U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Heike CL, Luquetti DV, Hing AV. Craniofacial Microsomia Overview – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY. 2009 Mar 19 [Updated 2014 Oct 9]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Craniofacial Microsomia Overview – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

Carrie L Heike, MD, MS,[1] Daniela V Luquetti, MD, PhD,[2] and Anne V Hing, MD[1]

Created: March 19, 2009; Updated: October 9, 2014.

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 THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.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

Craniofacial microsomia (CFM) includes a spectrum of malformations primarily involving structures derived from the first and second branchial arches. Characteristic findings include facial asymmetry resulting from maxillary and/or mandibular hypoplasia; preauricular or facial tags; ear malformations that can include microtia (hypoplasia of the external ear), anotia (absence of the external ear), or aural atresia (absence of the external ear canal); and hearing loss. Severity can range from subtle facial asymmetry with a small skin tag in front of an otherwise normal-appearing ear to bilateral involvement (typically asymmetric), microtia/anotia with atresia of the ear canals, microphthalmia, and respiratory compromise from severe mandibular hypoplasia. Other craniofacial malformations including cleft lip and/or palate can be seen. Non-craniofacial malformations, especially vertebral, renal, cardiac, and limb, can be seen.

Diagnosis/testing

The diagnosis of CFM is based on clinical findings.

Genetic counseling

CFM most frequently occurs as a simplex case (i.e., occurrence in a single individual in a family) with unknown etiology; recurrence risks are empiric. If an individual with CFM is found to have an inherited or *de novo* chromosome abnormality, genetic counseling for that condition is indicated. Occasional autosomal dominant or autosomal recessive inheritance is observed. If a proband has CFM and no reported family history of CFM, the

Author Affiliations: 1 Associate Professor, Department of Pediatrics, Children's Craniofacial Center, Division of Craniofacial Medicine, University of Washington and Seattle Children's Hospital, Seattle, Washington; Email: carrie.heike@seattlechildrens.org; Email: anne.hing@seattlechildrens.org. 2 Assistant Professor, Department of Pediatrics, Children's Craniofacial Center, Division of Craniofacial Medicine, University of Washington and Seattle Children's Hospital, Seattle, Washington; Email: daniela.luquetti@seattlechildrens.org.

risk to sibs is 2%-3%, although this may be an underestimate because of low penetrance and the difficulty of obtaining an accurate family history for some of the subtle features of CFM.

Management

Treatment of manifestations: For optimal outcome children with CFM require timely and coordinated assessments and interventions. Ideally, children should be managed by an experienced multidisciplinary craniofacial team. The goals of treatment for CFM are to assure adequate respiratory support and feeding in infants with severe facial malformations, maximize hearing and communication, improve facial symmetry, and optimize dental occlusion. Treatment is age-dependent, with time-sensitive interventions at appropriate stages of craniofacial growth and development.

GeneReview Scope

Craniofacial Microsomia Overview: Included Phenotypes
• Hemifacial microsomia • Oculo-auriculo-vertebral spectrum • Goldenhar syndrome • First and second branchial arch syndrome • Otomandibular dysostosis • Facio-auriculo-vertebral syndrome • Lateral facial dysplasia

Definition

Craniofacial microsomia (CFM) includes a spectrum of malformations primarily involving structures derived from the first and second branchial arches.

Characteristic findings (Figure 1, Figure 2, and Figure 3):

- Facial asymmetry, a hallmark of this condition; common even when individuals demonstrate bilateral features
- Mandibular hypoplasia, also called micrognathia (see Figure 2 and Figure 3); usually the result of shortening of the ramus and often asymmetric
- Preauricular or facial tags and/or pits. Tags are common, variable in size, and generally distributed along the skin overlying the mandibular ramus. These branchial remnants can be simple skin tags, but may also contain cartilaginous structures that grow over time.
- Microtia (hypoplasia of the external ear) (see Figure 2)
- Anotia (absence of the external ear)
- Aural atresia (absence of the external ear canal and associated middle ear anomalies)
- Conductive, sensorineural, or mixed hearing loss

No diagnostic criteria have been established; thus, CFM is often a diagnosis of exclusion (see Differential Diagnosis).

Proposed minimal diagnostic criteria [Grabb 1965, Melnick et al 1979, Rollnick & Kaye 1983, Teconi & Hall 1983, Bennun et al 1985, Tasse et al 2007]:

- Hemifacial microsomia (asymmetric hypoplasia of facial structures) with preauricular tags
  OR
- Microtia (with or without preauricular skin tags)

The following evidence supports the notion that isolated microtia (i.e., microtia with no other malformations) may be a part of the continuum of CFM [Grabb 1965, Melnick et al 1979, Rollnick & Kaye 1983, Teconi & Hall 1983, Bennun et al 1985, Tasse et al 2007]:

- The ear malformations in isolated microtia and CFM are similar.
- The proposed causes for isolated microtia and CFM are similar.
- Mild features of CFM are frequently noted in individuals with the diagnosis of isolated microtia [Tanzer 1978, Bennun et al 1985, Keogh et al 2007].
- The prevalence of isolated microtia is much higher in family members of individuals with CFM than in the general population [Rollnick & Kaye 1983].

Several systems have been designed to define the spectrum of anomalies seen in CFM [Grabb 1965, Teconi & Hall 1983, David et al 1987, Rollnick 1988, Vento et al 1991, Cousley 1993, Gougoutas et al 2007].

Note: Individuals with features of CFM have been classified under a number of different diagnoses. It has not yet been established whether these diagnoses are distinct entities or represent the phenotypic continuum of CFM. In this *GeneReview*, the term CFM includes all of the following terms (listed from most common to least common):

- Hemifacial microsomia (asymmetric hypoplasia of facial structures)

  Note: The term CFM is more inclusive than the term "hemifacial microsomia" because the term CFM includes the large percent of individuals with bilateral involvement, including those diagnosed with hemifacial microsomia who have subtle differences in the "non-affected" side.
- Oculo-auriculo-vertebral spectrum
- Goldenhar syndrome
- First and second branchial arch syndrome
- Otomandibular dysostosis
- Facio-auriculo-vertebral syndrome
- Lateral facial dysplasia

Embryology

The head and neck originate from six embryonic structures called the pharyngeal apparati (see Figure 4A), which resemble the branchial apparatus in fish [Moore & Persaud 2003]. Each pharyngeal apparatus comprises a pouch, an arch, a groove, and a membrane. In the fourth week of gestation neural crest cells migrate from the neural tube to begin the development of the pharyngeal arch ectomesenchyme (see Figure 4B). Each arch has three layers (endoderm, mesenchyme from ectomesenchyme and mesoderm, and ectoderm), which produce the four primordial components: muscle, artery, nerve, and cartilage. The craniofacial structures most commonly affected in CFM develop from the first and second pharyngeal (branchial) arches (see Figure 4, Figure 5, Figure 6, and Figure 7).

The spectrum of anomalies involved in CFM may result from an embryonic "developmental field" functioning as a unit that responds in a similar manner to different insults such as chromosome abnormalities, mutation in a single gene, vascular disruption, and teratogens [Opitz 1985, Opitz & Lewin 1987, Cousley & Wilson 1992]. In support of this theory, CFM is causally heterogeneous (see Causes). In addition, malformations identical to CFM are observed in different vertebrate species, suggesting a developmental commonality.

The clinical findings in individuals with craniofacial microsomia can overlap with those observed in syndromes, developmental anomaly associations, and sequences. Examples include:

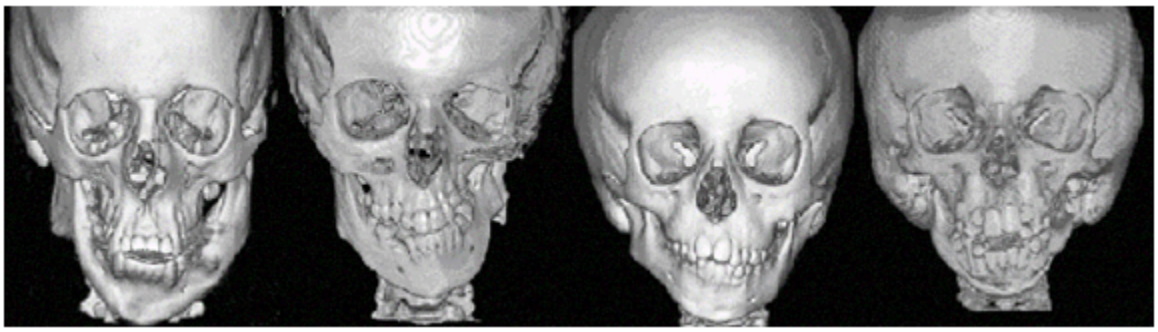

Figure 1. Examples of the variability of the skeletal malformations associated with craniofacial microsomia

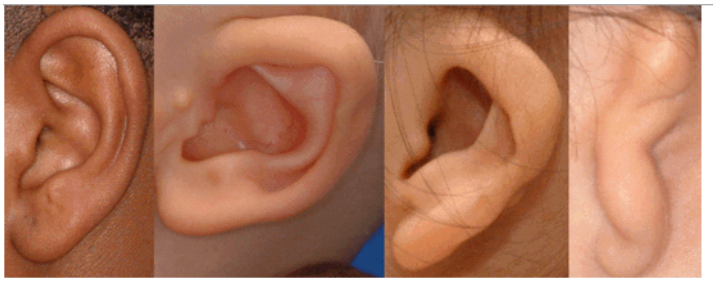

Figure 2. Grades of auricular malformations described by Marx [1926]

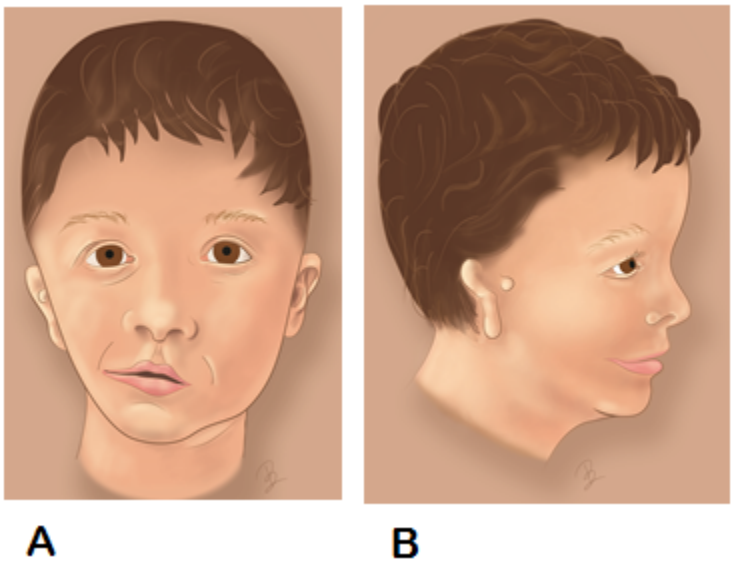

Figure 3. (A) Frontal and (B) lateral views of a boy with right-sided microtia, preauricular tag, macrostomia, and mandibular hypoplasia with soft tissue deficiency. Illustrations by Bridget Rafferty.

- VATER (expanded to VACTERL: *v*ertebral anomalies, *a*nal atresia, *c*ardiac anomalies, *t*racheoesophageal atresia, *r*enal anomalies, and *l*imb anomalies);
- CHARGE (*c*oloboma, *h*eart, *a*tresia choanae, *r*etardation of growth and development, and *g*enitourinary and *e*ar anomalies);

- MURCS (variable developmental anomalies of the *m*üllerian ducts, *u*nilateral *r*enal, *c*ervicothoracic, and *s*omite structures or their derivatives); and
- OEIS (*o*mphalocele, *e*xstrophy of the cloaca, *i*mperforate anus, and *s*pinal anomalies).

This overlap has led investigators to hypothesize that these conditions may represent developmental abnormalities which result in anomalies that may be a part of a broad spectrum, such as the axial mesodermal dysplasia spectrum [Hartsfield 2007].

Clinical Manifestations of CFM

Phenotypic variability is common in CFM. Whereas some individuals have subtle facial asymmetry with a small skin tag in front of an otherwise typical-appearing ear, others have bilateral involvement (commonly asymmetric), microtia/anotia with atresia of the ear canals, microphthalmia, and possibly respiratory compromise from severe mandibular hypoplasia (see Table 1).

In addition to the features that define CFM, the following are commonly observed in affected individuals:

Jaw

- Midface hypoplasia (underdevelopment of the midface, usually asymmetric)
- Ankylosis (limited opening of the mouth)
- Malocclusion

Eye

- Epibulbar dermoid
- Vertical displacement of the orbit
- Microphthalmia/anophthalmia (rare)
- Coloboma of the upper eye lid and/or iris

Oral region

- Macrostomia (lateral oral clefting). Unilateral macrostomia is the most common form of facial clefting associated with CFM, though all types of clefts can be observed.
- Cleft lip and/or palate

Skeleton. Vertebral anomalies [Stueckle et al 2014]:

- Malformed and/or fused cervical vertebrae are common, though anomalies can be noted throughout the spine.
- Hemivertebrae are also common.

Cranial nerves

- Facial palsy (unilateral or bilateral involvement of either part or all branches of cranial nerve VII)
- Sensorineural hearing loss
- Asymmetric palatal elevation
- Impairment of extraocular movements

An estimated 65% of individuals with CFM have some degree of facial asymmetry [Cohen et al 1989]. Individuals with facial asymmetry associated with CFM are more likely to have malformations that involve the right side of the face than the left side of the face. The ratio of affected individuals with right-sided to left-sided ear involvement is 3:2 [Gorlin et al 2001].

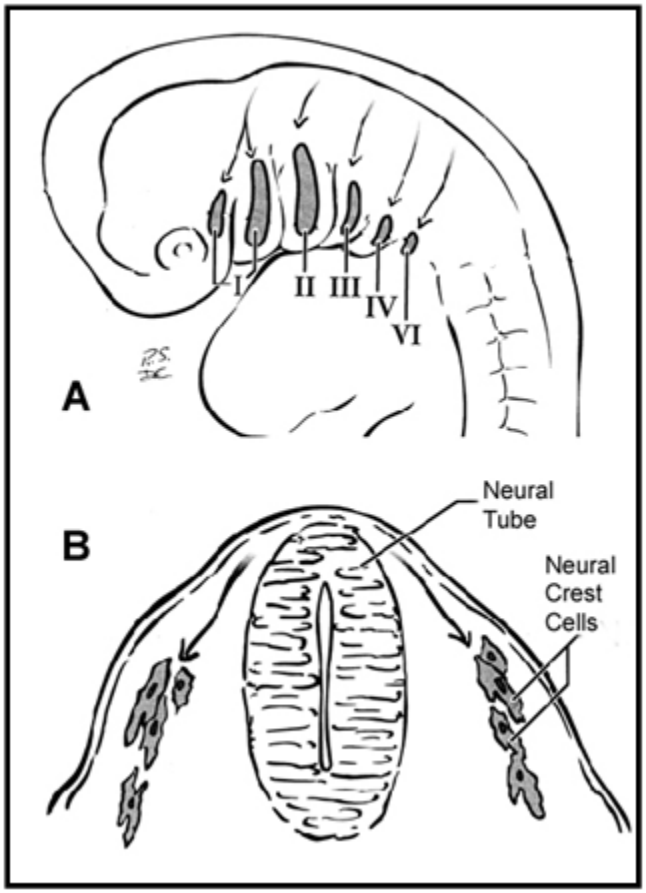

Figure 4. A. Lateral view of the six embryonic pharyngeal arches (I-VI)

B. Coronal view through the first pharyngeal arch showing the migration of cells from the neural tube to the neural crest where they will develop into the head, neck, and body

Adapted from Sze et al [2002], published with permission from AJR Am J Roentgenol

Of those individuals with bilateral facial involvement (e.g., left microtia and a right preauricular tag), most demonstrate asymmetric involvement [Grabb 1965, Burck 1983, Rollnick et al 1987].

Less common additional malformations:

- **Cardiac.** Tetralogy of Fallot, ventricular septal defects, transposition of the great vessels, and aortic arch anomalies [Gorlin et al 2001, Tasse et al 2005, Barisic et al 2014]
- **Renal.** Absent kidney, double ureter, crossed renal ectopia, hydronephrosis, hydroureter [Gorlin et al 2001, Tasse et al 2005, Barisic et al 2014, Stueckle et al 2014]
- **Limb.** Radial or ulnar ray anomalies [Barisic et al 2014]
- **Central nervous system.** Brain malformation, microcephaly, encephalocele, hydrocephaly, hypoplasia of the corpus callosum, Arnold-Chiari malformation, holoprosencephaly [Cohen et al 1989, Tasse et al 2005, Barisic et al 2014]

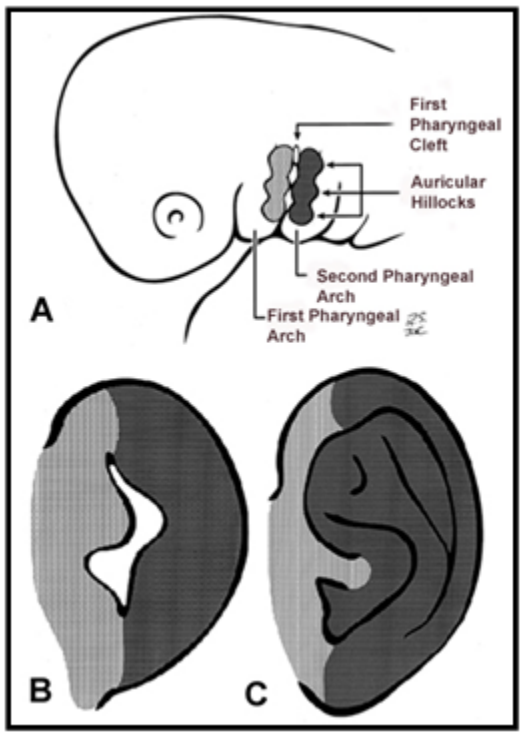

Figure 5. Origin of the external ear structures from the first and second pharyngeal arches
Adapted from Sze et al [2002], published with permission from AJR Am J Roentgenol

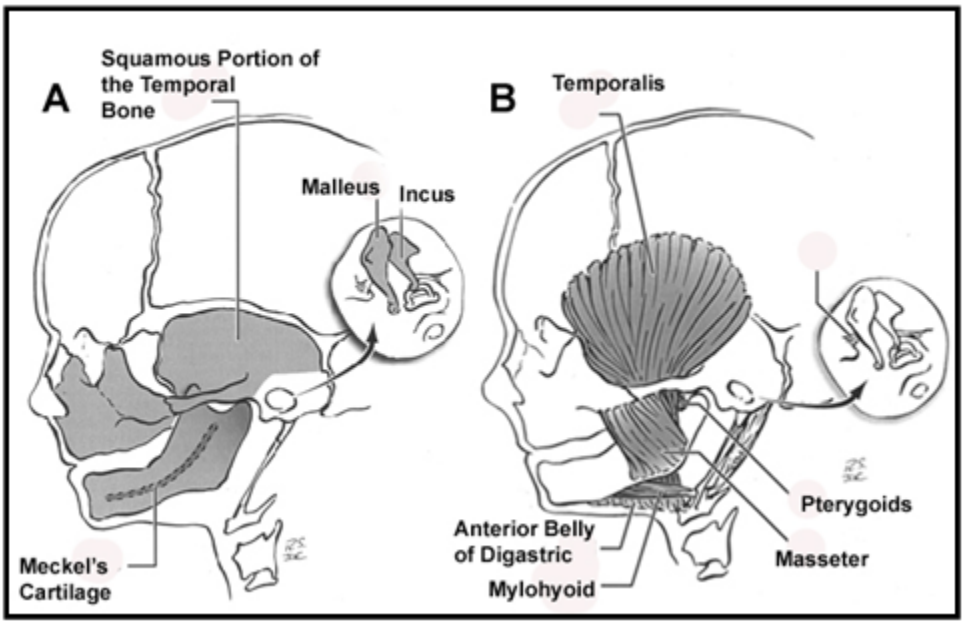

Figure 6. Bones (A) and muscles (B) derived from the first pharyngeal arch
Adapted from Sze et al [2002], published with permission from AJR Am J Roentgenol

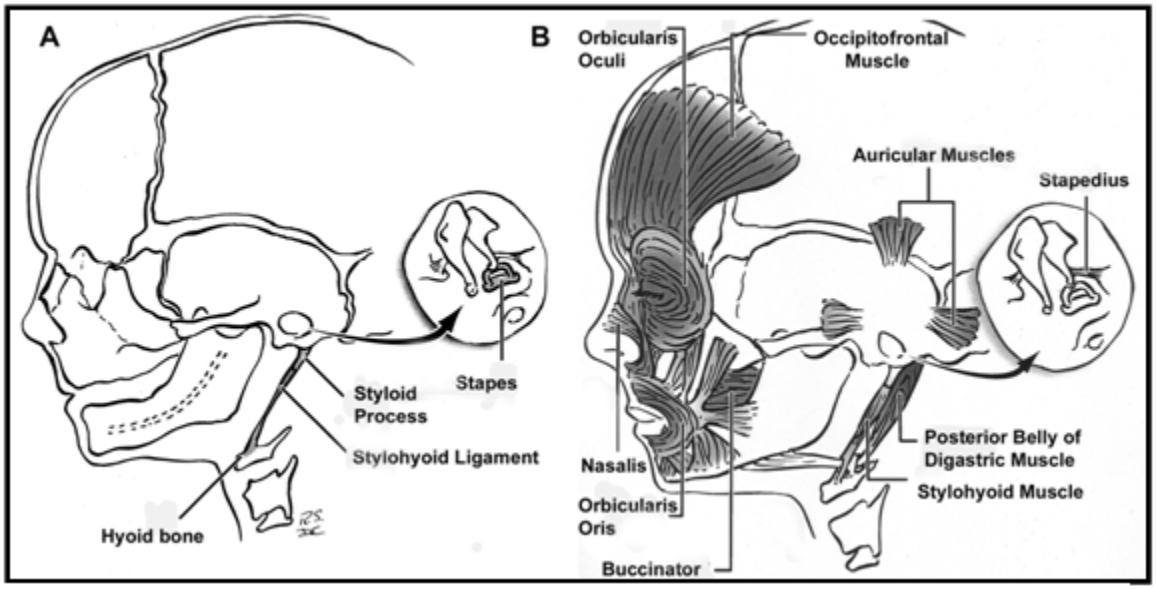

Figure 7. Bones (A) and muscles (B) derived from the second pharyngeal arch
Adapted from Sze et al [2002], published with permission from AJR Am J Roentgenol

Table 1. Prevalence of Selected Anomalies in Craniofacial Microsomia

Anomalies			Prevalence [1]
Principal	**Mandible**	Mandibular hypoplasia	49%-100%
		Malformed glenoid fossa	24%-27%
	Ear	Microtia	66%-99%
		Preauricular tags	34%-61%
		Conductive hearing loss	50%-66%
	Ocular	Orbital dystopia	15%-43%
		Epibulbar dermoids	4%-35%
	Nerve	VII nerve palsy	10%-45%
	Soft tissue	Masticatory muscle hypoplasia	85%-95%
		Macrostomia	17%-62%
Associated craniofacial	Velopharyngeal insufficiency		35%-55%
	Palatal deviation		39%-50%
	Cranial skull base abnormalities		9%-30%
	Cleft lip and/or palate		15%-22%
	Coloboma of the upper eyelid		4%-25%
	Hypodontia/dental hypoplasia		8%-25%
	Lacrimal duct atresia/stenosis		11%-14%
	Frontal plagiocephaly		10%-12%
	Sensorineural hearing loss		6%-16%
	Preauricular sinus		6%-9%

Table 1. continued from previous page.

Anomalies		Prevalence [1]
Other	Vertebral/rib	16%-60%
	Cervical spine	21%-42%
	Scoliosis	11%-26%
	Cardiac	4%-33%
	Pigmentation	13%-14%
	Limb	3%-21%
	Central nervous system	5%-18%
	Genitourinary	4%-15%
	Pulmonary	1%-15%
	Gastrointestinal	2%-12%

Adapted from Cousley & Calvert [1997]
1. Prevalence rates from more than 20 reports published between 1983 and 2014 are summarized. Studies based on selected samples were omitted to minimize selection bias.

Establishing the Diagnosis of CFM

The diagnosis of CFM can be established based on clinical examination alone.

Differential Diagnosis of CFM

As discussed in Embryology, the clinical features observed in individuals with CFM can also be associated with syndromes, developmental anomaly associations, and sequences. In this review, the diagnosis of CFM is only considered for those individuals who do not have features unique to these other conditions. Unlike CFM, individuals with the diagnoses listed below (in alphabetical order) typically have symmetric facial malformations. The similarities among the conditions are also illustrated in Table 2.

Auriculocondylar syndrome (OMIM 602483) is typically an autosomal dominant condition with variable mandibular hypoplasia frequently with temporomandibular joint ankylosis, cleft palate, and distinctive question mark appearance of the ears due to separation of the lobule from the external ear. Although findings are typically bilateral and symmetric, the occasional presence of preauricular tags and mandibular hypoplasia can overlap with CFM. Additional features include hearing loss, prominent cheeks, and microstomia. Heterozygous pathogenic variants have been noted in two genes in the endothelin receptor pathway, *PLCB4* and *GNAI3* [Rieder et al 2012].

Bixler syndrome (hypertelorism-microtia-clefting) (OMIM 239800) is a rare condition with presumed autosomal recessive inheritance based on recurrences in sibs and parental consanguinity. Clinical features include: hypertelorism, cleft lip and palate, broad nasal tip, and microtia. Etiology is not known [Amiel et al 2001].

Branchiootorenal (BOR) syndrome is characterized by malformations of the outer, middle, and inner ear associated with conductive, sensorineural, or mixed hearing impairment, branchial fistulae and cysts, and renal malformations. The diagnosis is based on clinical findings. A heterozygous pathogenic variant in any one of three genes is known to cause BOR: *EYA1* (locus name: BOR1) (approximately 40% of affected individuals), *SIX5* (locus name: BOR2) in 5%, and *SIX1* in 4%. Inheritance is autosomal dominant.

CHARGE syndrome is a mnemonic for *c*oloboma, *h*eart defects, choanal *a*tresia, *r*etarded growth and development, *g*enital abnormalities, and *e*ar anomalies. CHARGE syndrome typically involves unilateral or bilateral coloboma of the iris, retina-choroid, and/or disc, with or without microphthalmos; unilateral or bilateral choanal atresia or stenosis; cranial nerve dysfunction; abnormal ears (including abnormal external ear shape, middle ear anatomy, and inner ear findings including Mondini defect of the cochlea, and absent or hypoplastic semicircular canals); cryptorchidism in males and hypogonadotropic hypogonadism in males and females; developmental delay; cardiovascular malformation; and growth deficiency. Orofacial clefts and tracheoesophageal fistula are seen in a subset of individuals. A heterozygous pathogenic variant in *CHD7* is identified in 65%-70% of individuals with CHARGE syndrome. For those with a *CHD7* pathogenic variant, inheritance is autosomal dominant.

Hemifacial myohyperplasia sequence (OMIM 606773) is a rare craniofacial condition characterized by unilateral hypertrophy of the facial muscles and ipsilateral hypoplasia of the facial bones of unknown cause. The facial asymmetry is progressive after birth [Pereira-Perdomo et al 2010].

Mandibulofacial dysostosis with microcephaly is characterized by malar and mandibular hypoplasia; congenital- or postnatal-onset microcephaly; malformations of the outer ear, auditory canal, and/or middle ear (ossicles and semi-circular canals) with hearing loss; and facial features that include: prominent glabella, broad nasal bridge, bulbous nasal tip, and everted lower lip. Individuals may also have cleft palate, choanal atresia, and facial asymmetry. Intellectual disability is a prominent feature. Extracranial malformations include: esophageal atresia, congenital heart disease, and thumb abnormalities. Presence of a heterozygous pathogenic variant in *EFTUD2* is causative. Inheritance is autosomal dominant [Lines et al 2012, Lehalle et al 2014]. In one patient with a *de novo* heterozygous pathogenic variant in *EFTUD2*, clinical features included a unilateral epibulbar dermoid similar to findings seen in CFM [Luquetti et al 2013].

Miller syndrome (postaxial acrofacial dysostosis) (OMIM 263750) is characterized by postaxial limb deficiency (hypoplasia, syndactyly, absence of postaxial digits [the 5th digits and in some cases the 4^{th} and 3rd digits], and ulnar hypoplasia that causes shortening of the forearms) and distinctive facial features (malar hypoplasia, micrognathia, cleft palate, rarely cleft lip, small "cup-shaped" ears, and colobomas and/or ectropion [drooping] of the lower eyelids). Miller syndrome is rare. Biallelic pathogenic variants in *DHODH* are causative. Inheritance is autosomal recessive [Chrzanowska & Fryns 1993].

Nager syndrome (preaxial acrofacial dysostosis) (OMIM 154400) is characterized by preaxial limb anomalies (hypoplasia or absence of radius, hypoplasia/absence of the thumbs, triphalangeal thumbs, radioulnar synostosis) and facial anomalies (malar hypoplasia with downward slanting palpebral fissures, lower eyelid coloboma, severe micrognathia). Nager syndrome is rare, most cases are simplex (i.e., a single occurrence in a family); however, families with autosomal dominant and autosomal recessive inheritance have been reported [Hecht et al 1987, Bonthron et al 1993]. Heterozygous pathogenic variants in *SF3B4* have been reported in 58%-64% of individuals with clinical features of Nager syndrome [Bernier et al 2012, Czeschik et al 2013, Petit et al 2014].

Oculoauriculofrontonasal syndrome (OAFNS) (OMIM 601452) is a rare craniofacial condition with features of both frontonasal dysplasia and oculo-auriculo-vertebral spectrum [Gabbett et al 2008]. Characteristic findings include: ocular hypertelorism, notched or bifid nasal tip, microtia, ear and facial skin tags, eyelid colobomas, epibulbar dermoids, mandibular hypoplasia, and facial asymmetry. Extracranial findings are similar to those noted in individuals with CFM and include: cardiac (44%), renal (23%), and vertebral segmentation (37%). Cranial CT imaging showed distinctive nasal ossification in five of seven individuals studied [Evans et al 2013]. Most cases are simplex (i.e., a single occurrence in a family) and genetic cause is not known.

Parry Romberg syndrome (progressive hemifacial atrophy) (OMIM 141300) is characterized by slowly progressive unilateral atrophy of the skin and soft tissues of the face [Grippaudo et al 2004]. It is more common

in females than in males. Initial facial changes usually involve the tissues above the maxilla or near the nasolabial fold and later progress to involve the areas around the eye, lower face, and neck. The tongue and gums may also atrophy. The skin overlying affected areas may become darkly pigmented. Neurologic abnormalities include seizures and trigeminal neuralgia. In Parry-Romberg syndrome atrophy typically begins between ages five and 15 years, whereas in CFM the facial malformations are congenital (i.e., present at birth).

Townes-Brocks syndrome (TBS) is characterized by a triad of clinical findings: imperforate anus, dysplastic ears (overfolded superior helices andpreauricular tags) frequently associated with sensorineural and/or conductive hearing impairment, and thumb malformations (triphalangeal thumbs, duplication of the thumb, and rarely hypoplasia of the thumbs). Associated findings include: renal impairment, including end-stage renal disease, may occur with or without structural abnormalities (mild malrotation, ectopia, horseshoe kidney, renal hypoplasia, polycystic kidneys, vesicoureteral reflux), congenital heart disease, foot malformations, and genitourinary malformations. Intellectual disability occurs in approximately 10% of individuals. Most individuals with CFM do not have thumb and/or anal malformations; however, the overlap of the ear, renal, and cardiac findings in CFM and TBS is significant. Presence of a heterozygous pathogenic variant in *SALL1* is causative. Inheritance is autosomal dominant.

At least three individuals with predominant features of CFM had mutation of *SALL1* [Kohlhase et al 1999, Keegan et al 2001, Kosaki et al 2007]; however, each also had anterior displacement of the anus and/or preaxial polydactyly.

Treacher Collins syndrome (TCS) is characterized by malar (zygoma) and mandibular hypoplasia, external ear abnormalities (microtia), coloboma of the lower eyelid with deficient eyelashes, and a distribution of the scalp hair in the preauricular region (i.e., sideburn). An estimated 40%-50% of individuals with TCS have conductive hearing loss resulting from abnormalities/hypoplasia of middle ear structures. Extracranial malformations are rare and intellect is typically normal. Mutation in one of three genes – *TCOF1* (78%-93%); *POLR1C* and *POLR1D* (8%) – is causative. Inheritance is most often autosomal dominant (*TCOF1* and *POLR1D*) with rare reports of autosomal recessive inheritance as a result of biallelic pathogenic variants in *POLR1C* or *POLR1D* [Schaefer et al 2014].

Of note, one individual with a diagnosis of oculo-auriculo-vertebral spectrum (unilateral microtia, aural atresia, and unilateral mandibular hypoplasia with an absent zygomatic arch) had a *TCOF1* missense variant (1084G>A) resulting in the substitution Ala362Thr [Su et al 2007].

In another study, two individuals diagnosed with Goldenhar syndrome had silent (Glu621Glu; Gln54Gln) *TCOF1* sequence variants not noted in 150 controls [Splendore et al 2002].

Table 2. Comparison of Phenotypic Characteristics Among Conditions in the Differential Diagnosis of CFM

Condition	Gene(s)	Phenotypic Characteristics						
		Maxillary &/or mandibular hypoplasia	Facial asymmetry	Microtia	Facial / ear tags	Vertebral segmentation anomalies	Cardiac anomalies	Renal anomalies
Auriculocondylar syndrome [1]	*PLCB4, GNAI3*	X	X	X				
Axial mesodermal dysplasia complex [2]	Unknown	X	X	X	X	X	X	X
Bixler (hypertelorism -microtia-clefting) syndrome [3]	Unknown			X				

Table 2. continued from previous page.

Condition	Gene(s)	Phenotypic Characteristics						
		Maxillary &/or mandibular hypoplasia	Facial asymmetry	Microtia	Facial / ear tags	Vertebral segmentation anomalies	Cardiac anomalies	Renal anomalies
Branchiootorenal spectrum disorders	*EYA1, SIX1, SIX5*	X	X	X	X			X
Cat-eye syndrome [4]	Chromosome 22 marker	X	X	X	X	X	X	X
CHARGE syndrome	*CHD7*	X	X	X			X	X
Hemifacial myohyperplasia [5]	Unknown	X	X					
Mandibulofacial dysostosis with microcephaly [6]	*EFTUD2*	X	X	X	X	X	X	
Miller syndrome [7]	*DHODH*	X		X				
Nager syndrome [8]	*SF3B4*	X		X	X		X	X
Parry Romberg syndrome [9]	Unknown	X	X					
Townes-Brocks syndrome	*SALL1* (*SALL4*)	X	X	X	X	X	X	X
Treacher Collins syndrome	*TCOF1, POLR1C, POLR1D*	X		X				
VACTERL association [10]	Unknown					X	X	X

X indicates presence of phenotypic characteristic.

1. Rieder et al [2012], Gordon et al [2013]
2. Bergmann et al [2003]
3. Amiel et al [2001]
4. Quintero-Rivera & Martinez-Agosto [2013]
5. Pereira-Perdomo et al [2010]
6. Voigt et al [2013]
7. Vigneron et al [1991]
8. Czeschik et al [2013]
9. El-Kehdy et al [2012]
10. Solomon [2011]

Prevalence of CFM

CFM has an estimated prevalence of between 1:5600 and 1:26,550 live births – possibly an underestimate because of varying criteria used to define the disorder and underdiagnosis of milder cases.

The male to female ratio is 3:2 [Gorlin et al 2001].

Causes of CFM

The causes of craniofacial microsomia (CFM) can be divided into environmental, heritable, multifactorial, and unknown (the largest category).

Environmental (Acquired) Causes

Several studies have assessed the maternal environmental risk factors that may be associated with CFM in offspring. Because each study used different inclusion criteria, the authors have summarized the patient characteristics for each study in Table 3.

Table3. Minimal Diagnostic Criteria Used in Select Studies Assessing Risk Factors for CFM

Study	Minimal Inclusion Criteria for Participants
Grabb [1965], Rollnick & Kaye [1983], Lawson et al [2002], Wieczorek et al [2007]	Microtia
Taysi et al [1983]	Skin tags and a family history of features of hemifacial microsomia
Rollnick [1988]	Microtia and/or preauricular tags
Kaye et al [1992]	Microtia and mandibular hypoplasia
Araneta et al [1997]	(1) Microtia, anotia, or preauricular tags AND (2) hypoplasia of the mandible or select physical features of Goldenhar syndrome
Maris et al [1999]	Hemifacial microsomia, followed at a dental clinic affiliated with a craniofacial center
Kelberman et al [2001]	Skin tags and a family history of features of hemifacial microsomia
Wang et al [2002]	Any ear anomaly or at least 2 features of oculoauricular-vertebral spectrum
Werler et al [2004a]	Hemifacial microsomia, facial asymmetry, Goldenhar syndrome, oculoauricular-vertebral syndrome as diagnosed by a craniofacial geneticist or surgeon
Werler et al [2004b]	Hemifacial microsomia, facial asymmetry, Goldenhar syndrome, or unilateral anotia/microtia as diagnosed by a craniofacial geneticist or surgeon
Tasse et al [2005], Tasse et al [2007]	Microtia or hemifacial microsomia with preauricular tags
Van Bennekom et al [2013]	Microtia
Barisic et al [2014]	ICD9/BPA, ICD10/BPA and OMIM codes assigned to OAVS, Goldenhar syndrome, and hemifacial microsomia

Reported risk factors include:

- Maternal use of vasoactive drugs
- Maternal second trimester bleeding
- Maternal diabetes mellitus
- Multiple gestation
- Maternal use of assisted reproductive technology (ART)

Use of the vasoactive drugs pseudoephedrine, aspirin, or ibuprofen during pregnancy has been associated with a 1.5- to 2-fold increase in the risk for CFM [Werler et al 2004a]. However, a subsequent study of the National Birth Defects Prevention Study on nonsyndromic microtia found no association for any vasoactive mediations or smoking; either in isolated microtia or microtia associated with other birth defects [Van Bennekom et al 2013].

In general, greater concordance in monozygotic (MZ) twins compared to dizygotic (DZ) twins supports the influence of genetic factors. Conversely, the high levels of discordance for CFM in MZ twins argues in favor of the role of environmental factors [Grabb 1965, Burck 1983, Araneta et al 1997, Gorlin et al 2001, Lawson et al 2002, Wang et al 2002].

In an epidemiologic study of 239 individuals with CFM and 854 controls, risk factors identified for CFM included the following [Werler et al 2004b]:

- **Lower birth weight.** 29% of babies with CFM weighed less than 2500 g compared to 5% of the control group. The risk for CFM to infants with a birth weight below 3000 g was two to six times the risk to infants with a birth weight between 3000 and 3499 g. This was confirmed in a population-based study in Europe with 355 cases for which 21% of males and 37% of females weighed less than 2500 g [Barisic et al 2014].
- **Lower family income.** The average family income was lower in the case group compared with controls. For infants with a family income below $25K, the risk for CFM was twofold that of controls.
- **Very low maternal body-mass index** (BMI) (defined as weight in kg/height in meters squared). The risk for CFM was twofold greater for infants born to mothers with a BMI lower than 18 than women with a BMI between 19 and 23.9.
- **Native American or Hispanic race/ethnicity** [Werler et al 2004b]. This ethnic heterogeneity is consistent with that also reported for isolated microtia [Harris et al 1996, Lopez-Camelo & Orioli 1996, Shaw et al 2004].

Maternal ingestion of Accutane® during the first trimester of pregnancy can result in malformations associated with abnormal migration of neural crest cells, some of which overlap with those of CFM, including: microtia/anotia, mandibular hypoplasia, cleft palate, and cardiac defects (conotruncal and aortic arch). Additional findings include: central nervous system malformations, retinal or optic-nerve abnormalities, and thymus hypoplasia [Lammer 1991].

Maternal ingestion of the immunosuppressive medication mycophenolate mofetil during pregnancy can also lead to malformations (microtia, cleft lip/palate, micrognathia, cardiac malformations) that overlap with CFM. Additional findings distinct from CFM observed in infants exposed in utero to mycophenolate mofetil include hypoplastic fingers and toenails, diaphragmatic hernia, and tracheoesophageal fistula [Koren 2008, Parisi et al 2009].

Heritable Causes

Chromosomal Causes

Craniofacial microsomia has been observed in a number of chromosome disorders (Table 4).

- Some associations could have occurred by chance, but the repeated observation of deletion 5p, duplication 14q23.1, and abnormalities of chromosomes 18 and 22 may represent causal associations.
- Of note, several families with autosomal dominant inheritance of CFM have shown segregation of chromosome 14q23.1 duplication inclusive of the gene *OTX2* [Ballesta-Martínez et al 2013, Zielinski et al 2014].
- Chromosome imbalances (duplications and deletions) were detected by oligonucleotide array-CGH in 14% of 86 individuals with CFM using the minimal diagnostic criteria proposed by Tasse et al [2005] and Rooryck et al [2010].

Table 4. Chromosomal Abnormalities Reported in CFM

Chromosome	Abnormality	Reference
5	del(5p)	Dyggve & Mikkelsen [1965], Ladekarl [1968], Neu et al [1982], Choong et al [2003], Ala-Mello et al [2008]
	del(5q13.2)	Huang et al [2010b]
	t(5;8)(p15.31;p23.1)	Josifova et al [2004]

Table 4. continued from previous page.

Chromosome	Abnormality	Reference
7	Trisomy (mosaic)	Hodes et al [1981]
	dup(7q)	Hoo et al [1982]
9	Trisomy (mosaic)	Wilson & Barr [1983]
	Pericentric inversion	Stanojević et al [2000]
14	dup(14q23.1)	Ballesta-Martínez et al [2013], Zielinski et al [2014]
	inv(14)(p11.2q22.3)	Northup et al [2010]
18	del(18)	Curran et al [1970], Buffoni et al [1976]
	Trisomy	Bersu & Ramirez-Castro [1977], Greenberg [1987], Verloes et al [1991]
	Trisomy (mosaicism)	Clarren & Salk [1983]
	Recombinant chromosome	Sujansky & Smith [1981]
21	Ring chromosome	Greenberg [1987]
22	del(22q)	McGinn [personal communication], Herman et al [1988], Derbent et al [2003], Digilio et al [2009], Tan et al [2011], Torti et al [2013]
	dup(22q)	Hathout et al [1998], Quintero-Rivera and Martinez-Agosto [2013]
	Trisomy	Kobrynski et al [1993]
Other	47, XXY	Poonawalla et al [1980], Garavelli et al [1999]
	47, XXX	Aouchiche et al [1972]
	49, XXXXX	Schroeter et al [1980]
	49, XXXXY	Kushnick & Colondrillo [1975]

Single-Gene Causes

Approximately 1%-2% of families demonstrate autosomal dominant inheritance and rare families demonstrate autosomal recessive inheritance of CFM or isolated microtia [Burck 1983, Schmid et al 1985, Kaye et al 1992, Bestelmeyer et al 1996, Llano-Rivas et al 1999, Tasse et al 2005, Tasse et al 2007, Vendramini-Pittoli & Kokitsu-Nakata 2009, Farra et al 2011, Barisic et al 2014]. Table 5 compares oculo-auriculo-vertebral spectrum findings in families with autosomal dominant inheritance with findings in simplex cases (i.e., a single occurrence in a family) [Tasse et al 2007].

Table 5. Oculo-Auriculo-Vertebral Spectrum Findings in Families with Autosomal Dominant Inheritance vs Findings in Simplex Cases

Finding	Familial	Simplex [1]
Bilateral facial involvement	71%	46%
Hearing loss	26%	87%
Aural atresia	41%	79%

Tasse et al [2007]
1. Simplex= a single occurrence in a family

To date, the largest segregation analysis included clinical examination of 311 members of the families of 74 probands with CFM. The study provided evidence for genetic transmission, and more specifically, an autosomal dominant mode of inheritance with reduced penetrance [Taysi et al 1983, Kaye et al 1992].

To the authors' knowledge, two linkage studies have been performed in families with features of CFM [Kelberman et al 2001, Huang et al 2010a].

- In one family studied by Kelberman et al [2001], data suggested linkage to a region on chromosome 14q32, which harbors *Goosecoid* [Rivera-Pérez et al 1995, Yamada et al 1995], a gene expressed in the branchial arches during embryogenesis [Gaunt et al 1993]. Disruption of *Goosecoid* in mouse models results in craniofacial abnormalities associated with features of CFM [Rivera-Pérez et al 1995, Yamada et al 1995].
- Linkage to this region was excluded in two additional families with autosomal dominant pattern of inheritance, providing further evidence of genetic heterogeneity [Kelberman et al 2001].

Recently, a study reported on a *HOXA2* nonsense pathogenic variant (c.703C>T) in a three-generation family of European ancestry with bilateral nonsyndromic microtia and mixed hearing loss segregating as an autosomal dominant trait [Brown et al 2013]. Individuals from this family presented with middle ear abnormalities of the ossicular chain; the external auditory canals of all affected individuals had normal anatomy.

A missense variant in *HOXA2* had been previously associated with autosomal recessive bilateral microtia in a consanguineous Iranian family. Although the external and middle ear features of both families were similar, affected individuals in the Iranian family had more severe microtia and abnormalities of the ear canal, profound mixed hearing impairment, and partial cleft palate [Alasti et al 2008]. The more severe phenotype in this family is probably secondary to the presence of the pathogenic variant in both alleles.

As discussed in Differential Diagnosis, mutation of *TCOF1,* (Treacher Collins syndrome) *EFTUD2* (mandibulofacial dysostosis with microcephaly), and *SALL1* (Townes-Brocks syndrome) has also been identified in individuals with features that overlap with CFM.

Multifactorial Inheritance

Although most cases of CFM appear to be simplex (i.e., a single occurrence in a family), multifactorial inheritance is suggested by the following:

- Increased recurrence risk observed in families with an affected relative. The recurrence rate in first-degree relatives of affected individuals is estimated at 2%-3%. This may be an underestimate due to the difficulty of obtaining an accurate family history for some of the subtle features of CFM, such as preauricular tags [Rollnick & Kaye 1983, Rollnick et al 1987, Rollnick 1988].
- An increased prevalence of twinning [Lawson et al 2002] and use of maternal ART in individuals with CFM [Wieczorek et al 2007]
- Increased concordance in MZ twins. In general, greater concordance in MZ twins compared to DZ twins supports the influence of genetic factors. Conversely, the high levels of discordance in MZ twins observed in CFM argues in favor of the role for environmental factors [Grabb 1965, Araneta et al 1997, Gorlin et al 2001, Lawson et al 2002, Wang et al 2002].
- Increased relative risk with specific maternal exposures. See Environmental (Acquired) Causes.

Unknown Cause

Whereas some individuals have subtle facial asymmetry with a small skin tag in front of an otherwise normal-appearing ear, others have bilateral involvement (typically asymmetric), microtia/anotia with atresia of the ear canals, microphthalmia, and possibly respiratory compromise from severe mandibular hypoplasia.

Possible explanations for those with CFM of unknown cause include:

- Mutation of a yet-to-be-identified gene or regulatory region of gene

- Pathogenic variants or benign variants in multiple genes involved in craniofacial development (polygenic inheritance)
- Effects of both gene and environmental interactions (multifactorial inheritance)

Evaluation Strategy

A diagnosis of CFM should be considered in individuals with variable combinations of facial asymmetry, mandibular hypoplasia, preauricular tags, microtia, epibulbar dermoids, and/or upper-eyelid coloboma.

Once a diagnosis of CFM has been considered, the following approach can be used to exclude other conditions and to assist with discussions of prognosis and recurrence risk counseling.

The following information should be obtained from pregnancy and family history, physical examination, hearing and ophthalmologic evaluation, imaging studies, and genetic testing.

Pregnancy history. A history of maternal diabetes mellitus, second trimester bleeding, multiple gestation, assisted reproductive technology (ART), or exposure to teratogenic agents such as: vasoactive drugs or retinoic acid (Accutane®), and mycophenolate mofetil should be obtained.

Family history. A three-generation family history with attention to other relatives with facial asymmetry, ear tags, ear pits, hearing loss, anal atresia, cardiac malformations, and/or thumb abnormalities should be pursued.

Physical examination. A complete physical examination should be performed by a medical geneticist or physician who specializes in craniofacial disorders.

- Facial asymmetry should be noted as well as severity of mandibular hypoplasia.
- Ear findings should be noted, including presence of ear pits and/or tags and patency of the external auditory canal.
- Eyes should be examined for upper- and lower-eyelid colobomata and epibulbar dermoids. Ophthalmologic consultant should evaluate for chorioretinal colobomas (seen in CHARGE syndrome).
- The neck should be inspected for branchial sinuses or cysts and torticollis or impaired mobility.
- The heart; spine, and limbs should be evaluated.

Testing

- Audiologic diagnostic testing (ear-specific and frequency-specific) in all individuals
- Additional imaging studies. X-rays of the cervical spine, echocardiogram, and renal ultrasound examination
- CT scan of the temporal bone (commonly after age five years). Those with significant hearing impairment, aural atresia, and/or features of CHARGE syndrome. If temporal bone CT findings are consistent with CHARGE syndrome, testing for CHD7 is recommended.
- Consideration of array comparative genomic hybridization, particularly if there are atypical extracranial malformations, delays in development, or possible autosomal dominant inheritance (which can be caused by chromosome 14q23.1 duplication).

Molecular genetic testing. No specific molecular genetic testing is indicated for individuals with features characteristic of CFM.

One approach is **single-gene testing**. Molecular genetic testing should be considered for those whose clinical findings overlap with the following disorders:

- Branchiootorenal (BOR) syndrome (*EYA1*)
- CHARGE syndrome (*CHD7*)
- Mandibulofacial dysostosis with microcephaly (*EFTUD2*)

- Townes-Brocks syndrome (*SALL1*)
- Treacher Collins syndrome (*TCOF1*)

Alternative approaches include:

- Use of a **multigene panel** that includes the five genes and other genes of interest (see Differential Diagnosis). Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene 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.

- **Comprehensive genomic testing** such as exome sequencing, which has been shown to be effective in defining the genetic basis of CFM [Luquetti et al 2013]. For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

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.

Mode of Inheritance

Craniofacial microsomia (CFM) most frequently occurs as a simplex case (i.e., occurrence in a single individual in a family) with unknown etiology; recurrence risks are empiric.

If an individual with CFM has an inherited or *de novo* chromosome abnormality, genetic counseling for that condition is indicated.

Occasional autosomal dominant or autosomal recessive inheritance is observed.

Empiric Risks to Family Members

Sibs of a proband. If a proband has CFM and no reported family history of CFM, the risk to sibs is 2% to 3%. This may be an underestimate because of the difficulty of obtaining an accurate family history for some of the subtle features of CFM, such as preauricular tags [Rollnick & Kaye 1983, Rollnick et al 1987, Rollnick 1988].

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected.

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

Prenatal diagnosis of simplex cases has been reported rarely, and typically in those with severe (unilateral microphthalmia) or multiple malformations [Martinelli et al 2004, Hattori et al 2005, Castori et al 2006].

Molecular genetic testing. Because the gene(s) in which pathogenic variant(s) are responsible for craniofacial microsomia have not been identified, prenatal diagnosis using molecular genetic testing is not possible.

Fetal ultrasound examination. Recurrences in families are infrequent, and no reports in the literature have evaluated the ability of fetal imaging (2D or 3D ultrasound or MRI) to detect microtia, preauricular tags, and/or asymmetric mandibular hypoplasia. Prenatal ultrasound examination can be used to detect other craniofacial malformation syndromes, such as Treacher Collins syndrome [Rotten et al 2002]. In a European population-based study of oculo-auriculo-vertebral spectrum, prenatal anomalies were detected in 18.9% of pregnancies; however, the diagnosis of oculo-auriculo-vertebral spectrum was not established until delivery or later [Barisic et al 2014].

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.

- **Foundation for Faces of Children**
  258 Harvard Street
  #367
  Brookline MA 02446-2904
  Phone: 617-355-8299
  Email: info@facesofchildren.org
  Hemifacial Microsomia (HFM)

- **American Society for Deaf Children (ASDC)**
  800 Florida Avenue Northeast
  Suite 2047
  Washington DC 20002-3695
  Phone: 800-942-2732 (Toll-free Parent Hotline); 866-895-4206 (toll free voice/TTY)
  Fax: 410-795-0965
  Email: info@deafchildren.org; asdc@deafchildren.org
  www.deafchildren.org

- **AmeriFace: The Cleft/Craniofacial Advocates**
  PO Box 751112
  Las Vegas NV 89136
  Phone: 888-486-1209 (toll-free 24 hours); 702-769-9264
  Fax: 702-341-5351
  Email: info@ameriface.org
  www.ameriface.org

- **Children's Craniofacial Association (CCA)**

13140 Coit Road
Suite 517
Dallas TX 75240
Phone: 800-535-3643 (toll-free)
Email: contactCCA@ccakids.com
www.ccakids.org

- **Face Equality International**
  United Kingdom
  Email: info@faceequalityinternational.org
  www.faceequalityinternational.org
- **FACES: The National Craniofacial Association**
  PO Box 11082
  Chattanooga TN 37401
  Phone: 800-332-2373 (toll-free)
  Email: faces@faces-cranio.org
  Goldenhar Syndrome
- **National Association of the Deaf (NAD)**
  8630 Fenton Street
  Suite 820
  Silver Spring MD 20910
  Phone: 301-587-1788; 301-587-1789 (TTY)
  Fax: 301-587-1791
  Email: nad.info@nad.org
  www.nad.org

Management

Evaluations Following Initial Diagnosis

To establish the extent of involvement in an individual diagnosed with craniofacial microsomia (CFM), the authors recommend the following evaluations.

Upper airway obstruction. Evaluate all individuals with CFM for clinical findings of upper-airway obstruction with physical examination to assess for tachypnea, stridor, stertor, glossoptosis (e.g., tongue-based upper airway obstruction) increased work of breathing with visible retractions, and/or episodic upper-airway obstruction with apnea.

Children with findings of upper-airway obstruction should be referred to a craniofacial center and/or otolaryngologist.

For those without obvious findings of upper-airway obstruction, a sleep history should be obtained from caretakers to screen for airway obstruction during sleep, and a sleep study and/or sleep medicine consultation should be pursued in those with concerning reports.

Clinical feeding and nutrition evaluation. Assess the nutritional status of the infant/child as part of the general physical examination with weight and height plotted on standard growth charts.

If the child demonstrates both normal parameters for age and normal rate of growth, no further studies are needed.

If the child's rate of growth and/or current measurements is below the fifth percentile, consultation with a clinical dietitian/nutritionist should be considered. Caretakers should be queried regarding feeding history with particular attention to inadequate suction with breast/bottle feeding, nasal regurgitation, coughing or choking during meals, or recurrent pneumonia. If any of these findings are reported, evaluation by a clinical feeding specialist (often occupational therapist or speech pathologist) and/or videofluoroscopic swallowing study is indicated.

Hearing evaluation. An ear-specific diagnostic hearing evaluation (with either brain stem auditory evoked response or otoacoustic air emissions) in the first two months of life is recommended (see Deafness and Hereditary Hearing Loss). Timing of subsequent hearing evaluations should be determined by the patient's results and medical history.

Cervical spine films. Perform screening cervical spine imaging at age three years, or earlier if there are concerns (e.g., torticollis). If there are abnormalities on the radiographs, referral to an orthopedist is indicated.

Children should be screened for scoliosis at diagnosis and yearly thereafter with annual physical examination. Radiographs should be obtained for children with evidence of scoliosis.

Echocardiogram. If there are concerns based on history or physical examination, obtain an echocardiogram.

Renal ultrasound examination. A screening renal ultrasound examination should be obtained at the time of diagnosis.

Treatment of Manifestations

For optimal outcome children with CFM require timely and coordinated assessments and interventions. Ideally, children should be managed by an experienced multidisciplinary craniofacial team that includes the following (in alphabetical order):

- Audiologist
- Dietitian
- Clinical geneticist and genetic counselor
- Nurse coordinator
- Ophthalmologist
- Oral and maxillofacial surgeon
- Orthodontist
- Orthopedist
- Otolaryngologist
- Pediatric dentist
- Pediatrician
- Plastic and reconstructive surgeon
- Psychosocial professionals (psychologist, social worker)
- Speech pathologist

The goals of treatment for CFM are to assure adequate respiratory support and nutritional status, maximize hearing and communication, optimize development, improve facial symmetry, and treat dental malocclusion. Treatment is age dependent, with time-sensitive interventions at appropriate stages of craniofacial growth and development. Treatment plans should be individually tailored to ensure the best results.

The phenotype in CFM is quite variable (see Table 1 for associated anomalies). Details of common surgical interventions have been reviewed elsewhere [Birgfeld & Heike 2012]. The following medical issues may need to be addressed in an individual with CFM:

Feeding. Infants with significant micrognathia, macrostomia, or a cleft palate may have difficulty with feeding and may require specialized bottles designed for infants with cleft palate and/or dysphagia (e.g., Habermann feeder, Mead-Johnson Squeeze bottle, Pigeon nipple, Dr. Brown nipples), supplemental nasogastric (NG) feedings, and gastrostomy tube placement. Consultation with an infant feeding specialist and/or dietitian should be considered.

Respiratory

- Infants with severe mandibular hypoplasia may have significant upper-airway compromise and require tracheostomy placement and/or early mandibular advancement. Referral to a craniofacial center or otolaryngologist is recommended.
- Those children with moderate mandibular hypoplasia may develop obstructive sleep apnea and require either medical (CPAP) or surgical (tonsillectomy and adenoidectomy or mandibular surgery) intervention.

Face. Surgical repair is often recommended for facial tags and macrostomia within the first year. Surgery for palatal clefts typically occurs within the first year although this may be deferred for children with respiratory compromise.

Jaw and teeth

- Good oral hygiene is especially important for children with CFM. Children should have consistent primary preventative dental care.
- Orthodontic evaluations are important to assess for missing teeth, dental crowding, jaw growth, and dental malocclusion. Some children may need one or more dental appliances or braces to optimize facial growth, dental appearance, and function.
- Children with mandibular hypoplasia may require a bone graft and/or mandibular distraction osteogenesis to lengthen the mandible and/or create a functional TMJ. In a child without airway compromise, these options may be considered when the child is between ages five and seven years.
- The use of functional dental appliances to try and influence facial growth, vertical alveolar growth, and dental eruption in the younger patient may be considered, depending on the patient. When facial and jaw growth is nearly complete (age 13 to 16 years), most children with CFM require orthodontics, and many benefit from a final orthognathic surgery to create skeletal symmetry.

Hearing

- All infants with CFM should have a diagnostic hearing evaluation (brain stem auditory evoked response [BAER]) within the first six months of life (regardless of whether the child passed the newborn hearing screen). Timing and type of additional testing depend on results from this initial evaluation and the child's medical history. Early referral to an otolaryngologist is recommended. Early intervention for infants with hearing loss is important to optimize speech and language outcome.
- Children with hearing impairment should receive guidance regarding recommendations for hearing aids, appropriate academic accommodations, and avoidance of ototoxic medications to prevent further hearing loss.
- Conductive hearing loss, related to aural atresia in which the ossicles may be poorly formed or absent, may be treated with hearing aids. Children with unilateral conductive hearing loss and normal hearing in the contralateral ear are frequently not treated with amplification; however, their speech and language should be monitored closely.
- Prior to planning external ear surgery, the authors recommend obtaining a CT scan to assess the middle- and inner-ear structures to help determine if atresia repair is likely to improve hearing. This surgery typically occurs after age five years. The CT may also reveal cholesteatomas, which occur in a small proportion of children with aural atresia.

- Children with unilateral aural atresia should have serial screening (with hearing evaluations and tympanoscopy) to ensure maximal hearing of the unaffected ear.
- Individuals with eustachian tube dysfunction should continue to have hearing and otologic status monitored, with a low threshold for placing tympanostomy tube(s).

Speech. Children with CFM may have cranial nerve palsies, clefts of the palate, malocclusion, and muscular deficiencies that can contribute to abnormal speech patterns (including velopharyngeal insufficiency). The authors recommend a speech evaluation prior to age two years, and ongoing monitoring by a speech and language pathologist.

Ears. Surgical options for treating ear malformations include auricular reconstruction or creation of a prosthetic ear. Options for management of microtia include the following:

- No action
- Prosthetic management, either adhesive or implant-retained
- Staged surgical reconstruction, using autogenous rib or a synthetic framework

Because adult ear height is achieved by age six to eight years, surgical reconstruction or prosthetic management is often considered after age six years. Ear reconstruction should be coordinated with jaw surgeries for optimal long-term outcomes.

Eyes. Individuals with congenital or acquired epibulbar dermoids (pinkish-white growth on the sclerae) should be referred to the ophthalmologist. Large epibulbar dermoids and those that interfere with vision may require excision.

Cardiac. Children with physical examination findings suggestive of a cardiac anomaly should receive a timely referral to a pediatric cardiologist.

Renal. Individuals with renal anomalies should be referred to a nephrologist.

Skeletal

- Children should undergo screening with four-view cervical spine radiographs (i.e., AP, lateral, flexion, and extension) at age three years when the bones are ossified. Those with anomalies should be referred to an orthopedic surgeon.
- Children should be screened for scoliosis at diagnosis with annual physical examination. The authors recommend obtaining radiographs for children with evidence of scoliosis.

Family and social support. Children with CFM may be at increased risk for psychosocial difficulties [Maris et al 1999]. Social workers can provide support and guidance to children and their families, such as accessing community resources, making decisions about surgery, and adjusting to having facial differences.

Surveillance

Click here (pdf) for an overview of the common medical and surgical management recommendations for children with craniofacial microsomia (Adapted from Birgfeld & Heike [2012], published with permission from *Seminars in Plastic Surgery*).

Agents/Circumstances to Avoid

Individuals with any degree of hearing loss. Avoid exposure to ototoxic drugs.

Individuals with cervical spine anomalies. Follow guidelines outlined by the appropriate subspecialists (which likely include avoiding high-impact contact sports).

Individuals with a single kidney. Follow guidelines outlined by the appropriate subspecialists (which likely include avoiding high-impact contact sports).

For subsequent pregnancies of a woman who has had a child with CFM

- Avoid vasoactive medications (pseudoephedrine, phenylpropanolamine, ibuprofen, and aspirin);
- Manage diabetes mellitus to maintain good control and avoid hyperglycemia.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

References

Literature Cited

Ala-Mello S, Siggberg L, Knuutila S, von Koskull H, Taskinen M, Peippo M. Further evidence for a relationship between the 5p15 chromosome region and the oculoauriculovertebral anomaly. Am J Med Genet A. 2008;146A:2490–4. PubMed PMID: 18792983.

Alasti F, Sadeghi A, Sanati MH, Farhadi M, Stollar E, Somers T, Van Camp G. A mutation in HOXA2 is responsible for autosomal-recessive microtia in an Iranian family. Am J Hum Genet. 2008;82:982–91. PubMed PMID: 18394579.

Amiel J, Faivre L, Marianowskl R, Bonnet D, Couly G, Manach Y, Le Merrer M, Cormier-Daire V, Munnich A, Lyonnet S. Hypertelorism-Microtia-Clefting syndrome (Bixler syndrome): report of two unrelated cases. Clin Dysmorph. 2001;10:15–8. PubMed PMID: 11152141.

Aouchiche M, Boyer R, Nouar A. Caryotype results in Goldenhar's syndrome. Bull Mem Soc Fr Ophtalmol. 1972;85:57–69. PubMed PMID: 4671733.

Araneta MR, Moore CA, Olney RS, Edmonds LD, Karcher JA, McDonough C, Hiliopoulos KM, Schlangen KM, Gray GC. Goldenhar syndrome among infants born in military hospitals to Gulf War veterans. Teratology. 1997;56:244–51. PubMed PMID: 9408975.

Ballesta-Martínez MJ, López-González V, Dulcet LA, Rodríguez-Santiago B, Garcia-Miñaúr S, Guillen-Navarro E. Autosomal dominant oculoauriculovertebral spectrum and 14q23.1 microduplication. Am J Med Genet A. 2013;161A:2030–5. PubMed PMID: 23794319.

Barisic I, Odak L, Loane M, Garne E, Wellesley D, Calzolari E, Dolk H, Addor MC, Arriola L, Bergman J, Bianca S, Doray B, Khoshnood B, Klungsoyr K, McDonnell B, Pierini A, Rankin J, Rissmann A, Rounding C, Queisser-Luft A, Scarano G, Tucker D. Prevalence, prenatal diagnosis and clinical features of oculo-auriculo-vertebral spectrum: a registry-based study in Europe. Eur J Hum Genet. 2014;22:1026–33. PubMed PMID: 24398798.

Bennun RD, Mulliken JB, Kaban LB, Murray JE. Microtia: a microform of hemifacial microsomia. Plast Reconstr Surg. 1985;76:859–65. PubMed PMID: 4070453.

Bergmann C, Zerres K, Peschgens T, Senderek J, Hörnchen H, Rudnik-Schöneborn S. Overlap between VACTERL and hemifacial microsomia illustrating a spectrum of malformations seen in axial mesodermal dysplasia complex (AMDC). Am J Med Genet. 2003;121A:151–5. PubMed PMID: 12910495.

Bernier FP, Caluseriu O, Ng S, Schwartzentruber J, Buckingham KJ, Innes AM, Jabs EW, Innis JW, Schuette JL, Gorski JL, Byers PH, Andelfinger G, Siu V, Lauzon J, Fernandez BA, McMillin M, Scott RH, Racher H; FORGE Canada Consortium. Majewski J, Nickerson DA, Shendure J, Bamshad MJ, Parboosingh JS. Haploinsufficiency of SF3B4, a component of the pre-mRNA spliceosomal complex, causes Nager syndrome. Am J Hum Genet. 2012;90:925–33. PubMed PMID: 22541558.

Bersu ET, Ramirez-Castro JL. Anatomical analysis of the developmental effects of aneuploidy in man--the 18-trisomy syndrome: I. Anomalies of the head and neck. Am J Med Genet. 1977;1:173–93. PubMed PMID: 610429.

Bestelmeyer U, Weerda H, Siegert R, Greiwe M, Schwinger E. Familial occurrence of oculoauricolovertebral dysplasia and Franceschetti syndrome. HNO. 1996;44:452–5. PubMed PMID: 8805011.

Birgfeld CB, Heike C. Craniofacial microsomia. Semin Plast Surg. 2012;26:91–104. PubMed PMID: 23633936.

Bonthron DT, Macgregor DF, Barr DG. Nager acrofacial dysostosis: minor familial manifestations supporting dominant inheritance. Clin Genet. 1993;43:127–31. PubMed PMID: 8500258.

Brown KK, Viana LM, Helwig CC, Artunduaga MA, Quintanilla-Dieck L, Jarrin P, Osorno G, McDonough B, DePalma SR, Eavey RD, Seidman JG, Seidman CE. HOXA2 haploinsufficiency in dominant bilateral microtia and hearing loss. Hum Mutat. 2013;34:1347–51. PubMed PMID: 23775976.

Buffoni L, Tarateta A, Aicardi G, Vianello MG, Bonioli E. Pituitary dwarfism and "Goldenhar type" multiple deformities in a patient with deletion of the short arm of chromosome 18. Minerva Pediatr. 1976;28:716–29. PubMed PMID: 825713.

Burck U. Genetic aspects of hemifacial microsomia. Hum Genet. 1983;64:291–6. PubMed PMID: 6684097.

Castori M, Brancati F, Rinaldi R, Adami L, Mingarelli R, Grammatico P, Dallapiccola B. Antenatal presentation of the oculo-auriculo-vertebral spectrum (OAVS). Am J Med Genet A. 2006;140:1573–9. PubMed PMID: 16761296.

Choong YF, Watts P, Little E, Beck L. Goldenhar and cri-du-chat syndromes: a contiguous gene deletion syndrome? J AAPOS. 2003;7:226–7. PubMed PMID: 12825068.

Chrzanowska K, Fryns JP. Miller postaxial acrofacial dysostosis syndrome. Follow-up data of a family and confirmation of autosomal recessive inheritance. Clin Genet. 1993;43:270. PubMed PMID: 8375109.

Clarren SK, Salk DJ. Chromosome studies in hemifacial microsomia with radial ray defect. Am J Med Genet. 1983;15:169–70. PubMed PMID: 6859119.

Cohen MM Jr, Rollnick BR, Kaye CI. Oculoauriculovertebral spectrum: an updated critique. Cleft Palate J. 1989;26:276–86. PubMed PMID: 2680167.

Cousley RR. A comparison of two classification systems for hemifacial microsomia. Br J Oral Maxillofac Surg. 1993;31:78–82. PubMed PMID: 8471584.

Cousley RR, Calvert ML. Current concepts in the understanding and management of hemifacial microsomia. Br J Plast Surg. 1997;50:536–51. PubMed PMID: 9422952.

Cousley RR, Wilson DJ. Hemifacial microsomia: developmental consequence of perturbation of the auriculofacial cartilage model? Am J Med Genet. 1992;42:461–6. PubMed PMID: 1609829.

Curran JP, al-Salihi FL, Allderdice PW. Partial deletion of the long arm of Chromosome E-18. Pediatrics. 1970;46:721–9. PubMed PMID: 5481073.

Czeschik JC, Voigt C, Alanay Y, Albrecht B, Avci S, Fitzpatrick D, Goudie DR, Hehr U, Hoogeboom AJ, Kayserili H, Simsek-Kiper PO, Klein-Hitpass L, Kuechler A, López-González V, Martin M, Rahmann S, Schweiger B, Splitt M, Wollnik B, Lüdecke HJ, Zeschnigk M, Wieczorek D. Clinical and mutation data in 12 patients with the clinical diagnosis of Nager syndrome. Hum Genet. 2013;132:885–98. PubMed PMID: 23568615.

David DJ, Mahatumarat C, Cooter RD. Hemifacial microsomia: a multisystem classification. Plast Reconstr Surg. 1987;80:525–35. PubMed PMID: 3659162.

Derbent M, Yilmaz Z, Baltaci V, Saygili A, Varan B, Tokel K. Chromosome 22q11.2 deletion and phenotypic features in 30 patients with conotruncal heart defects. Am J Med Genet A. 2003;116A:129–35. PubMed PMID: 12494430.

Digilio MC, McDonald-McGinn DM, Heike C, Catania C, Dallapiccola B, Marino B, Zackai EH. Three patients with oculo-auriculo-vertebral spectrum and microdeletion 22q11.2. Am J Med Genet A. 2009;149A:2860–4. PubMed PMID: 19890921.

Dyggve HV, Mikkelsen M. Partial deletion of the short arms of chormosome of the 4-5 group (Denver). Arch Dis Child. 1965;40:82–5. PubMed PMID: 14259280.

Evans KN, Gruss JS, Khanna PC, Cunningham ML, Cox TC, Hing AV. Oculoauriculofrontonasal syndrome: case series revealing new bony nasal anomalies in an old syndrome. Am J Med Genet A. 2013;161A:1345–53. PubMed PMID: 23637006.

El-Kehdy J, Abbas O, Rubeiz N. A review of Parry-Romberg syndrome. J Am Acad Dermatol. 2012;67:769–84. PubMed PMID: 22405645.

Farra C, Yunis K, Yazbeck N, Majdalani M, Charafeddine L, Wakim R, Awwad J. A Lebanese family with autosomal recessive oculo-auriculo-vertebral (OAV) spectrum and review of the literature: is OAV a genetically heterogeneous disorder? Appl Clin Genet. 2011;4:93–7. PubMed PMID: 23776370.

Gabbett MT, Robertson SP, Broadbent R, Aftimos S, Sachdev R, Nezarati MM. Characterizing the oculoauriculofrontonasal syndrome. Clin Dysmorphol. 2008;17:79–85. PubMed PMID: 18388775.

Garavelli L, Virdis R, Donadio A, Sigorini M, Banchini G, Balestrazzi P, Fryns JP. Oculo-auriculo-vertebral spectrum in Klinefelter syndrome. Genet Couns. 1999;10:321–4. PubMed PMID: 10546106.

Gaunt SJ, Blum M, De Robertis EM. Expression of the mouse goosecoid gene during mid-embryogenesis may mark mesenchymal cell lineages in the developing head, limbs and body wall. Development. 1993;117:769–78. PubMed PMID: 8101169.

Gordon CT, Petit F, Kroisel PM, Jakobsen L, Zechi-Ceide RM, Oufadem M, Bole-Feysot C, Pruvost S, Masson C, Tores F, Hieu T, Nitschké P, Lindholm P, Pellerin P, Guion-Almeida ML, Kokitsu-Nakata NM, Vendramini-Pittoli S, Munnich A, Lyonnet S, Holder-Espinasse M, Amiel J. Mutations in endothelin 1 cause recessive auriculocondylar syndrome and dominant isolated question-mark ears. Am J Hum Genet. 2013;93:1118–25. PubMed PMID: 24268655.

Gorlin RJ, Cohen MM, Hennekam RCM. *Syndromes of the Head and Neck*. 4 ed. Oxford, UK: Oxford University Press; 2001.

Gougoutas AJ, Singh DJ, Low DW, Bartlett SP. Hemifacial microsomia: clinical features and pictographic representations of the OMENS classification system. Plast Reconstr Surg. 2007;120:112e–20e. PubMed PMID: 18090735.

Grabb WC. The first and second branchial arch syndrome. Plast Reconstr Surg. 1965;36:485–508. PubMed PMID: 5320180.

Greenberg F. Chromosome abnormalities associated with facio-auriculo-vertebral dysplasia. Minneapolis, MN: March of Dimes Clinical Genetics Conference: Neural Crest and Craniofacial Disorders. 1987.

Grippaudo C, Deli R, Grippaudo FR, Di Cuia T, Paradisi M. Management of craniofacial development in the Parry-Romberg syndrome: report of two patients. Cleft Palate Craniofac J. 2004;41:95–104. PubMed PMID: 14697063.

Harris J, Källén B, Robert E. The epidemiology of anotia and microtia. J Med Genet. 1996;33:809–13. PubMed PMID: 8933331.

Hartsfield JK. Review of the etiologic heterogeneity of the oculo-auriculo-vertebral spectrum (hemifacial microsomia). Orthod Craniofac Res. 2007;10:121–8. PubMed PMID: 17651128.

Hathout EH, Elmendorf E, Bartley J. Hemifacial microsomia and abnormal chromosome 22. Am J Med Genet. 1998;76:71–3. PubMed PMID: 9508069.

Hattori Y, Tanaka M, Matsumoto T, Uehara K, Ueno K, Miwegishi K, Ishimoto H, Miyakoshi K, Yoshimura Y. Prenatal diagnosis of hemifacial microsomia by magnetic resonance imaging. J Perinat Med. 2005;33:69–71. PubMed PMID: 15841618.

Hecht JT, Immken LL, Harris LF, Malini S, Scott CI Jr. The Nager syndrome. Am J Med Genet. 1987;27:965–9. PubMed PMID: 3321996.

Herman GE, Greenberg F, Ledbetter DH. Multiple congenital anomaly/mental retardation (MCA/MR) syndrome with Goldenhar complex due to a terminal del(22q). Am J Med Genet. 1988;29:909–15. PubMed PMID: 3400736.

Hodes ME, Gleiser S, DeRosa GP, Yune HY, Girod DA, Weaver DD, Palmer CG. Trisomy 7 mosaicism and manifestations of Goldenhar syndrome with unilateral radial hypoplasia. J Craniofac Genet Dev Biol. 1981;1:49–55. PubMed PMID: 7341641.

Hoo JJ, Lorenz R, Fischer A, Fuhrmann W. Tiny interstitial duplication of proximal 7q in association with a maternal paracentric inversion. Hum Genet. 1982;62:113–6. PubMed PMID: 7160842.

Huang XS, Li X, Tan C, Xiao L, Jiang HO, Zhang SF, Wang DM, Zhang JX. Genome-wide scanning reveals complex etiology of oculo-auriculo-vertebral spectrum. Tohoku J Exp Med. 2010a;222:311–8. PubMed PMID: 21150135.

Huang XS, Xiao L, Li X, Xie Y, Jiang HO, Tan C, Wang L, Zhang JX. Two neighboring microdeletions of 5q13.2 in a child with oculo-auriculo-vertebral spectrum. Eur J Med Genet. 2010b;53:153–8. PubMed PMID: 20346424.

Josifova DJ, Patton MA, Marks K. Oculoauriculovertebral spectrum phenotype caused by an unbalanced t(5;8)(p15.31;p23.1) rearrangement. Clin Dysmorphol. 2004;13:151–3. PubMed PMID: 15194950.

Kaye CI, Martin AO, Rollnick BR, Nagatoshi K, Israel J, Hermanoff M, Tropea B, Richtsmeier JT, Morton NE. Oculoauriculovertebral anomaly: segregation analysis. Am J Med Genet. 1992;43:913–7. PubMed PMID: 1415339.

Keegan CE, Mulliken JB, Wu BL, Korf BR. Townes-Brocks syndrome versus expanded spectrum hemifacial microsomia: review of eight patients and further evidence of a "hot spot" for mutation in the SALL1 gene. Genet Med. 2001;3:310–3. PubMed PMID: 11478532.

Kelberman D, Tyson J, Chandler DC, McInerney AM, Slee J, Albert D, Aymat A, Botma M, Calvert M, Goldblatt J, Haan EA, Laing NG, Lim J, Malcolm S, Singer SL, Winter RM, Bitner-Glindzicz M. Hemifacial microsomia: progress in understanding the genetic basis of a complex malformation syndrome. Hum Genet. 2001;109:638–45. PubMed PMID: 11810276.

Koren G. Mycophenolate mofetil: emerging as a potential human teratogen. Can Fam Physician. 2008;54:1112–3. PubMed PMID: 18697969.

Keogh IJ, Troulis MJ, Monroy AA, Eavey RD, Kaban LB. Isolated microtia as a marker for unsuspected hemifacial microsomia. Arch Otolaryngol Head Neck Surg. 2007;133:997–1001. PubMed PMID: 17938322.

Kobrynski L, Chitayat D, Zahed L, McGregor D, Rochon L, Brownstein S, Vekemans M, Albert DL. Trisomy 22 and facioauriculovertebral (Goldenhar) sequence. Am J Med Genet. 1993;46:68–71. PubMed PMID: 8494034.

Kohlhase J, Taschner PE, Burfeind P, Pasche B, Newman B, Blanck C, Breuning MH, ten Kate LP, Maaswinkel-Mooy P, Mitulla B, Seidel J, Kirkpatrick SJ, Pauli RM, Wargowski DS, Devriendt K, Proesmans W, Gabrielli O, Coppa GV, Wesby-van Swaay E, Trembath RC, Schinzel AA, Reardon W, Seemanova E, Engel W.

Molecular analysis of SALL1 mutations in Townes-Brocks syndrome. Am J Hum Genet. 1999;64:435–45. PubMed PMID: 9973281.

Kosaki R, Fujimaru R, Samejima H, Yamada H, Izumi K, Iijima K, Kosaki K. Wide phenotypic variations within a family with SALL1 mutations: Isolated external ear abnormalities to Goldenhar syndrome. Am J Med Genet A. 2007;143A:1087–90. PubMed PMID: 17431915.

Kushnick T, Colondrillo M. 49, XXXXY patient with hemifacial microsomia. Clin Genet. 1975;7:442–8. PubMed PMID: 1149315.

Ladekarl S. Combination of Goldenhar syndrome with cri-dre-chat syndrome. Acta Ophthalmol (Copenh). 1968;46:605–10. PubMed PMID: 4974461.

Lammer E. Preliminary observations on isotretinoin-induced ear malformations and pattern formation of the external ear. J Craniofac Genet Dev Biol. 1991;11:292–5. PubMed PMID: 1812130.

Lawson K, Waterhouse N, Gault DT, Calvert ML, Botma M, Ng R. Is hemifacial microsomia linked to multiple maternities? Br J Plast Surg. 2002;55:474–8. PubMed PMID: 12479420.

Lehalle D, Gordon CT, Oufadem M, Goudefroye G, Boutaud L, Alessandri JL, Baena N, Baujat G, Baumann C, Boute-Benejean O, Caumes R, Decaestecker C, Gaillard D, Goldenberg A, Gonzales M, Holder-Espinasse M, Jacquemont ML, Lacombe D, Manouvrier-Hanu S, Marlin S, Mathieu-Dramard M, Morin G, Pasquier L, Petit F, Rio M, Smigiel R, Thauvin-Robinet C, Vasiljevic A, Verloes A, Malan V, Munnich A, de Pontual L, Vekemans M, Lyonnet S, Attié-Bitach T, Amiel J. Delineation of EFTUD2 haploinsufficiency-related phenotypes through a series of 36 patients. Hum Mutat. 2014;35:478–85. PubMed PMID: 24470203.

Lines MA, Huang L, Schwartzentruber J, Douglas SL, Lynch DC, Beaulieu C, Guion-Almeida ML, Zechi-Ceide RM, Gener B, Gillessen-Kaesbach G, Nava C, Baujat G, Horn D, Kini U, Caliebe A, Alanay Y, Utine GE, Lev D, Kohlhase J, Grix AW, Lohmann DR, Hehr U, Böhm D; FORGE Canada Consortium. Majewski J, Bulman DE, Wieczorek D, Boycott KM. Haploinsufficiency of a spliceosomal GTPase encoded by EFTUD2 causes mandibulofacial dysostosis with microcephaly. Am J Hum Genet. 2012;90:369–77. PubMed PMID: 22305528.

Llano-Rivas I, González-del Angel A, del Castillo V, Reyes R, Carnevale A. Microtia: a clinical and genetic study at the National Institute of Pediatrics in Mexico City. Arch Med Res. 1999;30:120–4. PubMed PMID: 10372445.

Lopez-Camelo JS, Orioli IM. Heterogeneous rates for birth defects in Latin America: hints on causality. Genet Epidemiol. 1996;13:469–81. PubMed PMID: 8905393.

Luquetti DV, Hing AV, Rieder MJ, Nickerson DA, Turner EH, Smith J, Park S, Cunningham ML. "Mandibulofacial dysostosis with microcephaly" caused by EFTUD2 mutations: expanding the phenotype. Am J Med Genet A. 2013;161A:108–13. PubMed PMID: 23239648.

Maris CL, Endriga MC, Omnell ML, Speltz ML. Psychosocial adjustment in twin pairs with and without hemifacial microsomia. Cleft Palate Craniofac J. 1999;36:43–50. PubMed PMID: 10067761.

Marx H. Die Missbildungen des Ohres. In: Henke F, Lubarsh O, eds. *Handbuch der Speziellen Pathologische Anatomie und Histologie.* Berlin, Germany: Springer; 1926:620-5

Martinelli P, Maruotti GM, Agangi A, Mazzarelli LL, Bifulco G, Paladini D. Prenatal diagnosis of hemifacial microsomia and ipsilateral cerebellar hypoplasia in a fetus with oculoauriculovertebral spectrum. Ultrasound Obstet Gynecol. 2004;24:199–201. PubMed PMID: 15287060.

Melnick M, Myrianthopoulos NC, Paul NW. External ear malformations: epidemiology, genetics, and natural history. Birth Defects Orig Artic Ser. 1979;15:i–ix,1-140. PubMed PMID: 393325.

Moore KL, Persaud TYN. *The Developing Human: Clinically Oriented Embryology.* Philadelphia, PA: Saunders; 2003.

Neu KW, Friedman JM, Howard-Peebles PN. Hemifacial microsomia in cri du chat (5p-) syndrome. J Craniofac Genet Dev Biol. 1982;2:295–8. PubMed PMID: 7183708.

Northup JK, Matalon D, Hawkins JC, Matalon R, Velagaleti GV. Pericentric inversion, inv(14)(p11.2q22.3), in a 9-month old with features of Goldenhar syndrome. Clin Dysmorphol. 2010;19:185–9. PubMed PMID: 20571379.

Opitz JM. The developmental field concept. Am J Med Genet. 1985;21:1–11. PubMed PMID: 4003434.

Opitz JM, Lewin SO. The developmental field concept in pediatric pathology--especially with respect to fibular a/hypoplasia and the DiGeorge anomaly. Birth Defects Orig Artic Ser. 1987;23:277–92. PubMed PMID: 3580552.

Parisi MA, Zayed H, Slavotinek AM, Rutledge JC. Congenital diaphragmatic hernia and microtia in a newborn with mycophenolate mofetil (MMF) exposure: phenocopy for Fryns syndrome or broad spectrum of teratogenic effects? Am J Med Genet A. 2009;149A:1237–40. PubMed PMID: 19449404.

Pereira-Perdomo DF, Vélez-Forero J, Prada-Madrid R. Hemifacial myohyperplasia sequence. Am J Med Genet A. 2010;152A:1770–3. PubMed PMID: 20583183.

Petit F, Escande F, Jourdain AS, Porchet N, Amiel J, Doray B, Delrue MA, Flori E, Kim CA, Marlin S, Robertson SP, Manouvrier-Hanu S, Holder-Espinasse M. Nager syndrome: confirmation of SF3B4 haploinsufficiency as the major cause. Clin Genet. 2014;86:246–51. PubMed PMID: 24003905.

Poonawalla HH, Kaye CI, Rosenthal IM, Pruzansky S. Hemifacial microsomia in a patient with Klinefelter syndrome. Cleft Palate J. 1980;17:194–6. PubMed PMID: 6930993.

Quintero-Rivera F, Martinez-Agosto JA. Hemifacial microsomia in cat-eye syndrome: 22q11.1-q11.21 as candidate loci for facial symmetry. Am J Med Genet A. 2013;161A:1985–91. PubMed PMID: 23794175.

Rieder MJ, Green GE, Park SS, Stamper BD, Gordon CT, Johnson JM, Cunniff CM, Smith JD, Emery SB, Lyonnet S, Amiel J, Holder M, Heggie AA, Bamshad MJ, Nickerson DA, Cox TC, Hing AV, Horst JA, Cunningham ML. A human homeotic transformation resulting from mutations in PLCB4 and GNAI3 causes auriculocondylar syndrome. Am J Hum Genet. 2012;90:907–14. PubMed PMID: 22560091.

Rivera-Pérez JA, Mallo M, Gendron-Maguire M, Gridley T, Behringer RR. Goosecoid is not an essential component of the mouse gastrula organizer but is required for craniofacial and rib development. Development. 1995;121:3005–12. PubMed PMID: 7555726.

Rollnick BR. Oculoauriculovertebral anomaly: variability and causal heterogeneity. Am J Med Genet Suppl. 1988;4:41–53. PubMed PMID: 3144985.

Rollnick BR, Kaye CI. Hemifacial microsomia and variants: pedigree data. Am J Med Genet. 1983;15:233–53. PubMed PMID: 6881197.

Rollnick BR, Kaye CI, Nagatoshi K, Hauck W, Martin AO. Oculoauriculovertebral dysplasia and variants: phenotypic characteristics of 294 patients. Am J Med Genet. 1987;26:361–75. PubMed PMID: 3812588.

Rooryck C, Souakri N, Cailley D, Bouron J, Goizet C, Delrue MA, Marlin S, Lacombe FD, Arveiler B. Array-CGH analysis of a cohort of 86 patients with oculoauriculovertebral spectrum. Am J Med Genet A. 2010;152A:1984–9. PubMed PMID: 20635336.

Rotten D, Levaillant JM, Martinez H, Ducou le Pointe H, Vicaut E. The fetal mandible: a 2D and 3D sonographic approach to the diagnosis of retrognathia and micrognathia. Ultrasound Obstet Gynecol. 2002;19:122–30. PubMed PMID: 11876802.

Schaefer E, Collet C, Genevieve D, Vincent M, Lohmann DR, Sanchez E, Bolender C, Eliot MM, Nürnberg G, Passos-Bueno MR, Wieczorek D, van Maldergem L, Doray B. Autosomal recessive POLR1D mutation with decrease of TCOF1 mRNA is responsible for Treacher Collins syndrome. Genet Med. 2014;16:720–4. PubMed PMID: 24603435.

Schmid M, Schröder M, Langenbeck U. Familial microtia, meatal atresia, and conductive deafness in three siblings. Am J Med Genet. 1985;22:327–32. PubMed PMID: 4050865.

Schroeter C, Jährig K, Weinke I. Helv Paediatr Acta. 1980;35:233–41. [A new case of pentasomy X]. PubMed PMID: 6773908.

Shaw GM, Carmichael SL, Kaidarova Z, Harris JA. Epidemiologic characteristics of anotia and microtia in California, 1989-1997. Birth Defects Res A Clin Mol Teratol. 2004;70:472–5. PubMed PMID: 15259037.

Solomon BD. VACTERL/VATER association. Orphanet J Rare Dis. 2011;6:56. PubMed PMID: 21846383.

Splendore A, Passos-Bueno MR, Jabs EW, Van Maldergem L, Wulfsberg EA. TCOF1 mutations excluded from a role in other first and second branchial arch-related disorders. Am J Med Genet. 2002;111:324–7. PubMed PMID: 12210332.

Stanojević M, Stipoljev F, Koprcina B, Kurjak A. Oculo-auriculo-vertebral (Goldenhar) spectrum associated with pericentric inversion 9: coincidental findings or etiologic factor? J Craniofac Genet Dev Biol. 2000;20:150–4. PubMed PMID: 11321600.

Stueckle L, Saltzman BS, Luquetti D, Hing AV, Evans KN. Renal and spine screening in sub-phenotypic populations of patients with craniofacial microsomia. Poster presentation. Indianapolis, IN: American Cleft Palate – Craniofacial Conference; 2014.

Su PH, Yu JS, Chen JY, Chen SJ, Li SY, Chen HN. Mutations and new polymorphic changes in the TCOF1 gene of patients with oculo-auriculo-vertebral spectrum and Treacher-Collins syndrome. Clin Dysmorphol. 2007;16:261–7. PubMed PMID: 17786119.

Sujansky E, Smith A. Recombinant chromosome 18 in two male sibs with first and second branchial arch syndrome. Am J Hum Genet. 1981;33:92A.

Sze RW, Paladin AM, Lee S, Cunningham ML. Hemifacial microsomia in pediatric patients: asymmetric abnormal development of the first and second branchial arches. AJR Am J Roentgenol. 2002;178:1523–30. PubMed PMID: 12034632.

Tan TY, Collins A, James PA, McGillivray G, Stark Z, Gordon CT, Leventer RJ, Pope K, Forbes R, Crolla JA, Ganesamoorthy D, Burgess T, Bruno DL, Slater HR, Farlie PG, Amor DJ. Phenotypic variability of distal 22q11.2 copy number abnormalities. Am J Med Genet A. 2011;155A:1623–33. PubMed PMID: 21671380.

Tanzer RC. Microtia. Clin Plast Surg. 1978;5:317–36. PubMed PMID: 359217.

Tasse C, Böhringer S, Fischer S, Lüdecke HJ, Albrecht B, Horn D, Janecke A, Kling R, König R, Lorenz B, Majewski F, Maeyens E, Meinecke P, Mitulla B, Mohr C, Preischl M, Umstadt H, Kohlhase J, Gillessen-Kaesbach G, Wieczorek D. Oculo-auriculo-vertebral spectrum (OAVS): clinical evaluation and severity scoring of 53 patients and proposal for a new classification. Eur J Med Genet. 2005;48:397–411. PubMed PMID: 16378924.

Tasse C, Majewski F, Böhringer S, Fischer S, Lüdecke HJ, Gillessen-Kaesbach G, Wieczorek D. A family with autosomal dominant oculo-auriculo-vertebral spectrum. Clin Dysmorphol. 2007;16:1–7. PubMed PMID: 17159507.

Taysi K, Marsh JL, Wise DM. Familial hemifacial microsomia. Cleft Palate J. 1983;20:47–53. PubMed PMID: 6572575.

Teconi R, Hall B. Hemifacial microsomia: Phenotypic classification, clinical implications and genetic aspects. In: Harvold E, ed. *Treatment of Hemifacial Microsomia.* New York, NY: Alan R Liss; 1983:39-49

Torti EE, Braddock SR, Bernreuter K, Batanian JR. Oculo-auriculo-vertebral spectrum, cat eye, and distal 22q11 microdeletion syndromes: a unique double rearrangement. Am J Med Genet A. 2013;161A:1992–8. PubMed PMID: 23894059.

Vendramini-Pittoli S, Kokitsu-Nakata NM. Oculoauriculovertebral spectrum: report of nine familial cases with evidence of autosomal dominant inheritance and review of the literature. Clin Dysmorphol. 2009;18:67–77. PubMed PMID: 19305190.

Vento AR, LaBrie RA, Mulliken JB. The O.M.E.N.S. classification of hemifacial microsomia. Cleft Palate Craniofac J. 1991;28:68–76. PubMed PMID: 1848447.

Verloes A, Seret N, Bernier V, Gonzales M, Herens C, Koulischer L. Branchial arch anomalies in trisomy 18. Ann Genet. 1991;34:22–4. PubMed PMID: 1952786.

Vigneron J, Stricker M, Vert P, Rousselot JM, Levy M. Postaxial acrofacial dystosis (Miller) syndrome: a new case. J Med Genet. 1991;28:636–8. PubMed PMID: 1683410.

Voigt C, Mégarbané A, Neveling K, Czeschik JC, Albrecht B, Callewaert B, von Deimling F, Hehr A, Falkenberg Smeland M, König R, Kuechler A, Marcelis C, Puiu M, Reardon W, Riise Stensland HM, Schweiger B, Steehouwer M, Teller C, Martin M, Rahmann S, Hehr U, Brunner HG, Lüdecke HJ, Wieczorek D. Oto-facial syndrome and esophageal atresia, intellectual disability and zygomatic anomalies - expanding the phenotypes associated with EFTUD2 mutations. Orphanet J Rare Dis. 2013;8:110. PubMed PMID: 23879989.

Van Bennekom CM, Mitchell AA, Moore CA, Werler MM; National Birth Defects. Vasoactive exposures during pregnancy and risk of microtia. Birth Defects Res A Clin Mol Teratol. 2013;97:53–9. PubMed PMID: 23180593.

Wang R, Martínez-Frías ML, Graham JM Jr. Infants of diabetic mothers are at increased risk for the oculo-auriculo-vertebral sequence: A case-based and case-control approach. J Pediatr. 2002;141:611–7. PubMed PMID: 12410187.

Werler MM, Sheehan JE, Hayes C, Mitchell AA, Mulliken JB. Vasoactive exposures, vascular events, and hemifacial microsomia. Birth Defects Res A Clin Mol Teratol. 2004a;70:389–95. PubMed PMID: 15211707.

Werler MM, Sheehan JE, Hayes C, Padwa BL, Mitchell AA, Mulliken JB. Demographic and Reproductive Factors Associated With Hemifacial Microsomia. Cleft Palate Craniofac J. 2004b;41:494–50. PubMed PMID: 15352870.

Wieczorek D, Ludwig M, Boehringer S, Jongbloet PH, Gillessen-Kaesbach G, Horsthemke B. Reproduction abnormalities and twin pregnancies in parents of sporadic patients with oculo-auriculo-vertebral spectrum/Goldenhar syndrome. Hum Genet. 2007;121:369–76. PubMed PMID: 17297623.

Wilson GN, Barr M Jr. Trisomy 9 mosaicism: another etiology for the manifestations of Goldenhar syndrome. J Craniofac Genet Dev Biol. 1983;3:313–6. PubMed PMID: 6662905.

Yamada G, Mansouri A, Torres M, Stuart ET, Blum M, Schultz M, De Robertis EM, Gruss P. Targeted mutation of the murine goosecoid gene results in craniofacial defects and neonatal death. Development. 1995;121:2917–22. PubMed PMID: 7555718.

Zielinski D, Markus B, Sheikh M, Gymrek M, Chu C, Zaks M, Srinivasan B, Hoffman JD, Aizenbud D, Erlich Y. OTX2 duplication is implicated in hemifacial microsomia. PLoS One. 2014;9:e96788. PubMed PMID: 24816892.

Chapter Notes

Author Notes

Web: Seattle Children's Craniofacial Center

Acknowledgments

We thank the following Seattle Children's Craniofacial Center members for their valuable contributions to this article: Dr Michael Cunningham, Dr Kathleen Sie, Dr Craig Birgfeld, Dr Mark Egbert, Dr Jacqueline Starr, Marsha Ose, and Cassandra Aspinall.

Revision History

- 2 April 2020 (ma) Chapter retired: rarely genetic
- 9 October 2014 (me) Comprehensive update posted live
- 19 March 2009 (cg) Review posted live
- 29 August 2008 (clh) Original submission