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Congenital Fibrosis of the Extraocular Muscles Overview

Synonym: CFEOM

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Summary

The purpose of this overview is to:

1. Describe the clinical characteristics of congenital fibrosis of the extraocular muscles (CFEOM);
2. Review the genetic causes of CFEOM;
3. Review the disorders to consider the differential diagnosis of CFEOM;
4. Provide an evaluation strategy to identify the genetic cause of CFEOM in a proband (when possible);
5. Review management of CFEOM;
6. Inform genetic counseling of family members of an individual with CFEOM.

1. Clinical Characteristics of Congenital Fibrosis of the Extraocular Muscles

Congenital fibrosis of the extraocular muscles (CFEOM) is diagnosed based on characteristic eye findings: congenital non-progressive ophthalmoplegia (inability to move the eyes) with or without ptosis (droopy eyelids) affecting part or all of the oculomotor nucleus and nerve (cranial nerve III) and its innervated muscles (superior, medial, and inferior recti, inferior oblique, and levator palpabrae superioris) and sometimes the trochlear and abducens nuclei and nerves (cranial nerves IV and VI) and their innervated muscles (superior oblique muscle and lateral rectus muscle, respectively).

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In general, affected individuals have severe limitation of vertical gaze (usually upgaze) and variable limitation of horizontal gaze. Individuals with CFEOM frequently compensate for the ophthalmoplegia by maintaining abnormal head positions (chin up) at rest and by moving their heads rather than their eyes to track objects. Binocular vision is typically absent. Refractive errors are common.

Although once felt to result from primary fibrosis of the extraocular muscles, neuroanatomic, genetic, and neuroimaging findings suggest that the various forms of CFEOM result from abnormal development of oculomotor neurons and their processes [Whitman & Engle 2017]. Magnetic resonance imaging suggests that the trochlear, abducens, and optic nerves can also be hypoplastic [Demer et al 2005, Demer et al 2010].

Phenotypes of CFEOM based on specific eye findings, CNS malformations, and other non-ocular findings are summarized in Table 1.

Table 1. Congenital Fibrosis of the Extraocular Muscles: Phenotypes

Finding	CFEOM Subtype					
	CFEOM1	CFEOM2	CFEOM3	CFEOM5 [1]	Tukel syndrome	CFEOM3 w/ polymicrogyria
Congenital non-progressive external ophthalmoplegia	Bilateral, profound; limited upgaze	Bilateral, profound, w/ eyes in exotropic (outward deviating) position	Bilateral OR unilateral; primarily affecting muscles in the oculomotor distribution	Nl OR variable restrictions in vertical &/or horizontal gaze, bilateral OR unilateral	Bilateral OR unilateral; primarily affecting muscles in the oculomotor distribution	Bilateral; limited upgaze
Lid position	Congenital non-progressive bilateral ptosis	Congenital non-progressive bilateral ptosis	Nl OR congenital non-progressive bilateral or unilateral ptosis	Nl OR congenital non-progressive bilateral or unilateral ptosis	Nl OR congenital non-progressive bilateral or unilateral ptosis	Congenital non-progressive bilateral ptosis
Primary vertical position of each eye	Infraducted (downward)	Nl or positioned slightly above or below midline	Infraducted or nl (primary position)	Nl (primary position)	Infraducted or nl (primary position)	Infraducted
Vertical eye movements	Inability to elevate eyes above horizontal midline	Severely restricted (up- & downgaze)	Variable restriction w/or w/o upgaze above midline	Nl or w/mildly restricted upgaze	Variable restriction w/or w/o upgaze above midline	Severely restricted
Primary horizontal position of each eye	Orthotropic (nl), esotropic (inward), or exotropic (outward)	Typically exotropic; rarely, orthotropic	Orthotropic or exotropic more frequent than esotropic	Orthotropic or exotropic	Orthotropic or exotropic may be more frequent than esotropic.	Orthotropic or exotropic
Horizontal eye movements	Nl to severely restricted	Severely restricted; only abduction preserved	Nl to severely restricted	Nl to severely restricted	Nl to severely restricted	Variably restricted

Table 1. continued from previous page.

Finding	CFEOM Subtype					
	CFEOM1	CFEOM2	CFEOM3	CFEOM5 [1]	Tukel syndrome	CFEOM3 w/ polymicrogyria
Aberrant eye movements	Frequent, esp both eyes turning inward on attempted upgaze	Small amplitude, if present	Sometimes present	Sometimes present as Duane retraction syndrome w/ synergistic divergence	Sometimes present	Convergent nystagmus w/ attempted upgaze
	CFEOM1	**CFEOM2**	**CFEOM3**	**CFEOM5 [1]**	**Tukel syndrome**	**CFEOM3 w/ polymicrogyria**
Positive forced duction test for restriction	+	+	At least in attempted upgaze	Unreported	At least in attempted upgaze	+
Binocular vision	Usually absent	Absent	Rarely present	Unreported	Rarely present	Usually absent
Refractive errors (hyperopia, myopia, or astigmatism)	Frequently high astigmatism	Frequent	Common	Rare	Common	Frequent, high astigmatism
Amblyopia	Frequent; may be strabismic or refractive	Frequent	Frequent	Unspecified	Frequent	Frequent
Pupils	Nl	Often small & sluggishly reactive to light	Typically nl, occasionally small & sluggishly reactive to light	Nl	Nl	Nl
CNS malformations	None	None	See **CNS malformations** following this table.	None reported	Postaxial oligodactyly/ oligosyndactyly	Agenesis or hypoplasia of corpus callosum, schizencephaly, polymicrogyria, basal ganglia dysmorphism, thalamus dysmorphisms, cerebellar dysplasia
Non-ocular findings	None	None	See **Non-ocular findings** following this table.		Postaxial oligodactyly or oligosyndactyly of the hands	ID, microcephaly, &/or progressive sensorimotor axonal polyneuropathy sometimes present

CNS = central nervous system; ID = intellectual disability; nl = normal

1. This phenotype, caused by *COL25A1* pathogenic variants, is described per authors' personal observations. A few clinical phenotyping parameters were not reported in detail.

Congenital non-progressive external ophthalmoplegia. Individuals with CFEOM are born with a severe form of incomitant strabismus referred to as ophthalmoplegia (inability to move the eyes) caused by dysfunction of specific ocular muscles innervated by the oculomotor and trochlear nerves. In general, affected individuals have severe limitation of vertical gaze and variable limitation of horizontal gaze. Individuals with CFEOM

compensate for the ophthalmoplegia by maintaining an abnormal head position at rest and by moving their heads rather than their eyes to track objects.

Ptosis is the drooping of the upper eyelid as a result of dysfunction of the levator palpebrae superioris. Individuals with CFEOM often have a compensatory chin-up head posture to both better position their infraducted eyes and to "see under" their droopy lids.

Refractive errors are common but not characteristic.

Amblyopia. Strabismus (with suppression of one eye), refractive error, and ptosis may cause amblyopia, which can lead to permanent loss of vision when untreated.

Strabismus is the deviation of the position of one eye relative to the other, resulting in misalignment of the line of sight of the two eyes. Individuals with CFEOM have incomitant strabismus, in which their misalignment varies with gaze direction. Incomitant strabismus often results from mechanical dysfunction in the orbit or neuromuscular dysfunction at the level of the brain stem, nerve, or muscle. The resting eye position of an individual with CFEOM is often abnormal. In general, hypotropic (downward) and exotropic (outward) positions are more common than hypertropic (upward) and esotropic (inward) positions. Strabismus in individuals with CFEOM can vary within a single family, and this can be particularly remarkable among affected members of families with CFEOM3. Among families with CFEOM1, the vertical strabismus is quite uniform, but the horizontal strabismus can vary.

CNS malformations. Individuals with CFEOM typically have hypoplastic oculomotor nerves on MRI. Some individuals with CFEOM3 have central nervous system malformations, including agenesis or hypoplasia of the corpus callosum and anterior commissure, pachygyria, polymicrogyria, schizencephaly, dysgenesis of the olfactory bulbs and sulci, expansion of the ventricular system, deficiency of the falx cerebri, paucity of white matter, colpocephaly, dysmorphic basal ganglia with or without internal capsule hypoplasia, malformations of the thalamus and hippocampus, hypoplasia of the cerebellar vermis and/or hemispheres, brain stem hypoplasia, facial nerve hypoplasia, absence of the cerebral peduncle in the midbrain, arachnoid cysts, encephalocele, and/or hydrancephaly. The CFEOM phenotype in most of these individuals meets the criteria of CFEOM3 [Demer et al 2010, Tischfield et al 2010, Cederquist et al 2012, Romaniello et al 2012, Chew et al 2013, Balasubramanian et al 2015, Whitman et al 2016, Jurgens et al 2021, Soliani et al 2021]. Some individuals, particularly those with CFEOM3 with polymicrogyria, also have microcephaly and intellectual disability.

Non-ocular findings

- **CFEOM3.** In a subset of individuals with CFEOM3 the non-ocular findings comprise distinct syndromes that can include facial paralysis and facial dysmorphisms, vocal cord paralysis, intellectual and/or social disability, Kallmann syndrome (hypogonadotropic hypogonadism with anosmia), progressive peripheral sensorimotor axonal polyneuropathy, congenital joint contractures, gait anomalies, cyclic vomiting, epilepsy, and microcephaly [Tischfield et al 2010, Chew et al 2013, Whitman et al 2016, Jurgens et al 2021].
- **Marcus Gunn phenomenon and other evidence of dysinnervation** have been reported in individuals with CFEOM [Pieh et al 2003, Yamada et al 2005, Kaçar Bayram et al 2015, Jurgens et al 2021]. The Marcus Gunn jaw winking phenomenon manifests as the momentary elevation of a ptotic upper eyelid with specific movements of the jaw. Often first noted in young infants when they are feeding, the phenomenon results from aberrant innervation of the levator palpebrae superioris muscle by axons intended to run in the motor branch of the trigeminal nerve and to innervate the pterygoid muscle. The association of these findings with CFEOM provides additional evidence that these syndromes are primarily neurogenic in cause.
- **Tukel syndrome.** Affected members of the family with CFEOM3 that maps to the Tukel syndrome locus also manifest bilateral postaxial oligodactyly/oligosyndactyly of the hands, more severe on the right.

2. Genetic Causes of CFEOM

Table 2a. CFEOM: Associated Genes

Gene [1]	% of All CFEOM	Associated CFEOM Phenotypes			
		CFEOM1	CFEOM2	CFEOM3	CFEOM5
COL25A1	<1%				+
KIF21A	~55%	+++		+	
PHOX2A	~10%		+		
TUBA1A	<1%	+		+	
TUBB2B	<1%			+	
TUBB3	~35%	+		+++	

1. Genes are listed alphabetically.

Table 2b. CFEOM: Gene-Phenotype Correlations

Gene [1]	Phenotype		
	ID/DD	MRI Findings	Other Features
COL25A1		Small extraocular muscles	Aberrant eye movements incl Duane retraction syndrome or synergistic divergence
KIF21A [2]	Rarely +	Hypoplastic oculomotor nerve & small extraocular muscles; small optic nerves. Other findings (extremely rare) incl cerebellar hypoplasia, arachnoid cyst, corpus callosal thinning, paucity of white matter, dysmorphic midbrain, small caudate bodies	Ptotic eyelid elevation assoc w/synkinetic jaw movements (Marcus Gunn phenomenon). Other syndromic features (extremely rare) incl facial weakness, pes cavus, sensorimotor peripheral neuropathy w/axonal denervation
PHOX2A		Absent oculomotor & trochlear nerves, small or absent extraocular muscles	Reported only in consanguineous families from the Middle East; minimally reactive pupils
TUBA1A	±	Hypoplastic oculomotor nerve & small extraocular muscles, ± perisylvian polymicrogyria, ± deficiency of the falx cerebri, asymmetry of caudate heads & lateral ventricles, nl anterior commissure, cerebellum, & brain stem	Aberrant eye movements w/convergence on attempted upgaze or divergence on attempted downgaze; rarely assoc w/cyclic vomiting, hypotonia, facial dysmorphisms, gait anomalies, &/or gastrointestinal symptoms
TUBB2B [3]	+	Small extraocular muscles; perisylvian polymicrogyria, ± schizencephaly, asymmetric basal ganglia, corpus callosal thinning, cerebellar dysplasia, nl brain stem	± epilepsy, microcephaly
TUBB3 [4]	±	Hypoplastic oculomotor nerve & small extraocular muscles, agenesis or hypoplasia of corpus callosum & anterior commissure, dysgenesis of olfactory bulbs & sulci, basal ganglia malformations	Aberrant eye movements & Marcus Gunn phenomenon; may be assoc w/facial dysmorphisms, Kallmann syndrome, vocal cord paralysis, axonal peripheral neuropathy, cyclic vomiting

DD = developmental delay; ID = intellectual disability; nl = normal
1. Genes are listed alphabetically.
2. KIF21A pathogenic variants most commonly result in ptosis and/or CFEOM without syndromic findings. Very rare specific pathogenic variants can result in syndromic features resembling those seen in *TUBB3*-associated CFEOM [Soliani et al 2021].
3. Allelic w/*TUBB2B*-related tubulinopathy: malformations of cortical development without CFEOM (See Tubulinopathies Overview.)
4. Allelic w/*TUBB3*-related tubulinopathy: microlissencephaly or polymicrogyria, usually accompanied by abnormalities of the corpus callosum and cerebellar, basal ganglia, and brain stem dysplasia, but without CFEOM (See Tubulinopathies Overview.)

Genotype-Phenotype Correlations

KIF21A. Clinical examinations and high-resolution orbital MRI of individuals with CFEOM1 resulting from several different specific *KIF21A* pathogenic variants did not reveal a correlation between any specific pathogenic variant and clinical phenotype [Yamada et al 2003, Demer et al 2005].

Recently, one specific *KIF21A* pathogenic variant was reported to result in a syndromic CFEOM3 phenotype with a progressive peripheral neuropathy, reminiscent of the syndromic findings in *TUBB3*-CFEOM [Soliani et al 2021].

PHOX2A. No correlation between specific *PHOX2A* pathogenic variants and specific aspects of the CFEOM2 phenotype has been found.

TUBA1A. No correlation between specific *TUBA1A* pathogenic variants and specific aspects of the CFEOM phenotype has been found [Jurgens et al 2021].

TUBB2B. No correlation between specific *TUBB2B* pathogenic variants and specific aspects of the CFEOM phenotype has been found [Cederquist et al 2012, Romaniello et al 2012, Romaniello et al 2019].

TUBB3. Suggested correlations (based on data from a limited number of individuals) between specific *TUBB3* pathogenic variants and distinctive phenotypes are summarized in Table 3 (pdf) [Tischfield et al 2010, Chew et al 2013, Whitman et al 2016]. Additional data are necessary to determine if these described associations represent true genotype-phenotype correlations.

3. Differential Diagnosis of CFEOM

The term "congenital cranial dysinnervation disorders (CCDDs)" was coined to refer to disorders of innervation of cranial musculature [Gutowski et al 2003]. The various forms of CFEOM are included in the CCDDs. Other CCDDs include Duane syndrome, Moebius syndrome, and congenital facial palsy.

Genetic disorders with ophthalmoplegia in the differential diagnosis of CFEOM are summarized in Table 4.

Table 4. Genetic Disorders with Ophthalmoplegia in the Differential Diagnosis of Congenital Fibrosis of the Extraocular Muscles

Gene (Genetic Mechanism)	Disorder	MOI	Clinical Characteristics
Chromosome 8 anomalies	See Duane syndrome.		Duane syndrome w/various assoc congenital abnormalities incl other cranial nerve deficits, facial dysmorphisms, ID, cardiac defects
CHN1	*CHN1*-related Duane syndrome [1]	AD	Bilateral involvement, vertical movement abnormalities beyond the upshoot & downshoot often seen in Duane syndrome
DMPK	Myotonic dystrophy type 1	AD	
HOXA1	Athabascan brain stem dysgenesis syndrome (ABDS) & Bosley-Salih-Alorainy syndrome (BSAS) (See *HOXA1*-Related Disorders.)	AR	Duane syndrome type III or horizontal gaze palsy & (in most persons) bilateral SNHL. Depending on specific syndrome (ABDS vs BSAS), a subset manifest ID, autism, moderate-to-severe central hypoventilation, facial weakness, swallowing difficulties, vocal cord paresis, conotruncal heart defects, & skull & craniofacial abnormalities.
HOXB1	Hereditary congenital facial paresis 3 [2] (OMIM 614744)	AR	Isolated dysfunction of facial nerve, comitant esotropia

Table 4. continued from previous page.

Gene (Genetic Mechanism)	Disorder	MOI	Clinical Characteristics
MAFB	*MAFB*-related Duane syndrome [1]	AD	Bilateral Duane syndrome ± mild-to-severe SNHL
MYMK	Carey-Fineman-Ziter syndrome (OMIM 254940)	AR	Facial weakness w/congenital non-progressive myopathy, Pierre Robin sequence
mtDNA deletions ranging in size from 2-10 kb	Chronic progressive external ophthalmoplegia caused by mtDNA deletions (See Mitochondrial DNA Deletion Syndromes.)	Mat	Progressive ptosis, paralysis of extraocular muscles (ophthalmoplegia), variably severe proximal limb weakness
PABPN1	Oculopharyngeal muscular dystrophy	AD	Late-onset severe dysphagia
POLG *RRM2B* *SLC25A4* *TK2* *TMPO* *TWNK*	Ophthalmoplegia caused by mtDNA maintenance defects (See Mitochondrial DNA Maintenance Defects Overview.)	AD AR	
ROBO3	Horizontal gaze palsy w/progressive scoliosis (OMIM 607313)	AR	Congenital horizontal gaze palsy (no horizontal eye movements) w/progressive scoliosis
SALL4	*SALL4*-related disorders incl Duane-radial ray syndrome (DRRS) & acro-renal-ocular syndrome (AROS)	AD	• DRRS: uni- or bilateral Duane anomaly & radial ray malformation • AROS: radial ray malformations, renal abnormalities, ocular coloboma, & Duane anomaly

AD = autosomal dominant; AR = autosomal recessive; CFEOM = congenital fibrosis of the extraocular muscles; ID = intellectual disability; Mat = maternal; MOI = mode of inheritance; mtDNA = mitochondrial DNA; SNHL = sensorineural hearing loss

1. Duane syndrome is characterized by horizontal eye movement limitation, usually of abduction, with retraction of the globe and narrowing of the palpebral fissure on attempted adduction. It is believed to result from abnormal development of the abducens nucleus and nerve (cranial nerve VI). Although the majority of cases of Duane syndrome are simplex and isolated (i.e., not associated with other malformations), rare families with autosomal dominant or autosomal recessive inheritance of Duane syndrome with or without accompanying anomalies have been reported.

2. Hereditary congenital facial paresis 1 (HCFP1) maps to chromosome 3q21-q22 (OMIM 601471); HCFP2 maps to chromosome 10q21.3-q22.1 (OMIM 604185).

Other disorders with ophthalmoplegia in the differential diagnosis of CFEOM

- **Brown syndrome** (OMIM 616407) – "superior oblique tendon sheath syndrome" – is characterized by the inability to elevate the adducted eye actively or passively. Most congenital Brown syndrome is simplex (i.e., a single occurrence in a family) and believed to result from anomalies of the tendon or the trochlear apparatus or possibly from aberrant innervation. Rare familial cases have been reported. The genetic cause of Brown syndrome is not known.
- **Myasthenia gravis** (fluctuating weakness and diplopia). See Congenital Myasthenic Syndromes.
- **Cranial nerve III palsy.** Few reports of congenital familial third-nerve palsy exist and those that do may be misdiagnosed CFEOM.
- **Moebius syndrome (MBS)** (OMIM 157900) is characterized by facial weakness or diplegia with ocular abduction deficit. The vast majority of individuals with Moebius syndrome represent simplex cases and many affected individuals also have developmental defects of additional lower cranial nerves and distal extremities. Individuals with MBS have normal vertical eye movements and do not have ptosis [MacKinnon et al 2014].

4. Evaluation Strategy to Identify the Genetic Cause of CFEOM in a Proband (When Possible)

Establishing a specific genetic cause of CFEOM:

- Can aid in discussions of prognosis (which are beyond the scope of this *GeneReview*) and genetic counseling;
- Usually involves a medical history, physical examination, laboratory testing, family history, and genomic/genetic testing.

Medical history. A thorough medical history should be taken, including pre- or perinatal findings, developmental history, and growth trajectory. A history of perinatal distress, developmental delay, and slow growth is most consistent with CFEOM3 and a pathogenic variant in one of the tubulin genes (see also Tubulinopathies Overview).

Physical examination. A thorough physical examination (including of the extremities and genitalia), comprehensive eye examination, and neurologic examination should be performed. See Table 2b and Table 3 (pdf) for more details.

- Bilateral CFEOM with ptosis and upgaze restriction without other physical findings can be caused by pathogenic variants in *KIF21A* or *TUBB3*.
- Unilateral CFEOM or CFEOM without ptosis is most often caused by pathogenic variants in *TUBB3*.
- The combination of CFEOM3 with facial weakness, other cranial nerve dysfunction, peripheral neuropathy, microphallus and/or cryptorchidism, or congenital joint contractures strongly suggests specific *TUBB3* pathogenic variants.

Family history. A three-generation family history should be taken, with attention to relatives with manifestations of CFEOM and documentation of relevant findings through direct examination or review of medical records including results of molecular genetic testing.

Molecular Genetic Testing

Testing approaches can include a combination of gene-targeted testing (multigene panel) and comprehensive genomic testing (exome sequencing, genome sequencing). Gene-targeted testing requires the clinician to hypothesize which gene(s) are likely involved (see Option 1), whereas genomic testing does not (see Option 2).

Option 1

A multigene panel that includes some or all of the genes listed in Table 2a is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. 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*. (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.

Option 2

Comprehensive genomic testing (which does not require the clinician to determine which gene[s] are likely involved) may be considered. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

5. Management of CFEOM

Evaluations Following Initial Diagnosis

To establish the extent of ophthalmologic involvement and needs in an individual diagnosed with congenital fibrosis of the extraocular muscles, the following evaluations are recommended:

- Consultation with a clinical geneticist and/or genetic counselor
- Ophthalmologic examination:
  - Determination of resting gaze position, head position with eyes in resting gaze position, and vertical and horizontal gaze restrictions
  - Evaluation for aberrant movements including synergistic convergence and divergence, globe retraction, Marcus Gunn jaw wink
  - Measurement of palpebral fissure size
  - Anterior segment evaluation to detect corneal exposure
  - Levator function testing
  - Optional forced duction testing
  - Refraction, including cycloplegic refraction in children
  - Photographic documentation for future comparison
- Strongly recommended if eye muscle surgery is planned:
  - Brain and brain stem MRI scan to determine the size and/or course of the oculomotor and trochlear nerves
  - High-resolution orbital MRI (1- to 3-mm cuts) to detect abnormalities in the size and/or course of the extraocular muscle(s) and atrophy of the superior rectus-levator complex
- Referral to relevant specialists regarding evaluation of associated CNS findings/malformations and/or non-ocular findings

Treatment of Manifestations

Nonsurgical treatment of ophthalmologic findings:

- Refractive errors may be managed with spectacles or contact lenses. Specialist examination is required to detect refractive errors early in life, when affected individuals may be asymptomatic, to prevent amblyopia and avoid compounding the motility problem with a focusing problem.
- Amblyopia can be treated effectively with occlusion or penalization of the better-seeing eye. Early detection (in the first years of life) maximizes the likelihood of a good response to treatment.
- Lubrication of ocular surface (particularly cornea) may be required. In cases of severe exposure, a PROSE lens can be of significant benefit [Papakostas et al 2015, Heidary et al 2019].

Surgical treatment of ophthalmologic findings (extraocular muscle and/or ptosis surgery):

- Correction of ptosis
- Eye muscle surgery
  - To correct or improve a compensatory head posture

- To improve alignment in primary gaze position
- To improve ambulation and gross motor development in young children

- Principles of surgical approach:
  - Orbital imaging is recommended before surgery to assess muscle size and position.
  - Extraocular muscles may be found at surgery to be attached in unexpected locations.
  - Resections or plications may be helpful in some cases to provide traction against large recessions during healing.
  - Surgery is likely to be technically difficult because of tightness of rectus muscles.
  - Recessions need to be larger – sometimes considerably larger – than indicated by standard tables, especially recessions of the inferior rectus muscles.
  - Dysinnervation causing esotropia in attempted upgaze may mask an underlying exotropia that will be unmasked after inferior rectus muscle weakening.
  - Inferior rectus muscle weakening may be enhanced by superior oblique weakening.
  - Most individuals with CFEOM have abnormally inserted superior oblique tendons and/or tight muscles or abnormally thin tendons [Shoshany et al 2019].
  - Profound weakening procedures (e.g., suturing muscle to orbital rim, rectus muscle myectomy) may be necessary.
  - Botulinum toxin may be helpful for residual misalignment in some cases.

Surveillance

CFEOM is congenital and is believed to be non-progressive.

Surveillance is important for prevention of amblyopia, and to treat amblyopia and complications of corneal exposure [Yazdani & Traboulsi 2004].

Routine ophthalmologic care is indicated, with visits every three to four months during the first years of life, and annual or biannual examinations in affected individuals not at risk for amblyopia.

In individuals with specific *TUBB3* pathogenic variants, surveillance for endocrine abnormalities and facial or vocal cord weakness and interventions for developmental delays are indicated as per treating specialists.

6. Genetic Counseling of Family Members of an Individual with CFEOM

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

Congenital fibrosis of the extraocular muscles (CFEOM) caused by pathogenic variants *KIF21A*, *TUBA1A*, *TUBB2B,* or *TUBB3* is inherited in an autosomal dominant manner.

CFEOM caused by pathogenic variants in *COL25A1* or *PHOX2A* is inherited in an autosomal recessive manner.

Tukel syndrome (a disorder of unknown genetic cause) is thought to be inherited in an autosomal recessive manner.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Some individuals diagnosed with autosomal dominant CFEOM have an affected parent.
- A proband with autosomal dominant CFEOM may have the disorder as the result of a *de novo* pathogenic variant.
  - *De novo* pathogenic variants in *KIF21A* [Yamada et al 2003], *TUBA1A* [Jurgens et al 2021], and *TUBB2B* [Cederquist et al 2012] have been reported. The proportion of individuals with *KIF21A*-, *TUBA1A*-, or *TUBB2B*-related CFEOM as the result of a *de novo* pathogenic variant is unknown.
  - The frequency of *de novo* pathogenic variants in individuals with *TUBB3*-related isolated CFEOM (no other neurologic deficits) is 25% (in 4/16 pedigrees) [Tischfield et al 2010].
  - The frequency of *de novo* pathogenic variants in individuals with *TUBB3*-related CFEOM with additional neurologic deficits is 85% (in 17/20 pedigrees) [Tischfield et al 2010, Chew et al 2013, Balasubramanian et al 2015, Whitman et al 2016].
- If the proband appears to be the only affected family member (i.e., a simplex case), ophthalmologic examination and/or molecular genetic testing (for the *KIF21A*, *TUBA1A*, *TUBB2B,* or *TUBB3* pathogenic variant identified in the proband) are recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
  - Presumed parental germline mosaicism has been reported in *KIF21A*- and *TUBB3*-related CFEOM [Khan et al 2010, Tischfield et al 2010, Liu et al 2014]. Parental germline mosaicism has not been reported in *TUBA1A*-related or *TUBB2B*-related CFEOM to date.
- The family history of some individuals diagnosed with autosomal dominant CFEOM may appear to be negative because of failure to recognize the disorder in family members or reduced penetrance. Therefore, an apparently negative family history cannot be confirmed unless appropriate evaluations (e.g., ocular examination and/or molecular genetic testing) have been performed on the parents of the proband.

Sibs of a proband. The risk to sibs of a proband depends on the clinical/genetic status of the proband's parents:

- If a parent has clinical characteristics consistent with CFEOM and/or a known *KIF21A*, *TUBA1A*, *TUBB2B,* or *TUBB3* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%.
- If the proband has a known pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Khan et al 2010, Tischfield et al 2010, Liu et al 2014].
- If the parents of a proband with autosomal dominant CFEOM are clinically unaffected but their genetic status is unknown, sibs are still presumed to be at increased risk for CFEOM because of the possibility of reduced penetrance in a heterozygous parent or of parental germline mosaicism.

Offspring of a proband. Each child of an individual with autosomal dominant CFEOM has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected and/or has a pathogenic variant, the parent's family members may be at risk.

Autosomal Recessive – Inheritance Risk to Family Members

Parents of a proband

- The parents of an individual with autosomal recessive CFEOM are obligate heterozygotes (i.e., presumed to be carriers of one pathogenic variant based on family history).
- If biallelic *COL25A1* or *PHOX2A* pathogenic variants have been identified in the proband, molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *COL25A1* or *PHOX2A* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Pseudodominant inheritance (i.e., an autosomal recessive condition present in individuals in two or more generations) of *PHOX2A*-related CFEOM has been reported in two consanguineous families [Wang et al 1998]. Two-generation involvement can occur in autosomal recessive disorders when a parent (who has biallelic pathogenic variants) is affected and the parent's reproductive partner is a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an autosomal recessive CFEOM-related pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with autosomal recessive CFEOM are obligate heterozygotes (carriers) for a pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a pathogenic variant.

Carrier detection. Carrier testing for relatives of a proband with *COL25A1*-related or *PHOX2A*-related CFEOM requires prior identification of the *COL25A1* or *PHOX2A* pathogenic variants in the family.

Carrier testing is not possible for relatives of a proband with Tukel syndrome because the associated gene has not been identified.

Related Genetic Counseling Issues

Evaluation of relatives at risk. It is appropriate to evaluate relatives of a proband with CFEOM in order to identify as early as possible those who would benefit from prompt initiation of treatment and prevention of secondary complications.

- If the pathogenic variant(s) in the family are known, molecular genetic testing can be used to clarify the genetic status of at-risk relatives.
- If the pathogenic variant(s) in the family are not known, clinical ophthalmologic exam can be used to clarify the disease status of at-risk relatives.

Prenatal Testing and Preimplantation Genetic Testing

Once the CFEOM-causing pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing for CFEOM are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

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.

- **Moebius Syndrome Foundation**

  Individuals with CFEOM do not have Moebius syndrome, but many individuals with syndromic CFEOM3 that includes facial weakness have found the resources of the Moebius syndrome foundation helpful.

  Phone: 844-MOEBIUS (844-663-2487)

  Email: info@moebiussyndrome.org

  www.moebiussyndrome.com

- **National Eye Institute**

  Phone: 301-496-5248

  Email: 2020@nei.nih.gov

  www.nei.nih.gov

- **Prevent Blindness America**

  211 West Wacker Drive

  Suite 1700

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  Email: info@preventblindness.org

  www.preventblindness.org

Chapter Notes

Author Notes

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Dr Whitman's website: www.childrenshospital.org/research/labs/whitman-lab

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