adult eyes. The vascularization of the corneal stroma is similar to that of the mesenchyme underlying the conjunctiva, where Wnt/β-catenin signaling is naturally high, demonstrating the importance of canonical Wnt/β-catenin-signaling regulation in the specification of the conjunctiva versus cornea (Gage et al. 2008).

Pitx2 interacts physically with Foxc1 to negatively regulate its transcriptional activation potential. Consistently, the two proteins share a common subnuclear compartment (Berry et al. 2006) and a similar pattern of expression during eye development (Table 2). *Foxc1−/−* mice are born without an anterior chamber and open eyelids associated with severe skeletal and cardiovascular defects. They die in the perinatal period from hemorrhagic hydrocephalus probably due to abnormal development of the arachnoid through which cerebrospinal fluid must drain. Heterozygous *Foxc1*± animals display multiple *Pitx2*± associated ocular anomalies, including iris hypoplasia with pupil displacement and iridocorneal angle malformations (small or absent Schlemm's canal, abnormal trabeculum, displaced Schwalbe's line), but without elevated IOP. The penetrance of these abnormalities is variable, likely depending on genetic background (Smith et al. 2000).

Diseases of retinoic-acid signaling in humans

In humans, mutations affecting RA availability and signaling in early stages of eye development have been shown to cause anophthalmia and microphthalmia with or without multiorgan malformations.

Mutations in RBP4 affecting vitamin A supply cause recessive and dominant anophthalmia and microphthalmia

In humans, five unique missense and two donor splice-site RBP4 mutations have been described in 21 individuals from seven families (Carss et al. 2017; Chou et al. 2015; Cukras et al. 2012; Khan et al. 2017; Riera et al. 2017; Seeliger et al. 1999) (Table S1 and Fig. 3). Three individuals from two families carried a homozygous consensus-splice-site mutation (c.111+1G>A (Cukras et al. 2012) and c.248+1G>A (Carss et al. 2017; Khan et al. 2017) and two siblings harbored compound heterozygous missense changes affecting evolutionary conserved residues (c.176T>A p.I59N and c.278G>A, p.G93D, also reported as p.I41N and p.G75D, respectively) (Biesalski et al. 1999; Seeliger et al. 1999). All displayed a distinctive disease consisting of a rod-cone dystrophy with chorioretinal atrophy, iris coloboma (4/5) with choroido-retinal coloboma, small cornea, nuclear sclerotic cataract (1/4) or microphthalmia (1/4), and severe persistent acne (4/5). Hypercholesterolemia with or without cardiac malformation has been additionally described in two siblings (Biesalski et al. 1999; Carss et al. 2017; Cukras et al. 2012; Khan et al. 2017; Seeliger et al. 1999). No or low circulating RBP and retinol has been reported in all individuals (Chou et al. 2015) and in vitro mutant p.I59N and p.G75D monomers have been shown to aggregate in the endoplasmic reticulum and to bind TTR poorly, suggesting loss-of-function, (Biesalski et al. 1999; Cukras et al. 2012). Low circulating retinol concentrations might explain skin disease, since it is known that vitamin A has an immunomodulatory role and that skin diseases have significant contributions from the immune system (Lucas et al. 2018). Whether occasional defects of cholesterol homeostasis and cardiac development are associated with RBP4 mutations is open to debate. Consistent with recessive loss-of-function mutations, a two-to-one reduction of circulating vitamin concentration has been demonstrated in a related carrier individual displaying no anomalies upon examination (Cukras et al. 2012). Ocular anomalies in homozygous and compound heterozygous individuals born to heterozygous

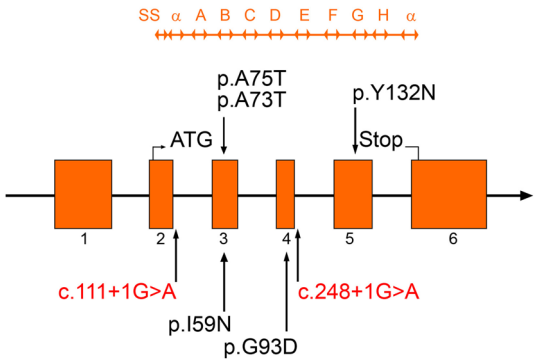

Fig. 3 Organization of the RBP4 protein and gene and review of mutations causing disease in humans. Dominant and recessive mutations are presented above and below the gene representation, respectively. Loss-of-function mutations are highlighted in red. *SS* signal sequence; α alpha helices; A–H beta-sheets

carrier mothers suggest that dietary retinyl esters do not provide an alternative source of vitamin A for the eye, the development and function of which seems to require holo-RBP4 (Biesalski et al. 1999; Seeliger et al. 1999; Shi et al. 2017).

In addition, heterozygosity for three unique missense variations introducing polar residues into the hydrophobic retinol ligand pocket have been described in four families comprising 16 individuals affected with variable ocular anomalies (Chou et al. 2015; Riera et al. 2017) (Table S1 and Fig. 3). The c.223G>A (p.A75T) mutation has been detected in a seven-generation pedigree totaling 11 individuals affected with a range of anomalies from iris and/or chorioretinal colobomas to anophthalmia. The c.217G>A (p.A73T) change identified on two distinct haplotypes caused bilateral anophthalmia or severe microphthalmia with neurodevelopmental delay and seizures in a proband and his maternal cousin, and unilateral optic disk pit with normal vision and left microphthalmia, iris coloboma, and congenital eyelid vascular anomaly in a mother and her daughter, respectively (Chou et al. 2015).

Circulating levels of vitamin A but not RBP4 and TTR are decreased in p.A73T and p.A75T carriers. Consistently, in vitro, stable mutant p.A73T and p.A75T RBP4 monomers are secreted and interact normally with TTR but not retinol with which binding is reduced. In contrast, the avidity for STRA6 is increased, suggesting a dominant negative effect of the mutations, most likely by blocking vitamin A delivery at its receptor (Chou et al. 2015). Interestingly, 12 individuals carrying the p.A75T ($n=9$) or p.A73T ($n=3$) changes have been reported to have no eye anomaly. All of them inherited the mutation from the father, contrasting with symptomatic carriers who typically inherited the disease allele from a carrier mother. This maternally skewed disease transmission has also described in mutant RPB4 dogs, and the congenital eye defects of which have been ascribed to the depletion of vitamin A supply from both placental and fetal holo-RBP4 during eye development (Chou et al. 2015; Kaukonen et al. 2018).

The third dominant *RBP4* mutation c.394T>A (p.Y132N) was identified in an individual affected with bilateral microphthalmia and irido-retinal colobomas. His parents and seven siblings were reportedly unaffected, suggesting that the mutation de novo occurence in the proband (Riera et al. 2017). This substitution, which further affects the retinol ligand pocket, might exert a dominant negative effect.

Mutations in STRA6 affecting vitamin A uptake cause recessive and dominant anophthalmia and microphthalmia with a large range of multiorgan anomalies

Biallelic *LRAT* and *STRA6* but not *CRBP1* mutations have been described in humans. Individuals carrying LRAT mutations, such as lrat−/− mice, suffer from a non-syndromic early onset and severe rod-cone dystrophy known as Leber congenital amaurosis type 2 (Hanein et al. 2004; Thompson et al. 2001). In contrast, the STRA6-associated disease differs strikingly from the chorioretinal-specific phenotype in the mouse (Golzio et al. 2007; Pasutto et al. 2007). The 51 individuals (31 males, 18 females, two not documented) from 31 families (16 multiplex, 15 consanguineous) reported to carry STRA6 mutations display a spectrum of ocular anomalies from choroid or iris coloboma to anophthalmia, without ($n=12$) or with ($n=39$, including 19 stillborn children and nine aborted fetuses) multiorgan anomalies (Casey et al. 2011; Chassaing et al. 2009; Gerth-Kahlert et al. 2013; Golzio et al. 2007; Makrythanasis et al. 2014; Marcadier et al. 2016; Ng et al. 2013; Pasutto et al. 2007, 2018; Patel et al. 2018; Sadowski et al. 2017; Segel et al. 2009; Slavotinek et al. 2015; West et al. 2009; White et al. 2008) (Table S2 and

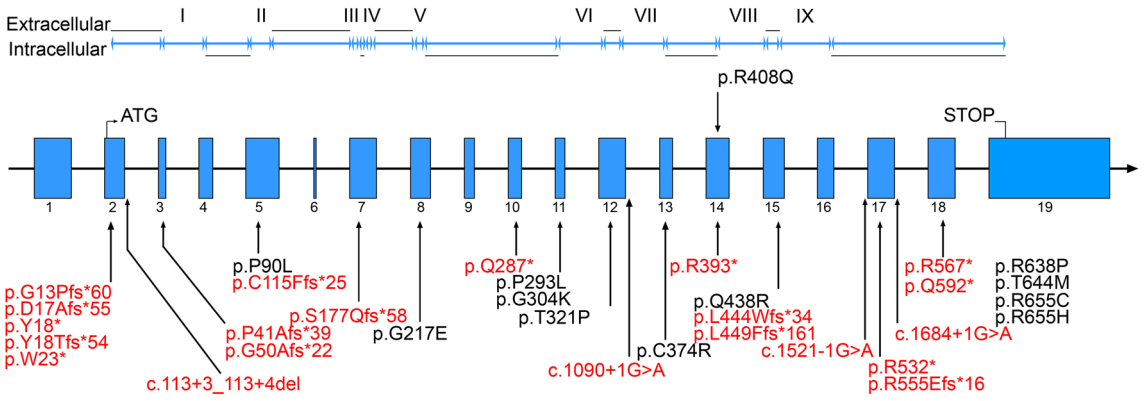

Fig. 4 Organization of the STRA6 protein and gene and review of mutations causing disease in humans. I–IX: denotes the nine transmembrane domains. The extracellular and intracellular domains are represented by bars. The p.R408Q mutation identified in single heterozygosity is shown at the upper side of the gene. Loss-of-function mutations are highlighted in red

Fig. 4). Thirty-three unique disease alleles are described, including 22 unequivocal loss-of-function (LOF) alleles (11 frameshift mutations, six nonsense changes, one large intragenic deletion, four splice-site variants), and 12 missense changes. Five mutations were identified in more than one family. The c.50_52delinsCC (p.D17Afs*55), c.878C>T (p.P293L), and c.1931C>T (p.T644M) variants were shared by two Central European families (one Polish and one Turkish families), one Jordan family and two pedigrees of unspecified origin, respectively (Golzio et al. 2007; Pasutto et al. 2007; Sadowski et al. 2017; Ng et al. 2013; Makrythanasis et al. 2014). Whether the recurrence results from a founder effect is not known, contrasting with the c.113+3_113+4del and c.910_911delinsAA (p.G304K) founder mutations identified in homozygosity in two Hmong and three Irish Traveler families, respectively (Marcadier et al. 2016; Casey et al. 2011). Irish Travelers ($n = 12$) have been reported to present with severe, yet variable, ocular phenotypes [bilateral anophthalmia or microphthalmia (simple or colobomatous) or either anomaly on one eye and anophthalmia, microphthalmia, choroid coloboma or iris coloboma on the other] and infrequent extraocular malformations (2/12 in two families; Table S2) (Casey et al. 2011). Other individuals displayed syndromic bilateral anophthalmia (19 individuals from 13 families carrying two LOF alleles, five from four families carrying an LOF allele in combination with a missense change and 13 cases from seven families with biallelic missense changes other than the p.G304K mutation) or microphthalmia (4/19 and 2/13 cases with biallelic LOF and missense mutations, respectively). No data about were available in three cases. The extent and severity of extraocular anomalies vary between and within families irrespective of genotypes, as shown by infantile mortality in families segregating biallelic missense mutations (nine cases in five families). Cardiac defects (72%), pulmonary disease (54%), and diaphragmatic hernia or eventration (31%) are common anomalies, the association of which with micro-anophthalmia is known as PDAC or Matthew-Wood syndrome (MWS). Renal defects (23%) and genital anomalies (18%) are not uncommon, as is severe intellectual disability (ID) affecting most of the surviving individuals (Table S2).

The stratification of STRA6 mutations by disease severity as determined by the extent of ocular anomalies and the number of organ systems involved suggests that all variants except the Irish Travelers mutation severely affect the uptake of vitamin A during embryonic development. Consistently, in vitro analysis have shown that STRA6 missense mutations (4/12) provoke protein misfolding and loss of cell-surface expression, leading to almost complete abolition of vitamin A uptake from holo-RBP4 (Kawaguchi et al. 2008). Remarkably, the p.G304K missense change has the same consequence on cell-surface expression and vitamin A uptake, raising questions about the origin of STRA6 pleiotropy, which could involve both genetic and environment factors (Casey et al. 2011).

STRA6 heterozygous carriers do not manifest symptoms of vitamin A deficiency. However, monoallelism for the STRA6 c.1223G>A (p.R408Q) missense variant has been reported in a mother presenting with bilateral microphthalmia and her son affected with bilateral microphthalmia and coloboma, unilateral retinal detachment, cardiac, and vascular malformations and ID (Slavotinek et al. 2015). The variant affects an evolutionary conserved arginine in a highly conserved intracellular region of the VII domain. Whether p.R408Q could act as a dominant negative allele has not been assessed functionally.

Interestingly, the multiorgan malformations of individuals with biallelic STRA6 mutations are in accordance with the spatiotemporal pattern of expression of the mouse ortholog (Table 2). Regarding the eye, Stra6 is expressed in the periocular mesenchyme, the lens and the inner nuclear layer (INL) of the retina by E9.5 and in the RPE by E10.5. It persists in post-natal lens and INL, and has a particularly high expression level in post-natal RPE, localizing predominantly in the basolateral membrane, where vitamin A is supplied from the choroidal circulation (Bouillet et al. 1997).

Mutations in ALDH1A3 affecting RA synthesis are a major cause of recessive anophthalmia or microphthalmia with frequent neurocognitive and behavioral problems

No anomaly has been reported in *ALDH1A1,* whereas some association between *ALDH1A2, CRALBP1, CYP26A1, CYP26B1, CYP26C1* polymorphisms, and/or rare variants and neural tube closure defects, but no ocular anomalies are described (Deak et al. 2005; Li et al. 2018). In contrast, *ALDH1A3* mutations are a major cause of A/M. At present, 24 unique *ALDH1A3* mutations have been identified in 25 families comprising 67 affected individuals, 60 of whom were born to consanguineous parents (Abouzeid et al. 2014; Alabdullatif et al. 2017; Dehghani et al. 2017; Fares-Taie et al. 2013; Lin et al. 2018; Liu et al. 2017; Mory et al. 2014; Plaisancié et al. 2016; Roos et al. 2014; Semerci et al. 2014; Ullah et al. 2016; Yahyavi et al. 2013) (Table S3 and Fig. 5). The mode of inheritance of ALDH1A3 mutations is uniquely recessive, with all patients carrying homozygous or compound heterozygous disease alleles. Despite the prevalence of consanguinity in *ALDH1A3*-related A/M cases, no founder effect has been described, even in the two pedigrees sharing the same mutation (c.709G>A, p.G237R) (Dehghani et al. 2017; Liu et al. 2017). In these two families of distinct ethnic background (Chinese and Iranian), the mutation

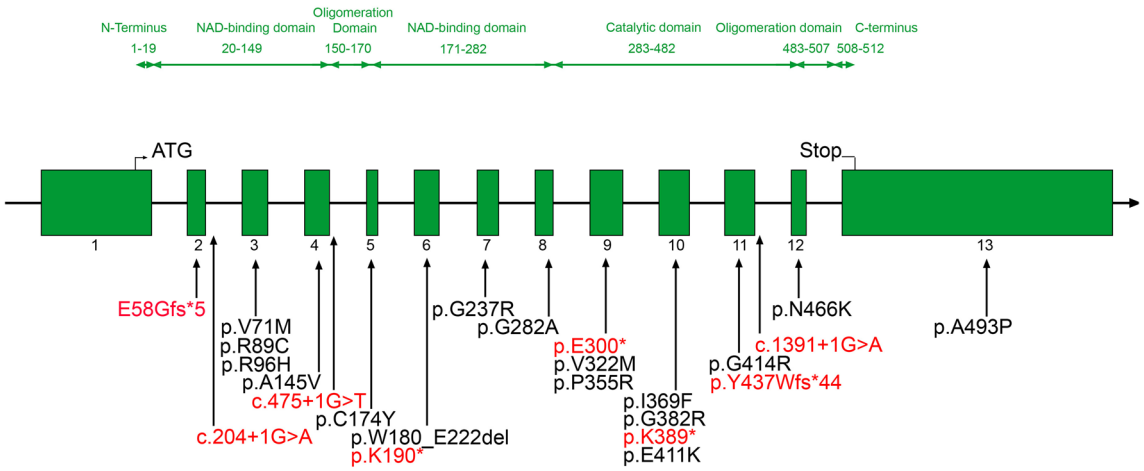

Fig. 5 Organization of the ALDH1A3 protein and gene and review of mutations causing disease in humans. Most of the mutations were found in homozygosity. Loss-of-function mutations are highlighted in red

most likely occurred by deamination of a cytosine, a well-known mechanism of nucleotide hypermutability (Zemojtel et al. 2009).

The 24 ALDH1A3 mutations are distributed along the sequence and include ten unequivocal or presumably LOF mutations (three nonsense variants, one 2-bp deletion, one 1-bp duplication, and four splice-site variants), 13 missense changes, and a one synonymous/splice variation (Fig. 5). Individuals carrying two LOF alleles (17/67, 16/18 consanguineous; eight families) or missense variants (43/67, 38/43 consanguineous; 16 families), and 6/7 siblings carrying the synonymous/splice variant in homozygosity were viable and presented with bilateral severe ocular malformations ranging from anophthalmia to severe microphthalmia (Table S3). The last of the seven siblings harboring the synonymous/splice change exhibited no eye anomaly upon thorough examination. Ocular cysts and hypoplastic optic nerves were not uncommon (18/67 and 21/67, respectively; Table S3), supporting induction and invagination of the optic vesicle but defective closure of the choroid fissure and retinal neuron projections (Fares-Taie et al. 2013).

Consistent with severe ocular malformations in individuals carrying nonsynonymous mutations, in vitro analysis has shown marked impairment of expression and tetramer formation of mutant *ALDH1A3* (i.e., c.265C>T, p.R89C; c.287G>A, p.R96H; c.709G>A, p.G237R; and c.1477G>C, p.A493P) (Fares-Taie et al. 2013). The synonymous/splice variant identified in homozygosity in seven siblings born to consanguineous Turkish parents affects the last nucleotide of exon 6 (c.666G>A). Analysis of lymphoblast mRNA has demonstrated comparable skipping of the in-frame exon 6 (p.W180_E222del) in all siblings, including the unaffected individual (Plaisancié et al. 2016). It has been proposed that modifying genes, environmental influences, and/or stochastic effects could compensate for the defective function of the mutant protein on the eye phenotype (Plaisancié et al. 2016).

Facial dysmorphy is occasionally seen in individuals carrying *ALDH1A3* mutations (12/67, one multiplex and two simplex families), but extraocular organ anomalies are very rare (cardiac, cerebellar, renal anomalies in 3/67 cases, and three families). In contrast, learning disability and autistic behavior are not uncommon (18/67 cases) (Table S3). The frequency of neurocognitive/behavioral problems and sibling concordance suggests a correlation with *ALDH1A3* mutations. Whether additional extraocular anomalies are due to defective RA synthesis during organogenesis is more debatable due to intra-familial variability and consanguinity (Table S3), which favors the expression of recessive alleles. Evidence for this comes from the report of homozygosity for *ALDH1A3* and *SMOC1* (Secreted Modular Calcium-Binding Protein 1; MIM#608488) mutations in two nuclear families of a large inbred family segregating bilateral anophthalmia or microphthalmia with or without learning problems or bi- or unilateral microphthalmia with syndactyly (Aldahmesh et al. 2013).

Recessive mutations in RARB affecting the RA-mediated transcriptional response cause an STRA6-like phenotype

CRABP2 mutations and/or rare polymorphisms may be associated with anomalies of neural tube closure but not eye anomalies in humans (Deak et al. 2005; Li et al. 2018). At present, the only RA receptor involved in disease is *RARB*. This gene encodes a 50 kDa protein with a domain structure similar to the other RA nuclear receptors. It contains an *N*-terminal ligand-independent AF1-containing

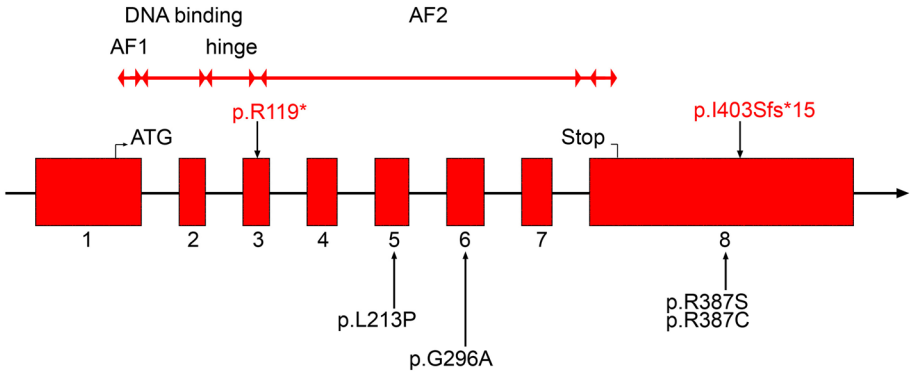

Fig. 6 Organization of the RARB protein and gene and review of mutations causing disease in humans. Dominant and recessive mutations are presented above and below the gene representation, respectively. Loss-of-function mutations are highlighted in red

binding domain (A/B), a DNA binding domain (C), a hinge domain (D), a *C*-terminal ligand-dependent transactivation AF2-containing domain (E/F) involved in dimerization, and coactivator or repressor recruitment (Fig. 6). A total of six unique RARB disease-causing variants are reported in 17 cases from 15 families presenting with an *STRA6*-like disease (Srour et al. 2013; Williamson and FitzPatrick 2014) (Table S4). Mutant alleles include a nonsense variant introducing a premature termination codon upstream of the ligand-binding domain (c.355C>T, p.R119*) and a frameshift change predicted to replace the last 52 residues by an aberrant extension of 15 amino acids (c.1205_1206dup, p.I403Sfs*15) identified in compound heterozygosity in four siblings (1/4 terminated for suspicion of MWS). The other mutant alleles consist of de novo missense variants: the c.1159C>T (p.R387C) and c.1159C>A (p.R387S) changes reported in ten individuals (nine families, 2/10 monozygotic twins) and a sporadic case and c.638T>C (p.L213P) and c.887G>C (p.G296A) each involving a sporadic case. In vitro analysis has demonstrated that the nonsense and frameshift variants abolish completely and almost completely the transcriptional activity in response to retinoids, respectively. In contrast, the missense substitutions consistently increased the transcriptional activity by two-to-threefold as compared with the wild type, suggesting a gain-of-function mechanism that could be due to increased RA-binding affinity or conformational changes modifying stability and coactivator recruitment (Srour et al. 2013, 2016). Despite variable pathogenic mechanisms, the ocular phenotype is rather homogeneous, consisting of bilateral (15/17) or unilateral (2/17) microphthalmia with frequent coloboma (≥ 8/17) and/or sclerocornea (≥ 10/17). A constellation of multiorgan anomalies is consistently associated, the extent and combination of which vary greatly, irrespective of the genotype with the exception of CNS anomalies (Chiari type 1; 7/17) associated with the c.1159C>T (p.R387C) mutation (Table S4). MWS-associated malformations are among the most common non-ocular symptoms, i.e., congenital diaphragmatic hernia (12/17), cardiac abnormalities (10/17), and pulmonary anomalies (6/17). Other features, i.e., craniofacial, skeletal, musculoskeletal, gastrointestinal, genitourinary, and metabolic anomalies, are occasional (Srour et al. 2016) (Table S4). 7/17 individuals were alive at the time of publication (3–18 years), whereas 7/17 succumbed in the first few hours or days of life from cardiorespiratory distress (5/7) or in teenage years from pulmonary or gastrointestinal infections (twins) and 2/17 were fetuses terminated for suspicion of MWS (1/17 case with no clinical information). All individuals surviving the neonatal period (9/17) have been reported to develop severe cognitive deficiency which could reflect abnormal circuitry of GABAergic interneurons, the development of which involves RA signaling (Duvarci et al. 2018) and progressive motor regression due to corticospinal and extrapyramidal defects (Srour et al. 2016).

The severity of the RARB disease contrasts with the *Rarβ-null* mouse presentation (Mark et al. 2009). This observation suggests that in humans RARA and RARG cannot compensate for most RARB developmental functions. In addition, the combination of phenotypic similarities associated with defective and excessive physiological response to retinoids and of genotype-independent extraocular variations (including among twins; Table S4) highlights the complexity of RA-signaling regulation during organogenesis as well as the importance of the micro-environment.

Dominant mutations in PITX2 and FOXC1 alter RA signaling in the POM, causing anterior segment dysgenesis

PITX2 (paired-like homeodomain 2) encodes a bicoid-like homeodomain transcription factor. Three isoforms are described which differ at the *N* terminus, but they all include the 60-amino-acid homeodomain (HD). The three isoforms have identical C termini with a conserved 14-amino-acid OAR domain (otp, aristaless, and rax), which is predicted to mediate protein–protein interactions and self-inhibitory interactions with the *N* terminus (Tümer and Bach-Holm 2009). At present, a total of 105 *PITX2* mutations are listed in the Human Gene Mutation Database (HGMD, http://

www.hgmd.cf.ac.uk/). They include 32 missense substitutions, 12 nonsense variants, seven splice-site changes, 23 micro-rearrangements (17 deletions, three insertions, three indels), 26 gross rearrangements (25 deletions, one insertion), and five complex rearrangements.

PITX2 mutations have been associated with a wide range of ocular malformations from iris hypoplasia to microphthalmia. However, individuals carrying heterozygous *PITX2* mutations typically present with ocular and extraocular malformations consistent with Axenfeld–Rieger syndrome (ARS) type 1 [(MIM 180500)]. These malformations include irido-corneal anomalies, i.e., iris hypoplasia with pupil anomalies (corectopia and polycoria), projections of peripheral iris tissue extending to the scleral spur or trabecular meshwork (iris processes) and central thickening and displacement of the Schwalbe line, which delineates the outer limit of the corneal endothelium layer (posterior embryotoxon)(Berry et al. 2006; D'haene et al. 2011; Tümer and Bach-Holm 2009). These anomalies confer to patients a 50% risk of developing glaucoma, which can develop in infancy, but usually occurs in teenage years or early adulthood (Chen and Gage 2016; Reese and Ellsworth 1966; Reis et al. 2012; Tanwar et al. 2010). In rare cases, additional corneal anomalies are noted such as thinning, clouding, and attachment to the iris (Peters anomaly), annular limbal dermoids with corneal and conjunctival extension or microcornea. The most frequent extraocular malformations involve micro- and hypodontia, redundant periumbilical skin, and maxillary hypoplasia (Hendee et al. 2018; Reis et al. 2012; Tümer and Bach-Holm 2009).

The high prevalence of *PITX2* loss-of-function and null alleles (complete gene deletions) supports haploinsufficiency, yet some mutations have been suggested to induce excessive *PITX2* activity(Reis et al. 2012; Semina et al. 1996). Most of the intragenic *PITX2* variations are located in the HD and *C*-terminal region and are loss-of-function mutations due to defective DNA binding, decreased transactivation capability of downstream genes, or both (Tümer and Bach-Holm 2009). Functional analysis of some variants associated with ocular anomalies of variable severity has suggested some correlation between disease expression and the level of residual PITX2 activity (e.g., p.R46W with significant transactivation activity involved in iris hypoplasia, p.R31H with less activity involved in iridogoniodysgenesis and p.L16Q, p.T30P, and p.R53P with no residual activity involved in ARS;(Kozlowski and Walter 2000). Some other mutations including missense, nonsense, frameshift, micro-, and gross deletions or insertions have been reported to cause similar anomalies(Priston et al. 2001; Reis et al. 2012; Souzeau et al. 2017; Vieira et al. 2006; Yin et al. 2014). Some other variants have been associated with inter- and/or intra-familial variability (e.g., c.253-11 A>G identified in eight unrelated families of different ethnicities displaying strabismus and amblyopia, typical ARS, or microphthalmia (Borges et al. 2002; D'haene et al. 2011; Reis et al. 2012; Semina et al. 1996; Sun et al. 2017); and c.47-1G>C causing ARS in most cases and iris hypoplasia without foveal hypoplasia in a mother and Rieger anomaly with iris hypoplasia, polycoria, and corectopia in her daughter (Perveen et al. 2000). Some missense, nonsense, and frameshift gain-of-function mutations (e.g., due to increased binding to the bicoid element) have been reported as well. These variants, as well as loss-of-function mutations, cause ARS or Rieger anomaly (Alward et al. 1998; Priston et al. 2001; Saadi et al. 2006; Semina et al. 1996; Tümer and Bach-Holm 2009).

FOXC1 recognizes and binds to specific DNA sequences through the conserved 110-amino-acid forkhead domain (FH), and thereby activates its target genes. Transactivaton function requires two activation domains, namely, AD-1 and AD-2, and the activity of these domains is attenuated by the inhibitory domain (ID) (Tümer and Bach-Holm 2009). 143 *FOXC1* variants affecting ocular development are currently listed in HGMD, comprising 38 missense, 14 nonsense, 35 micro-rearrangements (27 deletions, 24 of which disrupt the reading frame, six insertions, and two indels), 36 gross rearrangements (36 deletions, eight insertions, and nine complex rearrangements), and one regulatory mutation. Evidence from gross gene deletions and duplications supports the view that both decreased and increased FOXC1 activity can alter eye development (Ekong et al. 2004; Kaur et al. 2009; Mirza et al. 2004). Most *FOXC1* mutations are located in the FH domain and cause loss-of-function due to impaired protein folding, protein stability, DNA binding, protein phosphorylation, subcellular distribution, and/or transactivation capacity (Berry et al. 2006). Typically, individuals carrying these mutations present with the spectrum of ocular defects associated with ARS, i.e., anteriorly displaced Schwalbe's line, iris adhesions, irido-corneal angle dysgenesis, and corectopia, along with systemic anomalies, the most frequent of which are heart abnormalities and hearing loss (D'haene et al. 2011; Kaur et al. 2009; Reis et al. 2012; Strungaru et al. 2007; Tümer and Bach-Holm 2009). Interestingly, a number of *FOXC1* mutations (missense, nonsense, and duplications) have been described which affect the ID domain, leading to increased *FOXC1*-mediated transactivation. Iridogoniodysgenesis phenotypes are more commonly associated with these mutations than loss-of-function variants (Fetterman et al. 2009). However, the same *FOXC1* mutation can lead to considerably variable clinical presentations (i.e., Peters anomaly, primary congenital glaucoma, aniridia, and iris hypoplasia/iridogoniodysgenesis syndrome).

Glaucoma was thought to be more prevalent in individuals with *FOXC1* than *PITX2* mutations, affecting approximately 50% of carriers (Souzeau et al. 2017; Strungaru et al. 2007). Evidence of *FOXC1* but not *PITX2* as a primary open-angle glaucoma (POAG) susceptibility locus

was further consistent with this view (Bailey et al. 2016). However, it has been reported that glaucoma in individuals harboring *PITX2* mutations may be overlooked due to a later onset than in *FOXC1* carriers(Souzeau et al. 2017).

Interestingly, *PITX2* and *FOXC1* mutations have been reported in a unique family displaying highly variable anterior segment phenotypes. In this family, the father and the brother of the proband carried an *FOXC1* 1-bp deletion, c.609delC, that dramatically reduced protein function in vitro. They displayed iris hypoplasia, posterior embryotoxon, and peripheral irido-corneal adhesions. The mother carrying the *PITX2* variant p.Ser233Leu, which retains some function in vitro, manifested isolated bilateral posterior embryotoxon, and iris heterochromia. In contrast, the proband who inherited the paternal *FOXC1* and maternal *PITX2* mutations presented with severe abnormalities of the whole globe, involving both anterior and posterior segments (corneal opacification, lens extrusion, PHPV, and bilateral retinal detachment). Histological analysis revealed very severe anomalies of the corneal epithelium and stroma and partial or complete absence of Bowman's layer, Descemet's membrane and endothelium (Kelberman et al. 2011).

Discussion

The vertebrate eye is a highly complex organ, whose development depends upon tightly controlled retinoic-acid signaling from the very first stages of specification of the neural epithelium, to determination of the eye fields, specification of the retinal and optic nerves and patterning of anterior segment structures. Over the last 30 years, the number of contributors in RA signaling has grown, as have demonstrations that changes in their activity cause organogenesis anomalies in model organisms. Mouse models have been pivotal for the analysis of the spatiotemporal expression of genes involved in RA signaling and for understanding their contribution during eye development by analyzing phenotypes resulting from individual or combined invalidation. However, the vast majority of these mutant mice model loss-of function alleles. Gain-of-function mutations, which are not uncommon in inborn errors of human eye development, will require in vivo modeling to better understand the complex interplay of RA-signaling contributors. Mouse phenotypes often differ from those in humans, which are themselves rather variable depending on the gene involved and/or the mutation type (Table 1). That said, in the two species, RA-signaling deficiency tends to present in a similar way as vitamin A deficiency. This notion can be of interest, knowing that many ocular development defects with multiorgan involvement are unresolved. At least some of these cases will be resolved by scrutinizing coding and non-coding sequences of RA-signaling genes in whole exome and whole genome sequencing data sets in the search for recessive and dominant mutations. Furthermore, taking into consideration the synergistic impairment of organogenesis and development in some individuals carrying mutations in both *PITX2* and *FOXC1* and in some double mutant mouse models (e.g., *rar/rxr*), true digenic inheritance certainly merits consideration in human patients.

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