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REVIEW

Genetics of anophthalmia and microphthalmia. Part 2: Syndromes associated with anophthalmia–microphthalmia

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Abstract

As new genes for A/M are identified in the genomic era, the number of syndromes associated with A/M has greatly expanded. In this review, we provide a brief synopsis of the clinical presentation and molecular genetic etiology of previously characterized pathways involved in A/M, including the Sex-determining region Y-box 2 (*SOX2*), Orthodenticle Homeobox 2 (*OTX2*) and Paired box protein-6 (*PAX6*) genes, and the Stimulated by retinoic acid gene 6 homolog (*STRA6*), Aldehyde Dehydrogenase 1 Family Member A3 (*ALDH1A3*), and RA Receptor Beta (*RARβ*) genes that are involved in retinoic acid synthesis. Less common genetic causes of A/M, including genes involved in BMP signaling [Bone Morphogenetic Protein 4 (*BMP4*), Bone Morphogenetic Protein 7 (*BMP7*) and SPARC-related modular calcium-binding protein 1 (*SMOC1*)], genes involved in the mitochondrial respiratory chain complex [Holocytochrome c-type synthase (*HCCS*), Cytochrome C Oxidase Subunit 7B (*COX7B*), and NADH:Ubiquinone Oxidoreductase subunit B11 (*NDUFB11*)], the BCL-6 corepressor gene (*BCOR*), Yes-Associated Protein 1 (*YAP1*) and Transcription Factor AP-2 Alpha (*TFAP2α*), are more briefly discussed. We also review several recently described genes and pathways associated with A/M, including Smoothened (*SMO*) that is involved in Sonic hedgehog (*SHH*) signaling, Structural maintenance of chromosomes flexible hinge domain containing 1 (*SMCHD1*) and Solute carrier family 25 member 24 (*SLC25A24*), emphasizing phenotype–genotype correlations and shared pathways where relevant.

Introduction

Anophthalmia and/or microphthalmia (A/M) are defined as an absence or reduced size of the ocular globe compared to normal measurements for chronological age (Bardakjian et al. 2004; Ragge et al. 2007). Although A/M can occur as an isolated finding without systemic features, extraocular findings have been reported in 33–95% of patients, suggesting that, in many patients, the eye findings are part of a broader pattern of developmental defects (Fig. 1). A syndrome diagnosis is forthcoming in an estimated 20–45% of patients with A/M (Källén et al. 1996; Forrester and Merz 2006; Slavotinek 2011). The most frequently affected extraocular body systems include the craniofacial region, with anomalies of the face, ear and neck, and the limbs and musculoskeletal systems (Källén et al. 1996; Forrester and Merz 2006; Slavotinek 2011).

As new genes for A/M are identified in the genomic era, the number of syndromes associated with A/M has greatly expanded. In this review, we provide a brief synopsis of the clinical presentation and molecular genetic etiology of previously characterized pathways involved in A/M, including Sex-determining region Y-box 2 (*SOX2*), Orthodenticle Homeobox 2 (*OTX2*) and Paired box protein-6 (*PAX6*), and Stimulated by retinoic acid gene 6 homolog (*STRA6*), Aldehyde Dehydrogenase 1 Family Member A3 (*ALDH1A3*), and RA Receptor Beta (*RARβ*). Less common genetic causes of A/M, including genes involved in BMP signaling [Bone Morphogenetic Protein 4 (*BMP4*), Bone Morphogenetic Protein 7 (*BMP7*) and SPARC-related modular calcium-binding protein 1 (*SMOC1*)], genes involved in the mitochondrial respiratory chain complex [Holocytochrome c-type synthase (*HCCS*), Cytochrome C Oxidase Subunit 7B (*COX7B*), and NADH:Ubiquinone Oxidoreductase subunit B11 (*NDUFB11*)], the BCL-6 corepressor gene (*BCOR*), Yes-Associated Protein 1 (*YAP1*) and Transcription Factor AP-2 Alpha (*TFAP2α*), are more briefly discussed. We then

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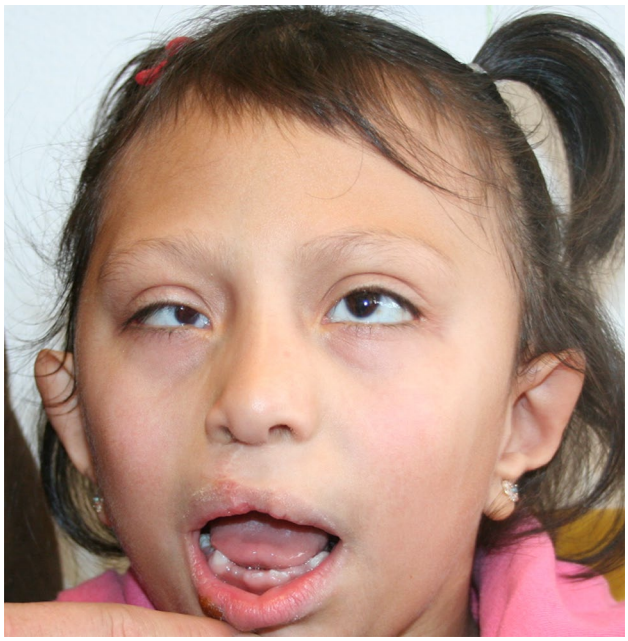

Fig. 1 Facial view of a female with right microphthalmia, bilateral colobomas and a repaired cleft lip as findings in Goltz syndrome. She is heterozygous for a missense variant, c.787G > A, predicting p.(Glu263Lys), in *PORCN* (NM_203475.1)

review several recently described genes and pathways associated with A/M including Structural maintenance of chromosomes flexible hinge domain containing 1 (*SMCHD1*), Solute carrier family 25 member 24 (*SLC25A24*) and Smoothened (*SMO*), emphasizing phenotype–genotype correlations and shared pathways where relevant. This review is selective and does not cover newly described genes for isolated A/M, animal models of A/M, or causative copy number variants.

Anophthalmia–esophageal–genital (AEG) syndrome and SOX2 variants

SOX2 is an HMG-box transcription factor and deleterious variants and deletions of this gene occur at an estimated frequency of 1 in 250,000 births, making *SOX2* the commonest genetic cause of A/M and accounting for an estimated 4–20% of cases (Verma and FitzPatrick 2007; Slavotinek 2011). In a recent review, the majority of the 89 reported patients with *SOX2* variants were ascertained because of their eye defects (Dennert et al. 2017). However, although haploinsufficiency for *SOX2* can cause isolated unilateral and bilateral A/M, a wide range of ocular and extraocular findings have been noted. Anophthalmia–esophageal–genital (AEG) syndrome comprises A/M, tracheo-esophageal fistula (TEF) and/or esophageal atresia, genitourinary tract malformations comprising cryptorchidism, micropenis and hypospadias in males and renal hypoplasia, horseshoe kidney or duplex kidney in both sexes, and is caused by *SOX2* variants and deletions (Bardakjian and Schneider 2005; Ragge et al. 2005a, b; Bakrania et al. 2007; Schneider et al. 2009; Slavotinek 2011). Vertebral and rib defects, including rib fusions, 11 pairs of ribs, hemivertebrae and butterfly vertebrae, are also seen as part of the AEG phenotype (Bardakjian and Schneider 2005; Chassaing et al. 2007). *SOX2* variants can cause brain malformations (Ramirez-Botero and Pachajoa 2016) and hypopituitarism with hypogonadotrophic hypogonadism (Macchiaroli et al. 2014; Takagi et al. 2014). Screening of patients with developmental delays with next-generation sequencing technologies has also uncovered deleterious *SOX2* variants in the absence of eye malformations (Dennert et al. 2017).

The spectrum of deleterious *SOX2* variants is broad and includes whole gene deletions, intragenic deletions, nonsense and frameshift variants causing haploinsufficiency, and missense substitutions (Suzuki et al. 2014; Dennert et al. 2017). The pathogenesis of *SOX2* variants has been attributed to haploinsufficiency, based on the phenotypic similarity between cases with premature protein truncation and deletions, but dominant negative effects are also possible. Although recurrent variants are relatively rare, a 20 bp deletion, c.70del20, predicting p.(Asn24fs88*), has been found in unrelated patients with A/M and AEG syndrome (Schneider et al. 2009; Reis et al. 2010). This deletion has also been observed in patients without major eye involvement (Errichiello et al. 2018). Two similar deletions of 17 bp and 23 bp have occurred in the same region as c.70del20, possibly caused by mispairing of a GGCGGC repeat sequence flanking the region (Ragge et al. 2005a, b; Bakrania et al. 2007; Chassaing et al. 2007; Reis et al. 2010).

Loss-of-function variants and deletions resulting in SOX2 haploinsufficiency can cause either unilateral or bilateral A/M, AEG syndrome or A/M and esophageal atresia (Dennert et al. 2017). Patients with microdeletions are more likely to exhibit postnatal growth retardation than those with missense variants, perhaps because of concomitant deletion of gene regulatory elements (Dennert et al. 2017). A phenotype–genotype correlation has been suggested, as missense variants affecting the DNA-binding or transactivation domains of SOX2 are typically associated with milder ocular phenotypes, including coloboma (Wang et al. 2008) and non-penetrance of the eye defects (Bakrania et al. 2007; Schneider et al. 2009). Missense variants are also associated with fewer developmental and systemic abnormalities (Schneider et al. 2009). However, not all authors agree that there is a definitive phenotype–genotype correlation (Suzuki et al. 2014) and family members with the same variant can demonstrate striking phenotypic variability due to the interaction of SOX2 with tissue-specific partner factors (Takagi et al. 2014).

Although the vast majority of deleterious *SOX2* variants have arisen as de novo events, deleterious variants can be inherited in an autosomal dominant pattern due to maternal mosaicism (Faivre et al. 2006; Kelberman et al. 2006; Chassaing et al. 2007; Schneider et al. 2008, 2009) and paternal transmission, with an absent or milder phenotype in the father (Kelberman et al. 2006; Wang et al. 2008).

Sox2 expression in mice occurred within the optic vesicle and stalk, neural retina, the lens and placodal area of the surface ectoderm; in humans, expression was also seen in the neural retina, optic stalk and lens (Kelberman et al. 2006; Reis et al. 2010). Sox2 interacts with Pax6 and Otx2 to activate δ-crystallin for lens formation and to co-regulate Rax expression (Kamachi et al. 2000; Danno et al. 2008). Haploinsufficiency for *SOX2* results in defects of the human ventral forebrain and its derivative structures and in an allelic series, mice with hypomorphic *Sox2* alleles exhibited upregulation of Sonic hedgehog (*Shh*) signaling in embryogenesis that disrupted development of the hypothalamus, optic stalks and optic cups (Langer et al. 2012). Functional studies in patients with both missense and loss-of-function variants in *SOX2* have also demonstrated greatly reduced efficiency or inability to transactivate the Homeobox expressed in ES cells 1 (*HESX1*) promoter (Suzuki et al. 2014).

Pituitary abnormalities and OTX2 variants

O*TX2* is a bicoid-type, homeodomain-containing gene that is the vertebrate ortholog of the Drosophila gene orthodenticle (Tajima et al. 2013). Absent or small eyes are characteristic clinical findings associated with heterozygous, deleterious variants in *OTX2*, which cause an estimated 2–8% of A/M (Verma and FitzPatrick 2007). The ocular phenotype is extremely variable, ranging from bilateral anophthalmia (Fig. 2) to nearly normal eye development (Tajima et al. 2013). Eye malformations that have been associated with *OTX2* variants in addition to A/M include anterior segment defects, Leber's congenital amaurosis, hypoplasia or aplasia of the optic nerve and optic chiasm and pattern dystrophy of the retinal pigment epithelium (Tajima et al. 2009; Ashkenazi-Hoffnung et al. 2010; Schilter et al. 2011; Slavotinek 2011; Vincent et al. 2014).

Although there is no syndrome eponym, variants in *OTX2* are associated with defects of the pituitary gland in 19–30% of cases, including hypoplasia of the gland, ectopic pituitary gland, growth hormone deficiency and combined pituitary hormonal deficiency (Tajima et al. 2009; Dateki et al. 2010; Schilter et al. 2011). The pituitary defects show variation in people with the same variant and have been reported in the absence of A/M (Dateki et al. 2010). Other extraocular features include brain abnormalities such as Chiari malformations, developmental delays ranging from mild to severe, attention deficit hyperactivity disorder and autistic features

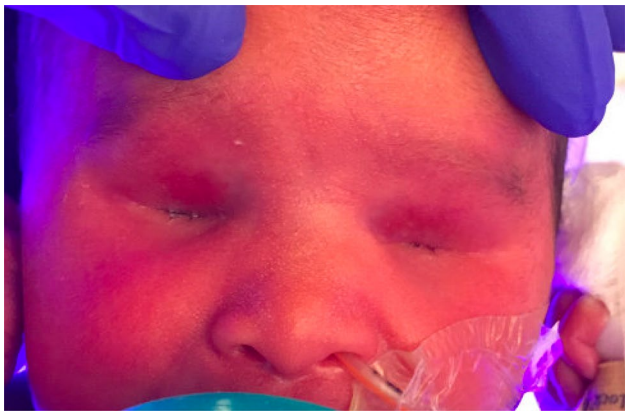

Fig. 2 Facial view of a female with bilateral anophthalmia in the neonatal period. The child is heterozygous for a missense variant, c.277T > C, predicting p.(Trp93Arg), in *OTX2* (NM_001270525.1)

(Schilter et al. 2011; Slavotinek 2011). Failure to thrive and growth retardation, microcephaly, feeding difficulties and hypotonia have been noted (Schilter et al. 2011; Slavotinek 2011). Genital hypoplasia, cleft palate, seizures and sensorineural hearing loss are rare (Ragge et al. 2005a, b; Ashkenazi-Hoffnung et al. 2010; Schilter et al. 2011; Slavotinek 2011).

More recently, loss-of-function variants in *OTX2* have been shown to cause agnathia–otocephaly complex, a pattern of malformations comprising mandibular hypoplasia/agenesis, ear anomalies, microstomia and microglossia (Chassaing et al. 2012; Patat et al. 2013; Sergouniotis et al. 2015). An *OTX2* variant was also associated with isolated mandibular dysostosis (Latypova et al. 2016).

The spectrum of *OTX2* variants has included nonsense alterations, insertions, intragenic deletions, missense substitutions and whole gene deletions at 14q22-14q23 (Tajima et al. 2013). Gene variants are spread across the gene (Ashkenazi-Hoffnung et al. 2010; Schilter et al. 2011; Tajima et al. 2013). Most *OTX2* variants predict premature protein truncation and loss-of-function (Tajima et al. 2013), but two missense variants, p.(Asn233Ser) and p.(Pro134Arg), have been shown to have a dominant negative effect on target gene expression (Diaczok et al. 2008; Wyatt et al. 2008; Schilter et al. 2011; Tajima et al. 2013). There is substantial intrafamilial variability and affected individuals have sometimes inherited their variant from a clinically normal parent due to mosaicism or incomplete penetrance (Ragge et al. 2005a, b; Diaczok et al. 2008; Schilter et al. 2011; Tajima et al. 2013).

A phenotype–genotype correlation for *OTX2* was noted by some authors, as pituitary abnormalities occur more frequently in patients with variants in the second half of the gene that retain the homeodomain and an SGQFTP motif that confers dominant negative effects (Schilter et al. 2011). Two amino acid substitutions located in the OTX2

family-specific domain, p.(Asn233Ser) and p.(Thr178Ser), were identified in patients with combined pituitary hormone deficiency without eye malformations (Tajima et al. 2013). However, other studies have not confirmed a phenotype–genotype relationship (Ashkenazi-Hoffnung et al. 2010).

Similar to SOX2, OTX2 is a co-regulator of Retina and anterior neural fold homeobox (RAX; Danno et al. 2008) and also binds to the *HESX1* promoter that is critical for pituitary development (Spieler et al. 2004). Functional studies have shown that heterozygous, loss-of-function variants in *OTX2* can fail to activate the *HESX1*, Gonadotropin-Releasing Hormone 1 (*GNRH1*), POU Class 1 Homeobox 1 (*POU1F1*), and Retinol-binding protein 3, interstitial *(RBP3*; also known as *IRBP*) gene promoters compared to wild-type *OTX2* (Dateki et al. 2010).

PAX6, eye and brain defects

Deleterious variants in *PAX6* are predominantly associated with aniridia (Jordan et al. 1992; Glaser et al. 1994), but missense substitutions affecting the paired domain can cause a wide spectrum of eye defects, including Peters anomaly, corectopia with nystagmus, macular and foveal hypoplasia and A/M (Glaser et al. 1994; Hever et al. 2006; Williamson and FitzPatrick 2014; Deml et al. 2016). Biallelic variants in *PAX6* are extremely rare, but were reported to cause bilateral anophthalmia and fused eyelids (Glaser et al. 1994). Although not classically associated with a syndrome, brain defects have been noted with deleterious *PAX6* variants, in particular agenesis of the corpus callosum, absence or hypoplasia of the anterior commissure and absence of the pineal gland, auditory processing defects and anosmia (Sisodiya et al. 2001; Mitchell et al. 2003; Abouzeid et al. 2009). The clinical features observed with *PAX6* variants relate well to the expression of the murine gene, which is present in the developing lens, the surface ectoderm of the head, the pit of the optic vesicle, prosencephalon, telencephalon, diencephalon and olfactory bulb (Hever et al. 2006).

Retinoic acid synthesis pathway members: STRA6 and Matthew-Wood syndrome/PDAC syndrome, ALDH1A3 and RARβ

Pathogenic variants in several genes in the retinoic acid (RA) synthesis pathway can cause A/M with phenotypic overlap in some cases, despite the involvement of distinct genes. Biallelic variants in the *STRA6* gene result in a clinically severe condition called pulmonary hypoplasia/agenesis, diaphragmatic hernia/eventration, anophthalmia/microphthalmia and cardiac defects (PDAC) syndrome (Pasutto et al. 2007; Golzio et al. 2007; White et al. 2008; Chassaing et al. 2009; West et al. 2009). Anophthalmia or severe microphthalmia are typical in patients with *STRA6* variants (Williamson and FitzPatrick 2014). Almost all patients have at least one other major phenotypic component of PDAC in addition to A/M and poor survival is the rule (Pasutto et al. 2007; Golzio et al. 2007; Chassaing et al. 2009; Segel et al. 2009; Williamson and FitzPatrick 2014). However, more mildly affected patients have been described and patients whose sole clinical manifestation was A/M have been reported (Golzio et al. 2007; Segel et al. 2009; Casey et al. 2011; Chassaing et al. 2013). Other characteristic findings are renal anomalies, including pelvic kidney, horseshoe kidney, renal hypoplasia and malrotation of the kidney, and genital malformations, with bicornuate or hypoplastic uterus and cryptorchidism (West et al. 2009; Chassaing et al. 2009). Gastrointestinal malformations, such as duodenal stenosis, an annular pancreas or absent pancreas, intestinal malrotation, an accessory spleen or a hypoplastic spleen, can be present (Pasutto et al. 2007; Chassaing et al. 2009; West et al. 2009). Less frequent findings are pre- and postnatal growth retardation, thymic hypoplasia, subglottic laryngeal stenosis, cleft palate, pulmonary capillary dysplasia, a thin or absent corpus callosum, small optic nerves, arrhinencephaly, Dandy–Walker malformation, contractures and camptodactyly (Chassaing et al. 2009; Segel et al. 2009; Marcadier et al. 2016). Craniofacial dysmorphism is frequent in PDAC syndrome and is characterized by prominent, 'bushy' eyebrows, hypoplastic nipples and hypoplastic toenails (Segel et al. 2009). Intellectual disability is common in those who survive the neonatal period, but a developmental profile within the expected range was described in a blind, 30-month-old female with two missense variants (Pasutto et al. 2007; Chassaing et al. 2009; Segel et al. 2009).

The spectrum of pathogenic variants in *STRA6* includes whole-gene deletions, nonsense and frameshift variants and missense substitutions that result in loss of function (Segel et al. 2009). A phenotype–genotype correlation has not been established (Chassaing et al. 2009).

STRA6 is widely expressed and is present in the optic vesicle and developing eye, optic nerve meninges, lung, endodermal gut derivatives, limbs and somites (Kawaguchi et al. 2007). The protein functions as a receptor that mediates the cellular uptake of retinol-binding protein-bearing circulating vitamin A (Kawaguchi et al. 2007). The subsequent intracellular metabolism of retinol to retinoic acid regulates the expression of multiple developmental target genes (Sun and Kawaguchi 2011) and it is possible that some of the phenotypic variability observed with *STRA6* variants can be explained by differences in vitamin A metabolism (Chassaing et al. 2009).

Biallelic deleterious variants in the *ALDH1A3* gene, another component of the RA synthesis pathway, are also associated with A/M (Aldahmesh et al. 2013; Fares-Taie et al. 2013; Yahyavi et al. 2013; Abouzeid et al. 2014; Williamson and FitzPatrick 2014). Ocular findings are

frequently severe and bilateral and include anophthalmia, microphthalmia and coloboma (Fig. 3), although non-penetrance of the eye findings has also been reported (Plaisancié et al. 2016). In patients with A/M due to *ALDH1A3* variants, a neurocognitive and behavioral phenotype that can include autism is common, but extraocular findings are rare (Fares-Taie et al. 2013). Survival is improved compared to those with *STRA6* variants (Williamson and FitzPatrick 2014).

Lastly, autosomal dominant, de novo, missense substitutions associated with gain of function of *RARβ* [p.(Arg387Cys) and p.(Arg387Ser)], and autosomal recessive, loss-of-function variants in *RARβ* have also been described in A/M (Srour et al. 2013; Ullah et al. 2016). Eye defects are similar to those connected to other RA synthesis genes, including A/M and coloboma (Ullah et al. 2016). The phenotype associated with variants in this gene has also been grave (Williamson and FitzPatrick 2014) and termination of pregnancy or neonatal death was reported for four of the five original cases (Srour et al. 2013). The clinical picture overlaps with that seen with *STRA6* variants and diaphragmatic hernia and/or eventration, pulmonary agenesis or hypoplasia and incomplete lung lobation, cardiac defects, bowel malrotation, bicornuate uterus, cryptorchidism, facial dysmorphism and severe developmental delays have been reported (Srour et al. 2013, 2016; Williamson and FitzPatrick 2014).

Fig. 3 Facial view of a female who is homozygous for a pathogenic, loss-of-function variant, c.1165A > T, predicting p.(Lys389*), in *ALDH1A3* (NM_000693.2), showing bilateral anophthalmia. Photograph from Dr. Daniel Schorderet and Hana Abouzeid, Institute for Research in Ophthalmology, Sion, Switzerland

SHH signaling: Curry–Jones syndrome, SMO and PTCH1 variants

Curry–Jones syndrome (CJS) is an exceedingly rare condition first described in two unrelated individuals with unilateral coronal craniosynostosis, bilateral preaxial polydactyly of the feet, cutaneous syndactyly and streaky skin lesions (Gorlin et al. 1990). The patchy nature of the skin manifestations was suggestive of somatic mosaicism (Temple et al. 1995). Additional features found in most patients with CJS include eye defects, abnormal brain development, intestinal malrotation and/or obstruction and ectopic hair growth (Temple et al. 1995; Grange et al. 2008). The eye defects comprise microphthalmia, colobomas involving the iris, choroid and retina, congenital glaucoma with secondary cataract, atypical pupil shape, corneal clouding, amblyopia and eyelid defects (Twigg et al. 2016).

The occurrence of medulloblastoma, odontogenic keratocysts, nevus sebaceous, trichoblastoma and bowel lesions identified as hamartomas and myofibromas lead to the hypothesis that CJS was caused by dysregulation of the Hedgehog signaling pathway due to clinical overlap with disorders caused by Protein-patched homolog 1 (*PTCH1*) and *GLI3* variants (Grange et al. 2008; Twigg et al. 2016). Exome sequencing of blood lymphocytes from affected patients failed to reveal pathogenic variants in this pathway, but testing of fibroblast cells and a sample of eyelid tissue demonstrated mosaicism for a single nucleotide substitution in *SMO*, c.1234C > T, predicting p.(Leu412Phe) (Twigg et al. 2016). The same variant, present at levels of less than 50% in all cases and thus indicative of mosaicism, was noted in tissues from eight unrelated patients with CJS, including the two individuals originally published by Curry and Jones (Twigg et al. 2016). The p.(Leu412Phe) substitution has also been detected in meningiomas (Clark et al. 2013) and an ameloblastoma (Sweeney et al. 2014) and was found to result in substantially elevated, constitutive activity of the Hedgehog pathway (Sweeney et al. 2014).

Vertebrates have three Hh ligands—SHH, desert hedgehog (DHH) and Indian hedgehog (IHH) (reviewed in Jia and Jiang 2006). Binding of these ligands to SMO, a frizzled G-protein-coupled transmembrane receptor, relieves the PTCH1- or PTCH2 -mediated suppression of SMO and enables signal transduction through activation of the GLI family of transcription factors that results in activation or repression of Hh target genes (Kerr et al. 2012; Briscoe and Therond 2013; Arensdorf et al. 2016; Twigg et al. 2016). Constitutional gene changes that mimic the clinical consequences of Hh activation include loss-of-function variants

in negative regulators acting at multiple stages of the Hh pathway, including *PTCH1* (Hahn et al. 1996; Johnson et al. 1996). In view of the microphthalmia associated with CJS, it is interesting to note that deleterious variants in *PTCH1* were recently associated with developmental eye defects (Chassaing et al. 2016). In a screen of patients with A/M and developmental eye defects including colobomas, cataract, sclerocornea and Peters anomaly, *PTCH1* carried the greatest burden of variants and was significantly enriched for rare, putative pathogenic variants in the 22 individuals from the patient cohort compared to more than 13,000 control chromosomes from in the Exome Variant Server (Chassaing et al. 2016). Four of the patients harbored rare, heterozygous *PTCH1* sequence variants that were predicted to be deleterious, including a frameshift variant, c.4delG, predicting p.(Glu2Asnfs*9) in exon 1 of *PTCH1* and three missense substitutions (Chassaing et al. 2016). In the three cases where segregation could be examined, all of the *PTCH1* variants were inherited from asymptomatic parents, indicating incomplete penetrance (Chassaing et al. 2016).

Ptch1 and Smo are expressed in the lens during embryogenesis and postnatal life (Choi et al. 2014). Transgenic mice with deletions in Smo manifest microphthalmia and lens defects and at E14.5, mutant lenses were typically smaller, with thinning of the lens epithelium and thickening of the cornea (Choi et al. 2014). More severe defects, such as anterior rupture of the lens or Peters anomaly, were also identified (Choi et al. 2014). At postnatal day (P) 21, mice had lenses that lacked an anterior epithelium, with disorganized lens fibers and evidence of fiber degeneration. Expression studies showed that *Ptch1* was markedly reduced or absent at E16.5, consistent with the loss of *Smo* and inhibition of Hh signaling (Choi et al. 2014). Mice with an activating Smo variant also develop abnormal lenses that are misshapen, with thickened epithelium and disorganization of the epithelial and fiber cells at E12.5 (Kerr et al. 2012).

Hh signaling is well-known to play a critical role in eye development and pathogenic gene variants in *SHH* are a rare cause of isolated A/M and/or coloboma (Schimmenti et al. 2003; Bakrania et al. 2010). *Ptch1, Smo, Gli2* and *Gli3* are all present in the embryonic lens and their expression patterns are consistent with a functional role soon after the formation of the lens vesicle (Choi et al. 2014). Studies of patients with Gorlin syndrome, also known as basal cell nevus syndrome (BCNS), that is caused by variants in *PTCH1*, show that an estimated 26% have ophthalmic abnormalities, including Peters anomaly, cataracts (Evans et al. 1993; Black et al. 2003; Maity et al. 2005; Taylor et al. 2006) and microphthalmia (Ragge et al. 2005a, b). Loss-of-function variants in *PTCH1* are also associated with unilateral epiretinal membrane without posterior vitreous separation or vitreous abnormality, and a bilateral, myelinated nerve fiber layer (Farley et al. 2017). Severe eye involvement with microphthalmia and coloboma has also been infrequently reported in patients with *PTCH1* variants (Richieri-Costa et al. 2017).

Genes involved in BMP signaling: BMP4, BMP7, and SMOC1

Patients with cytogenetic deletions spanning both *BMP4* and *OTX2* at chromosome 14q22 have manifest A/M and anterior segment dysgenesis with microcornea, in addition to the pituitary and brain malformations associated with haploinsufficiency for *OTX2* (Bakrania et al. 2008; Takenouchi et al. 2013). Deleterious variants in *BMP4* have caused a variety of eye findings, including Axenfeld-Rieger spectrum and anterior segment dysgenesis, coloboma and retinal dystrophy, in addition to A/M, glaucoma and sclerocornea described with *BMP4* deletions (Reis et al. 2011; Slavotinek 2011). Developmental delays, short stature and growth retardation, macrocephaly, hydrocephalus, diaphragmatic hernia and postaxial polydactyly have been observed and result in a syndromic presentation (Reis et al. 2011; Slavotinek 2011).

Three out of 279 patients with A/M and coloboma had variants in *BMP7* that were associated with unilateral or bilateral anophthalmia, unilateral microphthalmia and optic disc and chorioretinal colobomas (Wyatt et al. 2010). Extraocular features were sensorineural hearing loss, cleft palate, tracheoesophageal fistula, hemivertebrae, developmental delays, seizures and growth retardation (Wyatt et al. 2010). Two of the variants were predicted to result in loss of function and one was a missense variant; all three were maternally inherited, but clinical details on two of the mothers were not available.

BMP4 and *BMP7* both function as secreted signaling molecules in the TGFβ family (Williamson and FitzPatrick 2014). BMP signaling plays an important role in many aspects of eye development and both BMP4 and BMP7 are important ligands for lens induction (Wang et al. 2014). These genes are expressed widely during embryogenesis and the incomplete penetrance and pleiotropy associated with deleterious variants in these genes illustrate the complex nature of BMP-related diseases (Wang et al. 2014).

Waardenburg anophthalmia syndrome (WAS), also known as microphthalmia with limb anomalies and ophthalmo-acromelic syndrome, describes the rare association of anophthalmia and microphthalmia with limb anomalies that are best exemplified by postaxial oligosyndactyly, facial anomalies and intellectual disability (Abouzeid et al. 2011; Rainger et al. 2011; Jamshidi et al. 2017). WAS is caused by biallelic, loss-of-function variants in *SMOC1* (Abouzeid et al. 2011; Okada et al. 2011; Rainger et al. 2011). It is interesting to note mild clinical overlap with the limb defects associated with eye defects caused by *BMP4* variants and it has been hypothesized that *SMOC1* deficiency causes limb

and ocular defects by altering the BMP gradient within the limb bud and eye (Rainger et al. 2011).

Genes of the mitochondrial respiratory complex: HCCS, COX7B, and NDUFB11

Microphthalmia with linear skin defects syndrome (MLS; also known as microphthalmia, dermal aplasia and sclerocornea, or MIDAS) is recognizable due to characteristic manifestations of A/M, sclerocornea and corneal opacities, and patchy, erythrodermatous skin lesions (Al-Gazali et al. 1990; Morleo and Franco 2011; van Rahden et al. 2014). The skin lesions are congenital, frequently occur on the scalp, face and neck and often heal with minimal residual scarring in early childhood. Other ophthalmological findings are heterogeneous, comprising sclerocornea, corneal opacities and leukoma, iridocorneal adhesions, congenital glaucoma with anterior synechiae, aniridia and cataracts (Cape et al. 2004; Wimplinger et al. 2006; Morleo and Franco 2011). Central nervous system involvement with anencephaly, agenesis of the corpus callosum, hydrocephalus, mental retardation, infantile seizures and developmental delays, and congenital heart disease have also been described (Morleo and Franco 2011; van Rahden et al. 2014). Short stature, diaphragmatic hernia, nail dystrophy, preauricular pits and hearing loss, genitourinary tract malformations and anterior or imperforate anus are rare (Al-Ghazali et al. 1990; Wimplinger et al. 2006, 2007; Morleo and Franco 2011).

MLS is predominantly caused by chromosome deletions involving all or part of the *HCCS* gene located at chromosome Xp22.2; rarer missense substitutions and nonsense variants have also been described (Temple et al. 1990; Wimplinger et al. 2006; van Rahden et al. 2014). Inheritance is X-linked dominant and the syndrome has been reported to be lethal in males (Morleo and Franco 2011). More recently, genetic heterogeneity has been recognized in MLS. Indrieri et al. used a candidate gene approach to identify deleterious, de novo sequence variants predicting loss of function in the *COX7B* gene in 3 probands from 14 MLS patients and families (2012). All of the patients with *COX7B* variants had skin lesions, but the first two probands had normal eyes and the third family demonstrated only mild ocular manifestations, including myopia and pale optic discs (Indrieri et al. 2012). Finally, a de novo, nonsense variant in the *NDUFB11* gene at chromosome Xp11.23 was noted in one female patient and a heterozygous 1-bp deletion was detected in a second individual, her asymptomatic mother, and an affected fetus born to the subject's mother (van Rahden et al. 2015). The eye manifestations associated with *NDUFB11* were also mild, with myopia, nystagmus and strabismus, and no microphthalmia or sclerocornea were observed (van Rahden et al. 2015).

HCCS encodes an enzyme located in the inner mitochondrial membrane that adds heme to apocytochrome c and c1, resulting in mature holocytochrome c (Wimplinger et al. 2006). Similarly, both *COX7B* and *NDUFB11* are also involved in the mitochondrial respiratory chain, with *COX7B* deficiency impairing complex IV assembly and activity and *NDUFB11* encoding a structural component of complex I (Rea et al. 2017). Tissue-specific, differentially skewed inactivation of the X chromosome has been hypothesized to account for the intrafamilial variability in MLS.

Other genes causing syndromic A/M: BCOR, YAP1, and TFAP2α

Oculo-cardio-facial dental (OFCD) syndrome and Lenz microphthalmia syndrome are both caused by deleterious variants in the *BCOR* gene (Ng et al. 2004). Although congenital cataracts are the predominant ocular finding in OFCD syndrome, microphthalmia and/or microcornea can be present. This relatively easily recognized syndrome has been well-reviewed and includes characteristic facial features, with a long and narrow face, high nasal bridge, midface hypoplasia and a broad or septate nasal tip, atrial and ventricular septal defects, dental radiculomegaly and enlarged dental roots (Oberoi et al. 2005; Hilton et al. 2009; Slavotinek 2011; Feberwee et al. 2014; Ragge et al. 2018). The clinical findings of OFCD are only apparent in females and clinical variability can also occur due to somatic mosaicism and X chromosome inactivation (Hilton et al. 2009). Microphthalmia is not typically associated with *BCOR* variants in the absence of the OFCD phenotype (Hilton et al. 2009). In males, Lenz microphthalmia was first described in patients with A/M and colobomas, microcephaly and structural brain abnormalities, mental retardation, palatal defects, congenital heart disease, anomalies of the fingers and clavicles, unilateral renal aplasia and cryptorchidism in association with a specific missense variant in BCOR, c.254C > T, predicting p.(Pro85Leu) (Ng et al. 2004). However, Lenz microphthalmia is now known to be associated with other BCOR variants (Ragge et al. 2018).

Pathogenic gene variants in *YAP1* have been described in patients with A/M, colobomas of the iris and chorioretina, microphthalmia and cataract (Williamson et al. 2014). Extraocular features included cleft palate/uvula and cleft lip, hearing impairment, developmental delays and Asperger syndrome (Williamson et al. 2014; Holt et al. 2017); however, isolated iris and retinal colobomas with reduced penetrance have also been reported (Oatts et al. 2017). *YAP1* is a transcriptional co-activator that is a major effector of the Hippo pathway that regulates organ size and is directly regulated by *SOX2* (Holt et al. 2017). YAP1 may also affect β-catenin-dependent Wnt signaling and interacts with a number of genes and proteins that are implicated in A/M and coloboma (Holt et al. 2017).

Branchiooculofacial syndrome (BOFS) is characterized by orofacial clefting (cleft lip, prominent philtral pillars, cleft palate), eye defects (microphthalmia, anophthalmia, coloboma, and cataract), branchial skin anomalies (cervical or infra- or supra-auricular skin defects) and a characteristic facial appearance comprising ocular hypertelorism or telecanthus, broad nasal tip, upslanted palpebral fissures, upper lip pits, malformed and prominent pinnae (Li et al. 2013; Lin et al. 2011). Deleterious variants in *TFAP2a* resulting in reduced transcriptional activity are the only known cause to date, with different residual gene activities accounting for phenotypic variability (Li et al. 2013). Ocular malformations have been present in up to 83% of *TFAP2A*-associated BOFS cases in the literature (Aliferis et al. 2011). Inheritance is autosomal dominant and intellect is usually normal (Lin et al. 2011).

Bosma arhinia microphthalmia syndrome and deleterious variant in SMCHD1

Bosma arhinia microphthalmia syndrome (BAM) was first described in two unrelated males who manifest severe underdevelopment of the eyes and nose, palatal abnormalities, hypogonadotrophic hypogonadism with abnormal taste and smell, cryptorchidism and inguinal hernias (Gifford et al. 1972; Bosma et al. 1981). This panethnic, rare condition has less than 50 cases reported in the medical literature and is characterized by a triad comprising microphthalmia and coloboma, arhinia with hypoplasia of the maxilla and midface, and endocrine findings of hypogonadotropic hypogonadism, cryptorchidism and microphallus (Graham and Lee 2006; Brasseur et al. 2016; Shaw et al. 2017). A high-arched palate, anosmia, absent paranasal sinuses and absent olfactory bulbs are also frequent findings (Brasseur et al. 2016). Intelligence is typically normal (Graham and Lee 2006; Brasseur et al. 2016; Shaw et al. 2017).

Severe eye defects are recognized in BAM, including bilateral, congenital microphthalmia and microphthalmia with heminasal aplasia (Graham and Lee 2006). In a review of a new case and 13 patients from the literature, nine out of 14 had coloboma, seven had microphthalmia, one had anophthalmia and two were reported as normal (Graham and Lee 2006; Brasseur et al. 2016). Other eye defects associated with nasal aplasia have included microphthalmia and microcornea (Cusick et al. 2000), bilateral iris colobomata (Olsen et al. 2001), unilateral optic atrophy (McGlone 2003) and hypertelorism (Graham and Lee 2006).

Recurrence in siblings and in second-degree relatives has long established BAM as a genetic condition (Thiele et al. 1996; Ruprecht and Majewski 1978; Graham and Lee 2006). In a sequencing study on patients with arhinia ascertained from an international consortium, Shaw et al. noted rare, de novo, heterozygous, missense variants located in exons 3–13 of *SMCHD1* in 32/38 (84%) of the probands, including five familial cases (2017). This observation was confirmed by Gordon et al., (2017) who investigated 14 unrelated individuals with BAM or isolated arhinia, including six of the patients studied by Shaw et al. (2017), by trio or quartet whole exome sequencing. De novo, heterozygous, missense substitutions were identified in *SMCHD1* in all probands (Gordon et al. 2017). The deleterious sequence variants were located in exons 3, 8–10, 12 or 13 that encode the ATPase domain and an associated region immediately C-terminal to the ATPase domain (Gordon et al. 2017). Six of the 14 patients had variants affecting three adjacent amino acids—Ala134, Ser135 and Glu136 ,while p.(His348Arg) and p.(Asp420Val) were identified in three and two unrelated patients, respectively (Gordon et al. 2017). Familial cases exhibited marked variability in severity, implying that BAM represents the most severe end of a wider spectrum of manifestations that can extend to the subclinical range, demonstrating the importance of modifying factors in the clinical presentation.

Smchd1 is expressed in the developing nasal cavity at E14.5 (Shaw et al. 2017). The gene is a non-canonical member of the SMC family of proteins that are involved in chromatid cohesion, chromosome condensation and DNA repair (Wilkie 2017). SMCHD1 comprises two major protein domains: an N-terminal domain that contains a GHKL (gyrase, Hsp90, histidine kinase, and MutL) ATPase motif, and an SMC (structural maintenance of chromosomes) domain at the C-terminal end that shares homology with cohesins and condensins and provides an interface for homodimerization (Wilkie 2017).

Haploinsufficiency for *SMCHD1* also causes fascioscapulohumeral dystrophy type 2 (FSHD2) (Gordon et al. 2017; Shaw et al. 2017; Wilkie 2017). FSHD2 results from misexpression of the transcription factor *DUX4* that is encoded by an array of D4Z4 repeats on chromosome 4q, in skeletal muscle. A reduction in SMCHD1 repressive activity caused by loss-of-function variants, in combination with a permissive D4Z4 haplotype, allows for the ectopic expression of the transcript encoding DUX4, which is cytotoxic to skeletal muscle (Shaw et al. 2017). More than 80 unique, *SMCHD1* variants, with missense and truncating variants, map throughout the protein, have been reported in patients with FSHD2. However, there is no clinical overlap between FSHD2 and BAM, although one causal variant, p.(Gly137Glu), has been detected in a patient with arhinia and in an unrelated patient with FSHD2 (Shaw et al. 2017).

SMCHD1 variants causing FSHD2 span the entire gene, whereas BAM-associated missense variants have clustered tightly around the ATPase domain that controls the release of DNA bound by SMCHD1 (Shaw et al. 2017). One group found largely identical hypomethylation patterns at the D4Z4 locus in arhinia and FSHD2 probands, indicating that neither

a loss nor a gain of the gene silencing function of SMCHD1 alone explains the difference in phenotype (Shaw et al. 2017). Additional factors, such as interactions with variants at other loci or disruption of SMCHD1 protein interactions that are critical to its epigenetic functions, could therefore be involved in generating the distinct clinical manifestations of BAM and FSHD2 (Shaw et al. 2017). However, other authors have concluded that the phenotypic variation arises from different functional classes of genetic variants in *SMCHD1*, as functional studies in *Xenopus* with mRNAs encoding either wild-type or variant human SMCHD1 protein showed that only tadpoles overexpressing SMCHD1 mRNA with variants causing BAM developed craniofacial anomalies, including A/M (Gordon et al. 2017).

Gorlin–Chaudhry–Moss syndrome

Gorlin–Chaudhry–Moss syndrome (GCMS) is a complex pattern of multiple congenital anomalies characterized by microphthalmia with short downslanting palpebral fissures, craniosynostosis of the coronal suture and brachycephaly, severe midface hypoplasia and retrusion, hypertrichosis of the scalp, face, trunk and limbs, conductive hearing loss, a high-arched and narrow palate, dental anomalies with oligo- and microdontia and malocclusion, short stature with a stocky build, brachydactyly and genital hypoplasia (Gorlin et al. 1960; Ippel et al. 1992; Adolphs et al. 2011; Ehmke et al. 2017). Patients with GCMS can also demonstrate progeroid features, with translucent or loose skin and a reduction in adipose tissue (Ehmke et al. 2017). The eye defects are considered to be important in the recognizable facial gestalt (Ehmke et al. 2017). Hyperopia and short eyebrows have also been described (Adolphs et al. 2011).

Five unrelated female patients with GCMS were studied using next-generation sequencing and de novo, missense substitutions were identified in the same codon, arginine 217, in the *SLC25A24* gene in all patients (Ehmke et al. 2017). Four patients shared c.650G > A, predicting p.(Arg217His) and one patient had c.649C > T, predicting p.(Arg217Cys) (Ehmke et al. 2017) in *SLC25A24*. All five patients had microphthalmia with short and downslanting palpebral fissures (Ehmke et al. 2017). However, the exact same nucleotide variants in *SLC25A24* were also found in patients with a diagnosis of Fontaine syndrome, a rare human progeroid syndrome characterized by prenatal and postnatal growth retardation, decreased subcutaneous fat tissue, sparse hair, a triangular face, a widely open anterior fontanel, craniosynostosis, a convex and broad nasal ridge, micrognathia, small distal phalanges of the fingers and toes and premature demise (Writzl et al. 2017). None of the patients with Fontaine syndrome were reported to have eye malformations, suggesting ascertainment bias in phenotype delineation.

SLC25A24 consists of an N-terminal calcium-binding domain containing four EF-hand motifs followed by six, transmembrane helices and a short C terminus (del Arco and Satrústegui 2004). The gene encodes a mitochondrial inner membrane ATP-Mg/Pi carrier, also known as short Ca2++ binding mitochondrial carrier 1 (SCaMC1). This carrier mediates an exchange of ATP-Mg2++ for $HPO4^{2-}$, depending on the presence of Ca2++ in the intermembrane space (Ehmke et al. 2017; Harborne et al. 2017). Cultured fibroblasts from two affected patients showed no difference in gene expression using quantitative polymerase chain reaction (qPCR) or in protein stability with an immunoblot and wild-type and mutant proteins both localized to mitochondria (Ehmke et al. 2017). However, treatment of patient fibroblasts with H2O2 that induces oxidative stress resulted in mitochondrial swelling and ballooning. Transient expression of mutant SLC25A24 with p.(Arg217His) also caused mitochondrial swelling and increased fragmentation, with increased mitochondrial membrane potential, whereas the mitochondria in cells overexpressing wild-type SLC25A24 remained unchanged (Ehmke et al. 2017). A luciferase assay revealed that the ATP content of the mitochondrial matrix was reduced compared to controls (Ehmke et al. 2017). The amino acid changes, p.(Arg217His) and p.(Arg217Cys) are therefore likely to result in a gain of function that interferes with physiological SLC25A24 function (Ehmke et al. 2017). The relationship to eye disease is unknown.

Warburg Micro syndrome, Martsolf syndrome and RAB18 deficiency

Warburg Micro syndrome is a rare, autosomal recessive disorder characterized by severe eye and brain abnormalities (Martsolf et al. 1978; Warburg et al. 1993). Affected individuals have severe to profound intellectual disability, with absence of expressive speech, postnatal microcephaly, brain malformations with hypogenesis of the corpus callosum and polymicrogyria, feeding difficulties with gastroesophageal reflux and/or dysphagia, seizures, motor dysfunction with spastic paraplegia, hypogonadotrophic hypogonadism and short stature (Handley and Sheridan 2018). Eye manifestations are frequently the presenting feature of RAB18 deficiency, with bilateral congenital cataracts that are typically associated with microphthalmia and microcornea and small, atonic pupils (Handley and Sheridan 2018). Progressive optic atrophy and cortical visual impairment can further compromise vision (Handley and Sheridan 2018).

Biallelic variants in the *RAB3GAP1, RAB3GAP2, RAB18*, or *TBC1D20* genes cause the RAB18 deficiency that underlies both Warburg Micro syndrome and Martsolf syndrome (Handley and Sheridan 2018). Loss-of-function variants in these genes cause more severe phenotypic manifestations, as seen in Warburg Micro syndrome,

in contrast to hypomorphic variants that are associated with Martsolf syndrome and a milder clinical presentation (Handley et al. 2013). RAB3GAP1 and RAB3GAP2 form a binary 'RAB3GAP' complex that functions as a guanine–nucleotide exchange factor (GEF) for RAB18, whereas TBC1D20 shows modest RAB18 GTPase-activating (GAP) activity in vitro (Handley et al. 2015). In the absence of RAB18GEF activity, RAB18 is unable to fulfill its cellular role (Gerondopoulos et al. 2014; Handley et al. 2015).

Anophthalmia, rhizomelic skeletal dysplasia and MAB21L2 variants

Pathogenic variants in *MAB21L2* causing structural eye defects were first identified in eight individuals from five unrelated families with bilateral anophthalmia and colobomatous microphthalmia, rhizomelic skeletal dysplasia, macrocephaly, and intellectual disability (Rainger et al. 2014). Three of the variants affected the same Arg51 residue and one variant, c.151C > T, predicting p.(Arg51Cys), arose de novo in two unrelated patients. Interestingly, both autosomal dominant and autosomal recessive inheritance patterns were observed. One family demonstrated autosomal dominant inheritance of the same variant, with full penetrance of the eye defects and non-penetrance of the skeletal manifestations (Rainger et al. 2014). In another patient with bilateral colobomatous microphthalmia, recurrent dislocations of the patellae and cutaneous syndactyly of the third and fourth digits of his hands and of the second and third digits of both feet, c.145G > A, predicting p.(Glu49Lys) was noted in *MAB21L2* (Rainger et al. 2014). Other findings associated with deleterious variants in *MAB21L2* include short stature, joint contractures and bony bowing (Horn et al. 2015). Both homozygous and heterozygous variants have been described as pathogenic (Rainger et al. 2014; Horn et al. 2015). Functional assays have suggested both possible gain- and loss-of-function effects for dominant variants and as yet there is no clear phenotype–genotype correlation (Deml et al. 2015).

Mab21l2 is strongly expressed in the murine eye. Homozygous-targeted inactivation of *Mab21l2* in mouse embryos causes defects of the ventral body wall, severe eye malformations, and death in mid-gestation, whereas heterozygous null animals are apparently normal (Yamada et al. 2004). In zebrafish, expression of *mab21l2* in the eye field is *rx3* dependent. Morpholino or transcription activator-like effector nuclease (TALEN) knockdown of *mab21l2* in zebrafish has produced defective optic cup formation, with variable lens malformations and colobomas, and proliferation defect within the retinal progenitor cell population that result in small, but structurally normal eyes (Deml et al. 2015).

Discussion

We have summarized the ocular and extraocular clinical features for a selection of the genes involved in syndromic A/M, with an emphasis on genes that are involved in pathways, including *SOX2, OTX2, PAX6*, the genes involved in the RA synthesis pathway, *STRA6, ALDH1A3* and *RARβ*, and the genes that are involved in *SHH* signaling, including *SMO* and *PTCH1*. Less common genetic causes of A/M, including *BMP4, BMP7, SMOC1, HCCS, NDUFB11, BCOR, YAP1* and *TFAP2α* are also briefly discussed and the commonest clinical findings are summarized in Table 1. We have also discussed several genes that are newly identified to cause A/M, including *SMCHD1* and *SLC25A24*.

Common clinical themes include significant variability in the eye malformations associated with deleterious variants in a single gene (for example, *SOX2* and *OTX2*), with a wide range of additional ocular defects in addition to A/M, and non-penetrance of the A/M phenotype despite the inheritance of deleterious variants. Clear phenotype–genotype correlations were rarely apparent, although clinical manifestations can overlap between different genes that act in the same pathway (for example, the genes involved in RA synthesis). Different functional mechanisms have been hypothesized to explain eye phenotypes that can occur with either dominant or recessive inheritance patterns for the same gene (for example, gain or loss of function in *RARβ* and *MAB21L2*), but functional studies were often not conclusive. Regarding pathways, many of the genes are found in common pathways, but temporal and spatial variation in gene expression prevent simple formulations for the relationships between these genes. In the era of next-generation technologies, the number of novel genes involved in the pathogenesis of A/M is rising and further insights into the pathogenesis of eye defects such as A/M are likely to be rapidly forthcoming.

Table 1 Summary of clinical findings associated with syndromic anophthalmia and microphthalmia

	SOX2	*OTX2*	*PAX6*	*ALDH1A3*	*STRA6*	*RARB*	*BMP4*	*SMOC1*	*HCCS*	*BCOR*	*YAP1*	*TFAP2*	*PORCN*
Ocular findings													
A/M[a]	++	+	+	+	+	+	+	+	+	+	+	+	+
Coloboma	+	+	+	+	+		+	+			+	+	+
ASD[b]	+	+	+				+						
Aniridia			+++						+				+
Cataracts	+/−	+/−	+						+	+	+	+	
Congenital glaucoma			+				+		+				
Retinal dystrophy	+	+	+				+						
Optic nerve atrophy[c]	+	+	+		+			+					+
Sclerocornea/corneal opacity									+				
CNS[d]—structural defects		+											
Heterotopias	+												
ACC[e]/hypoplasia CC	+		+		+		+		+				+
Mesial temporal anomaly	+		+/−										
Abnormal white matter	+												
Arnold-Chiari malformation		+											+
Anterior commissure defect			+										
Olfactory bulb hypoplasia			+										
Absent pineal gland			+										
Hydrocephalus[f]	+						+		+				+
Arrhinencephaly					+								
Dandy–Walker malformation					+								
Developmental differences		+	+/−	+	+	+	+	+	+	+	+		+
Global delays	+				+								
Motor delays	+				+								
Seizures	+	+	+						+				
Hypotonia		+					+						
Endocrine													
Hypopituitarism	+	+											
Growth retardation	+	+			+		+		+/−				+
Microcephaly		+								+			+
Feeding difficulties		+											
Dysmorphic findings	+	+			+	+	+			+		+	+
Cardiac defects	+				+	+			+	+			
Pulmonary agenesis[g]					+	+							
GU tract malformations[h]	+	+			+	+		+	+/−	+			+
GI malformations[i]					+	+							+
Other													
Tracheo-esophageal fistula	+												
Vertebral/rib malformations	+												+
Hearing loss	+	+									+		+
Cleft lip/palate		+			+		+	+		+	+	+	+
Polydactyly/syndactyly							+	+					+
Oligodactyly								+					+
Diaphragmatic defects					+	+			+/−				+
Skin defects									+			+	+
Dental anomalies										+			+

+A/M[a] = anophthalmia/microphthalmia; ASD[b] = anterior segment dysgenesis; optic nerve atrophy[c] = includes optic nerve hypoplasia and dysplasia; CNS[d] = central nervous system; ACC[e] = agenesis of corpus callosum; hydrocephalus[f] = hydrocephalus/ventricular dilatation; pulmonary agenesis[g] = pulmonary agenesis/hypoplasia; GU tract malformations[h] = genitourinary tract malformations; GI malformations[i] = gastrointestinal tract malformations

Compliance with ethical standards

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

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