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Microphthalmia/Anophthalmia/Coloboma Spectrum – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

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Summary

NOTE: THIS PUBLICATION HAS BEEN RETIRED. THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.

Clinical characteristics

*M*icrophthalmia, *a*nophthalmia, and *c*oloboma comprise the MAC spectrum of ocular malformations.

- Microphthalmia refers to a globe with a total axial length that is at least two standard deviations below the mean for age.
- Anophthalmia refers to complete absence of the globe in the presence of ocular adnexa (eyelids, conjunctiva, and lacrimal apparatus).
- Coloboma refers to the ocular malformations that result from failure of closure of the optic fissure. Chorioretinal coloboma refers to coloboma of the retina and choroid. Iris coloboma causes the iris to appear keyhole-shaped.

Microphthalmia, anophthalmia, and coloboma may be unilateral or bilateral; when bilateral they may occur in any combination.

Diagnosis/testing

Molecular genetic testing (which can include sequence analysis, gene-targeted deletion/duplication analysis, and chromosome microarray analysis [CMA]) can identify a genetic cause in 80% of individuals with bilateral anophthalmia/severe microphthalmia and in up to 20% of all individuals with an ocular malformation in the MAC spectrum.

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Genetic counseling

When an inherited or *de novo* chromosome abnormality or a specific syndrome is identified either by phenotypic findings or by genetic/genomic testing, genetic counseling is indicated based on the mode of inheritance for that condition.

Management

Treatment of MAC spectrum: Prosthetic intervention is appropriate for those with severe microphthalmia and anophthalmia. In many infants, an ocularist can start shortly after birth to expand the palpebral fissures, conjunctival cul-de-sac, and orbit using conformers of progressively increasing size. An oculoplastic surgeon can help determine the most suitable options for surgical intervention after age six months (when postnatal growth of the orbit can be assessed) and before the age that orbital dimensions are fixed (after which extensive orbital reconstruction may be required).

Children with reduced vision may benefit from visual aids and other visual resources as well as early intervention to help optimize psychomotor development, educational endeavors, life skills, and mobility. Protection of the healthy eye in those with unilateral involvement is recommended.

Definition

*M*icrophthalmia, *a*nophthalmia, and *c*oloboma comprise the MAC spectrum of ocular malformations.

Microphthalmia refers to a globe with a total axial length (TAL) at least two standard deviations below the mean for age (see Table 1).

- For an adult eye, the lower 2.5% confidence limit for the TAL is approximately 21.0 mm.
- In children (in whom postnatal ocular growth continues into adolescence) the lower 2.5% confidence limit must be derived from a normative plot of TAL versus age [Gordon & Donzis 1985, Weiss et al 1989].

Table 1. Length of the Neonatal and Adult Eye

Age	Mean Length		
	Total Axial Length [1]	Anterior Segment Length [2]	Posterior Segment Length [3]
Neonate	17 mm	6.8 mm	10.2 mm
Adult	23.8 mm	7.3 mm	16.5 mm

1. Total axial length (TAL) is the axial distance (in mm) from the corneal apex to the back of the globe.
2. Anterior segment length (ASL) is the axial distance (in mm) from the cornea to the back of the lens.
3. Posterior segment length (PSL) is the axial distance (in mm) from the back of the lens to the back of the globe.

In microphthalmic eyes, measurements of ASL and PSL indicate that ASL is within or below the normal range, whereas PSL is uniformly at least two standard deviations below the mean for age [Weiss et al 1989].

Most postnatal growth of the eye occurs in the first three years of life, particularly during the first year. Growth of the posterior segment accounts for 60% of the prenatal and more than 90% of the postnatal increase in TAL. Although TAL is reduced at birth, the microphthalmic eye can grow by a variable amount in the postnatal period depending on the severity of the underlying malformation.

Classification of microphthalmia is according to the anatomic appearance of the globe and severity of axial length reduction. Severe microphthalmia refers to a globe that is severely reduced in size, with a corneal diameter <4 mm and a TAL <10 mm at birth or <12 mm after age one year. Although the globe is inconspicuous on clinical examination, CT or MRI reveals remnants of ocular tissue, an optic nerve, and extraocular muscles.

Without orbital imaging studies, severe microphthalmia can be mistaken for anophthalmia; thus, the term "clinical anophthalmia" is often interchangeably used for severe microphthalmia.

Anophthalmia refers to complete absence of the globe in the presence of ocular adnexa (eyelids, conjunctiva, and lacrimal apparatus).

Coloboma refers to any of the ocular malformations that result from failure of closure of the optic fissure extending inferonasally from the optic disk, retina, and choroid (in the posterior portion of the eye) to the ciliary body and lens zonules and to the iris (in the anterior portion of the eye) during embyrogenesis.

Chorioretinal coloboma refers to coloboma of the retina and choroid. Iris coloboma causes the pupil to be "keyhole" shaped.

Other abnormalities of the eye that can be seen with coloboma include:

- Sclerocornea: opacity and vascularization of portions of the normally transparent cornea which, as a result, resembles sclera
- Cataract: opacity of the lens
- Retinal dysplasia: histologic findings associated with developmental loss of structural and functional cellular components of the retina

Each of these three malformations may be unilateral or bilateral; when bilateral they may occur in any combination. For example:

- Colobomatous malformations may occur in any combination within an eye or between eyes of the same individual.
- Colobomatous malformations may occur with or without microphthalmia.
- Colobomatous malformations in one eye may be accompanied by microphthalmia or anophthalmia in the fellow eye.
- Anophthalmia may be bilateral or unilateral with or without colobomatous malformation of the fellow eye.

Establishing the Diagnosis of MAC Spectrum

The diagnosis of MAC is based on the following:

Clinical examination

- Gross inspection looking for evidence of a cornea/globe and palpation of the orbit to obtain an estimate of globe size
- Measurement of corneal diameter, which normally ranges from 9.0 to 10.5 mm in neonates and 10.5 to 12.0 mm in adults

Imaging study

- A-scan ultrasonography to measure total axial length and anterior and posterior segment lengths
- B-scan ultrasonography to evaluate the internal structures of the globe
- CT scan or MRI of the brain and orbits to evaluate the size and internal structures of the globe, presence of optic nerve and extraocular muscles, and brain anatomy

Differential Diagnosis of MAC Spectrum

Microphthalmia needs to be distinguished from mild microcornea with a normal-sized globe.

Anophthalmia needs to be distinguished from severe microphthalmia, cryptophthalmos, and cystic eye.

- Cryptophthalmos ("hidden eye") refers to abnormal fusion of the entire eyelid margin with absence of eyelashes, resulting in a continuous sheet of skin extending from the forehead to the cheek. Failure of eyelid separation can be associated with maldevelopment of the underlying cornea and microphthalmia. Cryptophthalmos is usually bilateral and occurs in association with other multiple malformations collectively referred to as Fraser syndrome (OMIM 219000). Inheritance is autosomal recessive.
- Cystic eye refers to a cyst of neuroglial tissue that lacks normal ocular structures. At birth, the cyst may be small, the palpebral fissures narrow, and orbital volume reduced, suggesting anophthalmia. Postnatal expansion of the cyst can lead to distention of the cyst with bulging behind the eyelids. Orbital imaging shows an intraorbital cyst with attached extraocular muscles but no optic nerve. Cystic eye should be distinguished from the cyst associated with colobomatous microphthalmia.

Causes

Recent studies indicate that molecular genetic testing that includes sequence analysis, gene-targeted deletion/duplication analysis, and chromosome microarray analysis (CMA) can identify a genetic cause in:

- 80% of individuals with bilateral anophthalmia/severe microphthalmia [Williamson & FitzPatrick 2014];
- Up to 20% of all individuals with an ocular malformation in the microphthalmia, anophthalmia, coloboma (MAC) spectrum (in which the laterality and severity of MAC can vary).

Chromosome Abnormalities

Chromosome abnormalities can be identified in an estimated 25%-30% of individuals with MAC (Table 2) [Verma & Fitzpatrick 2007].

Table 2. Common Chromosome Abnormalities Associated with Microphthalmia/Anophthalmia/Coloboma (MAC) Spectrum

Type of Chromosome Abnormality	Chromosome Abnormality
Aneuploidy	• Trisomy 9 mosaicism • Trisomy 13 • Trisomy 18
Triploidy	Triploidy
Deletion	• 4p- (Wolf-Hirschhorn syndrome) • Deletion 7p15.1-p21.1 • 13q-, ring 13 • Deletion 14q22.1-q23.2 • 18q- • Deletion 3q26 (includes *SOX2*)
Duplication	• Duplication 3q syndrome (3q21-ter dup) • Duplication 4p syndrome • Duplication 10q syndrome

Based on Verma & Fitzpatrick [2007]

Single-Gene Disorders

Single-gene causes of MAC spectrum that account for 1% or more of anophthalmia/microphthalmia/coloboma are listed in Table 3a. Single-gene causes that account for less than 1% of MAC spectrum are listed in Table 3b. The microphthalmia, anophthalmia, and coloboma (MAC) spectrum is present in all disorders listed in both tables.

Of note, the co-occurrence of any of the ocular findings within the MAC spectrum may be unilateral or bilateral and may be in any combination within an eye (e.g., chorioretinal coloboma and/or iris coloboma ±

microphthalmia) or between eyes of the same individual (e.g., colobomatous malformation in one eye and anophthalmia in the fellow eye).

Table 3a. Molecular Genetics of Anophthalmia/Microphthalmia/Coloboma (MAC) Spectrum: Most Common Genetic Causes

Gene [1]	Disease Name	% of MAC Attributed to Mutation of This Gene	MOI	Ocular Phenotype [2]	Distinguishing Clinical Features	Selected OMIM
SOX2	*SOX2*-related eye disorders	15%-20%	AD	Optic nerve hypoplasia	FTT, genital abnormalities, pituitary dysfunction, DD, ataxic gait, atypical seizures, SNHL, EA±TEF	184429 206900
OTX2	*OTX2*-related eye disorders	2%-5%	AD	AS; RD; optic nerve hypoplasia/aplasia [3]	Pituitary anomalies/ dysfunction, brain abnormalities, DD, autistic features [4]	600037 610125
RAX	Microphthalmia, isolated 3	3%	AR	Sclerocornea	DD	601881 611038
FOXE3	*FOXE3*-related ocular disorder [5]	2.5%	AR	Sclerocornea	Unknown (possible DD, ASD)	601094
BMP4	Orofacial cleft 11	2%	AD	RD; sclerocornea	Digital anomalies, pituitary anomalies/ dysfunction, learning disabilities	112262 600625
PAX6	*PAX6*-related anophthalmia [6, 7]	2%	AR	Aniridia	Cerebellar ataxia	607108
BCOR	Oculofaciocardiodental (OFCD) syndrome [8]	>1%	XL	OFCD: Cataract	OFCD syndrome (females only): cardiac abnormalities, tooth anomaly radiculomegaly, toe anomalies	300485 300166
	Lenz microphthalmia syndrome (LMS)				LMS (males only) (see *NAA10* in Table 3b)	
CHD7	CHARGE syndrome	>1%	AD		Heart defects, choanal atresia, renal anomalies, growth retardation, ear malformations	608892 214800
STRA6	Microphthalmia, isolated with coloboma 8	>1%	AR		Nonsyndromic	610745
	Microphthalmia, syndromic 9 (Matthew-Wood syndrome; PDAC)				Congenital diaphragmatic hernia, lung malformations, DD	601186

Table 3a. continued from previous page.

Gene [1]	Disease Name	% of MAC Attributed to Mutation of This Gene	MOI	Ocular Phenotype [2]	Distinguishing Clinical Features	Selected OMIM
GDF6	Microphthalmia, isolated 4	1%	AD			601147 613094
	Klippel-Feil syndrome 1				Klippel-Feil anomaly, vertebral/rib anomalies, polydactyly	118100

Pathogenic variants of any one of the genes included in this table account for ≥1% of anophthalmia/microphthalmia/coloboma (MAC).
MOI = mode of inheritance

Ocular phenotypes:

AS = anterior segment dysgenesis; RD = retinal dysplasia

Distinguishing clinical features:

ASD = autism spectrum disorders; DD = developmental delays; EA±TEF = esophageal atresia with or without tracheoesophageal fistula; FTT = failure to thrive; ID = intellectual disability; SNHL = sensorineural hearing loss

Footnotes:

1. Genes that cause ≥2% of MAC are listed from most frequent to least frequent genetic cause; they are followed in alphabetic order by genes that cause <2% but >1% of MAC.
2. Ocular features in addition to the typical findings in the MAC spectrum
3. Slavotinek [2011]
4. Schilter et al [2011]
5. Reis et al [2010], Jimenez et al [2011], Chassaing et al [2014], Williamson & FitzPatrick [2014], Islam et al [2015]
6. Author [personal observation]
7. Heterozygous *PAX6* pathogenic variants are associated with isolated aniridia.
8. Can also be caused by mutation of *NAA10* (see Table 3b)

Table 3b. Molecular Genetics of Anophthalmia/Microphthalmia/Coloboma (MAC) Spectrum: Less Common Genetic Causes

Gene [1]	Disease Name	MOI	Ocular Phenotype [2]	Distinguishing Clinical Features	Selected OMIM
CRYBA4	Cataract 23	AD	Cataract	Nonsyndromic	123631 610425
HCCS	Microphthalmia with linear skin defects (MIDAS syndrome)	XL	Sclerocornea	FTT, hydrocephalus, linear pigmentary changes, cardiac & brain anomalies, genital abnormalities	300056 309801
HESX1	Septooptic dysplasia	AD	Optic nerve hypoplasia	Pituitary hypoplasia, ACC, absence of septum pellucidum	601802 182230
IKBKG	Incontinentia pigmenti	XL	MAC [3] Retinal neovascularization	Skin lesions change w/age; hypodontia, alopecia, dystrophic nails, seizures, ID	300248 308300
NAA10	Lenz microphthalmia syndrome	XL		ID, short stature; clavicle, skeletal, & renal anomalies	300013 309800
NHS	Nance-Horan syndrome	XL	Cataract Microcornea	ID, tooth anomalies, short 4th metacarpal	300457 302350
PORCN	Focal dermal hypoplasia (Goltz syndrome)	XL		Atrophic skin patches, cutis aplasia, pigmentary changes, nail anomalies, notched alae nasi, CL/P	300651 305600

Table 3b. continued from previous page.

Gene [1]	Disease Name	MOI	Ocular Phenotype [2]	Distinguishing Clinical Features	Selected OMIM
PXDN	See footnote 4	AR	Sclerocornea	None reported; possible developmental delay	
RARB	Microphthalmia, syndromic 12	AD		Diaphragmatic hernia, DD, bicornuate uterus, intestinal malrotation, hypotonia	180220 615524
SHH	Microphthalmia with coloboma 5	AD		Nonsyndromic	600725 611638 142945
	Holoprosencephaly [5]			Holoprosencephaly, CL/P	
SMOC1	Microphthalmia with limb anomalies (Waardenburg anophthalmia syndrome)	AR		Oligosyndactyly, distal limb anomalies, ID	608488 206920
TFAP2A	Branchiooculofacial syndrome	AD	Cataract Ptosis	Branchial skin defect, cleft lip, upper lip pits malformed pinnae, hearing loss	107580 113620
VSX2	Isolated colobomatous microphthalmia-3	AR	Cataract	Nonsyndromic	142993 610092 610093
	Isolated microphthalmia-2				

Pathogenic variants in any one of the genes listed in this table are reported in only a few families (i.e., <1% of anophthalmia/microphthalmia/coloboma (MAC).
MOI = mode of inheritance
Ocular phenotypes:
RD = retinal dysplasia
Distinguishing clinical features:
ACC = absence of the corpus callosum; ASD = autism spectrum disorders; CL/P = cleft lip/palate; DD = developmental delays; EA±TEF = esophageal atresia with or without tracheoesophageal fistula; FTT = failure to thrive; ID = intellectual disability; SNHL = sensorineural hearing loss
Footnotes:
1. Genes are listed in alphabetic order.
2. Ocular features in addition to the typical findings in the MAC spectrum
3. Minić et al [2010]
4. Khan et al [2011], Choi et al [2015]
5. Slavotinek [2011]

Evaluation Strategy

Establishing the specific genetic cause of microphthalmia/anophthalmia/coloboma (MAC) spectrum in a given individual usually involves the following:

- **Ophthalmologic examination** by an ophthalmologist familiar with MAC to document both the ocular manifestations of MAC and any additional ocular findings.
- **Ocular/brain imaging studies**
  - Ultrasound examination of the orbits
  - MRI of the brain and orbits (or CT scan if unable to obtain an MRI)
- **Physical examination** (including dysmorphology examination) to determine the presence of distinguishing clinical features which may identify a specific genetic cause (see Tables 3a and 3b). Additional studies that may be warranted include:

- Endocrine evaluation
- Dental evaluation in older child
- Echocardiogram
- Renal ultrasound examination

- **Family history.** It is appropriate to obtain a three-generation family history of eye anomalies, including anophthalmia, microphthalmia, and coloboma. Complete eye examination of both parents is warranted.
- **Genomic/genetic testing**, which can include the following:
  - **Chromosomal microarray analysis (CMA)** to look for evidence of aneuploidy or chromosome duplication, deletion, or rearrangement (Table 2). Note: CMA will not detect balanced chromosomal rearrangements.
  - **Single-gene testing** in the order in which genes are most likely to be mutated, based on the individual's clinical findings and/or family history (see Table 3a and Table 3b). Single-gene testing should include sequence analysis as well as gene-targeted deletion/duplication analysis [Reis et al 2010, Chassaing et al 2014].
  - **Use of a multigene panel** that includes the genes of interest. Note: (1) The genes included and the sensitivity of multigene panels vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

    For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.
  - **More comprehensive genomic testing** (when available) including exome sequencing, genome sequencing, and mitochondrial sequencing may be considered if serial single-gene testing (and/or use of a multigene panel) fails to confirm a diagnosis in an individual with MAC spectrum.

    For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.
- If no diagnosis is established after the initial set of examinations and tests, reevaluation within two years is recommended.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

When an inherited or *de novo* chromosome abnormality (see Table 2) or a specific syndrome is identified either by features listed in Table 3a or Table 3b or by genetic/genomic testing, genetic counseling is indicated based on the mode of inheritance for that condition.

Related Genetic Counseling Issues

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing

Pregnancies known to be at increased risk for MAC spectrum due to a previous affected child and/or family history

- If the genetic/genomic cause **has been identified** in the affected relative, prenatal testing relies on testing that will detect the genetic/genomic change present in the affected relative.
- If the genetic/genomic cause **has not been identified** in the affected relative, prenatal testing relies on the following imaging studies:
  - Transvaginal ultrasound examination may identify the eyes from 12 weeks' gestation onward [Chen et al 2003, Mashiach et al 2004]. In most reports, eye malformations are detected only after 22 weeks' gestation. The sensitivity of transvaginal ultrasound examination in detecting anophthalmia/microphthalmia is not known [Wong et al 2008].
  - Three-dimensional and four-dimensional ultrasound examination may be used in some centers to detect complex malformations of the face, including anophthalmia/microphthalmia [Lee et al 1995, Wong et al 2008, Araujo Júnior et al 2012].
  - MRI may be a useful adjunct to ultrasound examination in detection of anophthalmia [Chen et al 2003, Araujo Júnior et al 2012].

Pregnancies not known to be at increased risk for MAC spectrum. When a MAC spectrum abnormality is detected on fetal ultrasound examination, further diagnostic work up is recommended including chromosome microarray analysis (CMA) and *SOX2* sequence analysis and gene-targeted deletion/duplication analysis. Use of a multigene panel of genes of interest can also be considered.

Preimplantation genetic testing may be an option for some families in which pathogenic variant(s) in a specific gene have been identified.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **International Children's Anophthalmia and Microphthalmia Network (ICAN)**
  c/o Center for Developmental Medicine and Genetics
  5501 Old York Road
  Genetics, Levy 2 West
  Philadelphia PA 19141
  Phone: 800-580-4226 (toll-free)
  Email: ican@anophthalmia.org
  www.anophthalmia.org

- **National Eye Institute**
  31 Center Drive
  MSC 2510

Bethesda MD 20892-2510
Phone: 301-496-5248
Email: 2020@nei.nih.gov
Low Vision

- **National Federation of the Blind (NFB)**
  200 East Wells Street
  (at Jernigan Place)
  Baltimore MD 21230
  Phone: 410-659-9314
  Fax: 410-685-5653
  Email: pmaurer@nfb.org
  www.nfb.org

- **eyeGENE - National Ophthalmic Disease Genotyping Network Registry**
  Phone: 301-435-3032
  Email: eyeGENEinfo@nei.nih.gov
  www.nei.nih.gov/eyegene

Management

Treatment of MAC Spectrum

Prosthetic intervention is appropriate in severe microphthalmia and anophthalmia.

- In many infants, an ocularist can start shortly after birth to expand the palpebral fissures, conjunctival cul-de-sac, and orbit using conformers of progressively increasing size. In some instances, conformers do not adequately expand the orbit, especially horizontally, causing an "hour glass" deformity.
- An oculoplastic surgeon can help determine the most suitable options for surgical intervention after age six months (when postnatal growth of the orbit can be assessed) and before the age that orbital dimensions are fixed (after which extensive orbital reconstruction may be required).

Surgical options include placement of orbital implants of fixed dimensions at one or more surgeries; placement of expandable implants (silicone balloon, hydrophilic polymers); or use of a dermis-fat graft, which has the capability of post-surgical growth.

Children with reduced vision may benefit from visual aids and other visual resources as well as early intervention to help optimize psychomotor development, educational endeavors, life skills, and mobility. Protection of the healthy eye in those with unilateral involvement is recommended.

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Chapter Notes

Revision History

- 7 November 2019 (ma) Chapter retired: outdated
- 9 July 2015 (me) Comprehensive update posted live – title change
- 15 February 2007 (cd) Revision: testing for mutations in *RAX* clinically available
- 26 May 2006 (me) Comprehensive update posted live
- 29 January 2004 (me) Overview posted live
- 7 March 2003 (as) Original submission

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