GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

Congenital Fibrosis of the Extraocular Muscles

[*CFEOM. Includes: Congenital Fibrosis of the Extraocular Muscles 1 (CFEOM 1), Congenital Fibrosis of the Extraocular Muscles 2 (CFEOM2), Congenital Fibrosis of the Extraocular Muscles 3 (CFEOM3), Congenital Fibrosis of the Extraocular Muscles 4 (CFEOM4), Tukel Syndrome*]

Caroline V Andrews, MSc
Research Study Coordinator, Program in Genomics
Children's Hospital Boston
Department of Pediatrics, Harvard Medical School
Boston
candrews@enders.tch.harvard.edu

Jigar Desai, PhD
Postdoctoral Fellow, Program in Genomics
Children's Hospital Boston
Department of Pediatrics, Harvard Medical School
Boston
jdesai@enders.tch.harvard.edu

David G Hunter, MD, PhD
Ophthalmologist-in-Chief, Department of Ophthalmology
Children's Hospital Boston
Associate Professor of Neurology, Harvard Medical School
Boston
david.hunter@childrens.harvard.edu

Elizabeth C Engle, MD
Program in Genomics & Department of Neurology
Children's Hospital Boston
Associate Professor of Neurology, Harvard Medical School
Boston
engle@enders.tch.harvard.edu

Initial Posting: April 27, 2004.
Last Revision: December 19, 2006.

Summary

Disease characteristics. Congenital fibrosis of the extraocular muscles (CFEOM) refers to at least four strabismus syndromes, CFEOM1, CFEOM2, CFEOM3, and Tukel syndrome, characterized by 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/or the trochlear nucleus and nerve (cranial nerve IV) and its innervated muscle (the superior oblique). 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 at rest and by moving their heads rather than their eyes to track objects. Individuals with Tukel syndrome also have postaxial oligodactyly or oligosyndactyly of the hands.

Diagnosis/testing. The diagnosis of CFEOM is based on ophthalmologic findings. Four phenotypes are recognized: CFEOM1, CFEOM2, CFEOM3, and Tukel syndrome. *KIF21A* mutations are associated with most familial CFEOM1 and simplex CFEOM1. Direct sequencing of exons 8, 20, and 21 of the *KIF21A* gene, which contain all mutations identified to date, detects missense mutations in 97% of individuals with the CFEOM1 phenotype. Such testing is clinically available. Testing for *PHOX2A*, the only gene known to be associated with the CFEOM2 phenotype, is available on a research basis only. The CFEOM3 phenotype has been linked to the FEOM3 locus. Tukel syndrome has been linked to the TUKLS locus.

Management. Refractive errors may be managed with glasses or contact lenses. Amblyopia can be treated effectively with occlusion or penalization of the better-seeing eye. Corneal lubrication may be helpful. Corrective eye muscle and/or ptosis surgery may be required. Surveillance is important for prevention and treatment of of amblyopia and to address complications of corneal exposure. Routine ophthalmologic care is indicated, with visits every three to four months during the first years of life, and annual or biannual examinations in older affected individuals not at risk for amblyopia.

Genetic counseling. CFEOM1 and CFEOM3 are inherited in an autosomal dominant manner. A proband with CFEOM1 or CFEOM3 may have inherited the disease-causing mutation or have a *de novo* gene mutation. Each child of an individual with CFEOM1 or CFEOM3 has a 50% chance of inheriting the condition. CFEOM2 and Tukel syndrome are inherited in an autosomal recessive manner. Parents of an individual with CFEOM2 or Tukel syndrome are obligate heterozygotes and carry one mutant allele (although *de novo* mutations are possible, none has been reported to date). Heterozygotes for CFEOM2 and Tukel syndrome are asymptomatic. At conception, each sib of an individual with CFEOM2 or Tukel syndrome has 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. Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3. Prenatal diagnosis is available for pregnancies at risk for CFEOM1 if the mutation has been identified in an affected family member. Prenatal testing for other forms of congenital fibrosis of the extraocular muscles may be available through laboratories offering custom prenatal mutation analysis for families in which the disease-causing mutation has been identified in an affected family member.

Diagnosis

Clinical Diagnosis

The term CFEOM (congenital fibrosis of the extraocular muscles) refers to at least four strabismus syndromes: CFEOM1, CFEOM2, CFEOM3, and Tukel syndrome [Doherty et al 1999, Nakano et al 2001, Yamada et al 2003, Aubourg et al 2005, Tukel et al 2005]. The syndromes are characterized by 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/or the trochlear nucleus and nerve (cranial nerve IV) and its innervated muscle (the superior oblique).

CFEOM1. CFEOM1 is the "classic" and most common form of CFEOM. Affected individuals exhibit the following:

- Congenital non-progressive bilateral external ophthalmoplegia
- Congenital non-progressive bilateral ptosis
- Primary vertical position of each eye: infraducted (downward)
- Vertical eye movements: Inability to elevate the eyes above the horizontal midline

- Primary horizontal position of each eye: normal (orthotropic), inward (esotropic), or outward (exotropic)
- Horizontal eye movements: normal to severely restricted
- Aberrant eye movements: common, especially both eyes turning inward on attempted upgaze
- Forced duction test (to assess passive movement of the globe to determine if the extraocular muscles are restricted): positive for restriction
- Binocular vision: usually absent
- Refractive errors: frequently high astigmatism
- Amblyopia: may be strabismic or refractive in nature
- Pupils: normal
- Family history: consistent with autosomal dominant inheritance; simplex cases (i.e., a single occurrence in a family) are observed

CFEOM2. Affected individuals exhibit the following:

- Congenital non-progressive bilateral external ophthalmoplegia
- Congenital non-progressive bilateral ptosis
- Primary vertical position of each eye: normal or positioned slightly above or below the midline
- Vertical eye movements: severely restricted
- Primary horizontal position of each eye: typically fixed outward (exotropic) or rarely fixed in a normal straight-ahead position (orthotropic)
- Horizontal eye movements: severely restricted
- Aberrant eye movements: small amplitude, if present
- Forced duction test: positive for restriction
- Binocular vision: absent
- Refractive errors: frequent
- Amblyopia: frequent
- Pupils: often small and sluggishly reactive to light
- Family history: consistent with autosomal recessive inheritance

CFEOM3. Affected individuals exhibit the following:

- Congenital non-progressive bilateral external ophthalmoplegia primarily affecting muscles in the oculomotor distribution (in individuals who do not meet CFEOM1 or CFEOM2 criteria)

Affected individuals may exhibit the following:

- Lid position and movement: normal or congenital non-progressive bilateral or unilateral ptosis
- Primary vertical position of each eye: downward (infraducted), normal (primary position), or upward (supraducted)

- Vertical eye movements: variable restriction with presence or absence of upgaze above the midline
- Primary horizontal position of each eye: normal (orthotropic), inward (esotropic), or outward (exotropic)
- Horizontal eye movements: Normal to severely restricted
- Aberrant eye movements: Absent or present
- Forced duction test: Positive for restriction
- Refractive errors: Absent or present
- Binocular vision: Absent or present
- Pupils: Normal
- Family history: Consistent with autosomal dominant or autosomal recessive inheritance. Note: The term "CFEOM3 pedigree" refers to a family in which all affected individuals have CFEOM3, as well as to a family in which some affected individuals have CFEOM3 and some have CFEOM1.

Tukel syndrome. Affected individuals exhibit the following:

- The CFEOM3 phenotype
- Postaxial oligodactyly or oligosyndactyly of the hands

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Genes. Two genes are known to be associated with CFEOM:

- ***KIF21A***
  - *KIF21A* mutations are associated with most familial cases of CFEOM1 that map to the FEOM1 locus and with most simplex cases (i.e., single occurrence in a family) [Yamada et al 2003, Tiab et al 2004, Traboulsi & Engle 2004, Ali et al 2004, Lin et al 2005, Shimizu et al 2005, Yamada et al 2005].
  - *KIF21A* mutations are a rare cause of CFEOM3 (CFEOM3A, OMIM 607034) [Yamada et al 2004].
  - *KIF21A* mutations in CFEOM1 and CFEOM3 are heterozygous missense changes that affect "hot-spot" amino acid residues in exons 8, 20, and 21.
- ***PHOX2A***
  - *PHOX2A* is the only gene known to be associated with the CFEOM2 phenotype [Nakano et al 2001]. To date, four homozygous mutations have been identified: two splice site mutations, one missense mutation, and one nonsense mutation [Nakano et al 2001, Yazdani et al 2003].
  - One reported CFEOM2-like pedigree does not map to the *PHOX2A* locus, but the phenotype of this family does not meet CFEOM2 criteria because the affected individuals do not have ptosis) [Traboulsi et al 2000].

Other loci

- **FEOM3.** The CFEOM3 phenotype in two large pedigrees has been mapped to the FEOM3 locus within a 5.6-cM region on chromosome 16q24.2-q24.3 [Doherty et al 1999, Mackey et al 2002]. In addition, individuals in several small CFEOM1 pedigrees that do not have *KIF21A* mutations are consistent with linkage to the FEOM3 locus [Engle et al 2002, Yamada et al 2003], suggesting that mutations in the as-yet unidentified gene at this locus may also be a rare cause of the CFEOM1 phenotype.
- **FEOM4.** A three-generation family that co-segregated CFEOM3 and a balanced/unbalanced reciprocal translocation t(2;13) (q37.3;q12.11) (CFEOM3B, OMIM 609384) permitted assignment of the FEOM4 locus to 13q27.3 [Aubourg et al 2005].
- **TUKLS.** A genome-wide linkage screen of a large consanguineous family whose affected family members have a CFEOM3 phenotype and postaxial oligodactyly/oligosyndactyly of the hands, referred to as Tukel syndrome, mapped the locus to a 1.5-Mb region on chromosome 21qter [Tukel et al 2005].

Clinical use

- Confirmatory diagnostic testing

Clinical testing

- **Sequence analysis: *KIF21A***

  CFEOM1 phenotype. Direct sequencing of exons 8, 20, and 21, which contain all mutations identified to date, identifies missense mutations in 97% (57/59) of individuals with the CFEOM1 phenotype [Yamada et al 2003, Tiab et al 2004, Traboulsi & Engle 2004, Ali et al 2004, Lin et al 2005, Shimizu et al 2005, Yamada et al 2005, Zhao et al 2005].

  CFEOM3 phenotype. Yamada et al (2004) and Lin et al (2005) identified *KIF21A* mutations in 13% of individuals with CFEOM3.

Researchtesting

- **Mutation scanning**

  KIF21A. If a mutation is not found by sequence analysis of exons 8, 20, 21, the remaining *KIF21A* exons can be screened on a research basis.

- **Sequence analysis**

  PHOX2A. To date, all reported families with the CFEOM2 phenotype are consanguineous and, with the exception of the family that does not map to the *PHOX2A* locus, all affected individuals have been found to have homozygous mutations in *PHOX2A* [Nakano et al 2001, Yazdani et al 2003].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in CFEOM

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Rate	Test Availability
KIF21A	Sequence variants	Sequence alterations in exons 8, 20, 21	97% in CFEOM1 [1] 13% in CFEOM3 [2]	Clinical Testing
	Mutation scanning	Sequence variants in remaining exons	Unknown	Research only [3]
PHOX2A	Sequence analysis	*PHOX2A* sequence variants	~100% in CFEOM2 [4]	

1. Yamada et al 2003, Ali et al 2004, Tiab et al 2004, Lin et al 2005, Shimizu et al 2005, Yamada et al 2005, Zhao et al 2005
2. Yamada et al 2004, Lin et al 2005
3. Confirmation of mutations identified under a research protocol is available on a clinic basis.
4. Nakano et al 2001, Yazdani et al 2003

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Genetically Related (Allelic) Disorders

No other phenotypes are associated with mutations in *KIF21A* or *PHOX2A*.

Clinical Description

Natural History

Congenital fibrosis of the extraocular muscles (CFEOM) refers to three strabismus syndromes, which are characterized by 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/or the trochlear nucleus and nerve (cranial nerve IV) and its innervated muscle (the superior oblique). Magnetic resonance imaging suggests that the abducens nerve and innervated muscle (the lateral rectus) may also be affected, as well as the optic nerve [Demer et al 2005].

Strabismus. Strabismus is the deviation of the position of one eye relative to the other, resulting in misalignment of the line of site of the two eyes. Individuals with CFEOM typically 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 brainstem, nerve, or muscle. The primary 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.

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. Ptosis is the drooping of the upper eyelid as a result of dysfunction of the levator palpabrae 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. Refractive errors are common.

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

CNS malformations. Some individuals with CFEOM have been reported to have central nervous system malformations, including agenesis of the corpus callosum, brain stem atrophy, cerebellar hemisphere atrophy, absence of the cerebral peduncle in the midbrain, colpocephaly, hypoplasia of the cerebellar vermis, expansion of the ventricular system, pachygyria, encephalocele and/or hydrancephaly [Pieh et al 2003, Harissi-Dagher et al 2004]. The CFEOM phenotype in most of these cases is atypical and meets the criteria of CFEOM3.

Marcus Gunn phenomenon and other evidence of misinnervation. *KIF21A* mutations have been reported in individuals with CFEOM1 and Marcus Gunn jaw winking phenomenon, hypertropia during tooth brushing, and facial weakness [Pieh et al 2003, Yamada et al 2005]. The Marcus Gunn jaw winking phenomenon manifests as the momentary elevation of a ptotic upper eyelid with specific movements of the jaw. It is also first noted in young infants when they are feeding. It 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 this phenomenon with CFEOM provides additional evidence that these syndromes are primarily neurogenic in cause [Brodsky 1998, Pieh et al 2003].

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.

Genotype-Phenotype Correlations

Each form of CFEOM has a defined phenotype.

KIF21A. The *KIF21A* mutations underlying CFEOM1 and rare cases of CFEOM3 alter only a few amino acids; in particular, the mutations alter amino acids in the third coiled-coil domain of the stalk and one amino acid in the distal motor domain. Clinical examinations and high-resolution orbital MR imaging of individuals with CFEOM1 resulting from several of these different specific *KIF21A* mutations, however, did not reveal a correlation between any specific mutation and clinical phenotype [Yamada et al 2003, Demer et al 2005].

PHOX2A. No correlation between specific *PHOX2A* mutations and the CFEOM2 phenotoype have been found. CFEOM2-causing mutations in *PHOX2A* all likely result in complete loss of function of paired mesoderm homeobox protein 2A [Nakano et al 2001, Bosley et al 2006].

Penetrance

Penetrance in CFEOM1 and CFEOM2 is complete.

Penetrance in CFEOM3 can be incomplete and is estimated to be 90% [Doherty et al 1999].

Nomenclature

Although long felt to result from primary fibrosis of the extraocular muscles, neuroanatomic [Engle et al 1997] and genetic [Nakano et al 2001, Yamada et al 2003, Demer et al 2005, Kim & Hwang 2005, Bosley et al 2006] findings suggest that the various forms of CFEOM result from abnormal development of oculomotor and/or trochlear nuclei and nerves. The suggestion

is supported by clinical and imaging studies and by what is known about *KIF21A* and *PHOX2A* gene function.

Prevalence

A minimum prevalence of CFEOM is 1/230,000 [Reck et al 1998].

CFEOM1 and CFEOM3 familial and simplex cases have been identified worldwide.

The few individuals reported with CFEOM2 have been offspring of consanguineous unions within Saudi, Turkish, and Iranian families [Traboulsi & Engle 2004].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

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.

The following conditions can be confused with CFEOM:

Brown syndrome ('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. Rare familial cases have been reported [Iannaccone et al 2002].

Duane syndrome (OMIM 126800) is characterized by horizontal eye movement limitation, narrowing of the palpebral fissure on attempted side gaze (usually adduction), and retraction of the globe 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 Duane syndrome with or without accompanying anomalies have been reported:

- An autosomal dominant locus for Duane syndrome has been mapped by linkage to 2q31 (DURS2, OMIM 604356).
- A contiguous gene deletion syndrome with Duane syndrome is located on 8q13 (DURS1, OMIM 126800).
- Duane-radial ray syndrome (DRRS) (Okihiro syndrome) results from mutations in *SALL4* (OMIM 607323) [Al-Baradie et al 2002, Kohlhase et al 2002]. DRRS is characterized by uni- or bilateral Duane anomaly and radial ray malformation that can include thenar hypoplasia and/or hypoplasia or aplasia of the thumbs; hypoplasia or aplasia of the radii; shortening and radial deviation of the forearms; triphalangeal thumbs; and duplication of the thumb (preaxial polydactyly). DRRS and acro-renal-ocular syndrome are autosomal dominant disorders caused by mutations in *SALL4*. Acro-renal-ocular syndrome is characterized by radial ray malformations, renal abnormalities (mild malrotation, ectopia, horseshoe kidney, renal hypoplasia, vesicoureteral reflux, bladder diverticula), ocular coloboma, and Duane anomaly. Additional clinical features include sensorineural and/or conductive deafness.

- Athabaskan brainstem dysgenesis syndrome (ABDS) [Holve et al 2003] and Bosley-Salih-Alorainy syndrome (BSAS) [Tischfield et al 2005] (OMIM 601536) are autosomal recessive disorders that result from mutations in *HOXA1* [Tischfield et al 2005]. They are characterized by Duane syndrome type III or horizontal gaze palsy and, in most individuals, bilateral sensorineural hearing loss caused by absent cochlea and rudimentary inner ear development. Depending upon the specific syndrome (ABDS vs. BSAS), a subset of individuals manifest mental retardation, autism, moderate to severe central hypoventilation, facial weakness, swallowing difficulties, vocal cord paresis, conotruncal heart defects, and skull and craniofacial abnormalities.

Chronic progressive external ophthalmoplegia (CPEO) is characterized by chronic progressive loss of extraocular eye movements and ptosis.

Mitochondrial DNA deletion syndromes comprise three overlapping phenotypes, which may be observed in different members of the same family or may evolve in a given individual over time. The three phenotypes are: Kearns-Sayre syndrome (KSS), Pearson syndrome, and progressive external ophthalmoplegia (PEO). These syndromes are caused by mtDNA deletions ranging in size from two to ten kilobases.

- **KSS** is defined by the triad of onset before age 20 years, pigmentary retinopathy, and PEO. Individuals additionally have at least one of the following: cardiac conduction block, cerebrospinal fluid protein concentration greater than 100 mg/dL, or cerebellar ataxia. Approximately 90% of individuals with KSS have a large-scale (i.e., 1.3-10 kb) mtDNA deletion that is usually present in all tissues; however, mutant mtDNA is often undetectable in blood cells, necessitating examination of muscle.
- **Pearson syndrome** is characterized by sideroblastic anemia and exocrine pancreas dysfunction. In Pearson syndrome, mtDNA deletions are usually more abundant in blood than in other tissues.
- **PEO** is characterized by progressive ptosis, paralysis of the extraocular muscles (ophthalmoplegia), and variably severe proximal limb weakness.

Other disorders associated with ophthalmoplegia include (with distinguishing features):

- Myasthenia gravis (fluctuating weakness and diplopia); see Congenital Myasthenic Syndromes
- Oculopharyngeal muscular dystrophy (late-onset severe dysphagia, autosomal dominant inheritance; caused by an expansion of a GCG trinucleotide repeat in the first exon of the polyadenylate binding protein nuclear 1 gene *PABPN1*)
- Myotonic dystrophy type 1 (myotonia, autosomal dominant inheritance; caused by expansion of a CTG trinucleotide repeat in the gene *DMPK*)
- Mendelian PEOs associated with multiple deletions of mtDNA caused by mutations in the nuclear genes *SLC25A4*, *PEO1*, *POLG*, and *TMPO* (autosomal dominant or recessive inheritance; affective disorders, gastrointestinal dysmotility)
- Maternally inherited PEOs caused by various mtDNA mutations

Cranial nerve III and IV palsy. Few reports of congenital familial third-nerve palsy or fourth-nerve palsy exist. The etiologies of these disorders are unknown.

Horizontal gaze palsy with progressive scoliosis (HGPPS) (OMIM 607313) is characterized by congenital horizontal gaze palsy (no horizontal eye movements) with progressive scoliosis inherited in an autosomal recessive manner and caused by mutations in *ROBO3* [Jen et al 2004]. Compound heterozygous *ROBO3* mutations have also been identified in children of

nonconsanguineous parents [Chan et al 2006]. Results of neuroimaging and neurophysiology studies undertaken on individuals with HGPPS found that the axons that make up the major motor and sensory pathways for communication between the brain and the body fail to cross the midline in the hindbrain [Jen et al 2004, Bosley et al 2005].

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 are associated with developmental defects of additional lower cranial nerves and distal extremities.
- Moebius sequence has also been reported in association with congenital non-progressive myopathy and Robin sequence (OMIM 254940)

Hereditary congenital facial paresis, the isolated dysfunction of the facial nerve, maps to chromosome 3q (locus name HCFP1) (OMIM 601471) and chromosome 10q (locus name HCFP2) (OMIM 604185).

Other. CFEOM has been identified in a single case of Noonan syndrome [Elgohary et al 2005.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- Family history
- Ophthalmologic examination
  - Determination of primary gaze position, head position with eyes in primary position, and vertical and horizontal gaze restrictions
  - Evaluation for aberrant movements including synergistic convergence and divergence, globe retraction, Marcus Gunn jaw wink
  - Palpebral fissure size measurement
  - Anterior segment evaluation to detect corneal exposure
  - Levator function testing
  - Optional forced duction testing
- Photographic documentation for future comparison
- Strongly recommended if surgery is planned:
  - MRI or scan to determine orbital anatomy (muscles and nerves)
  - Orbital MRI to detect aplasia of extraocular muscle(s) and defects in the size and/or course of the oculomotor and trochlear nerves

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.

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
- Principles of surgical approach:
  - Orbital imaging is recommended before surgery to assess muscle size and position.
  - Resections tend to be ineffective.
  - Surgery may be technically difficult because of tightness of rectus muscles.
  - Recessions need to be larger than indicated by standard tables.
  - Adjustable sutures allow "supramaximal" recession.
  - Profound weakening procedures (such as suturing muscle to orbital rim) may be necessary.
  - Botulinum toxin may be helpful for residual misalignment in some cases.
- Improvement of ambulation and gross motor development in young children

Prevention of Secondary Complications

- Amblyopia therapy to prevent vision loss in the less-preferred eye
- Eye lubrication to avoid dry eyes, particularly following ptosis surgery but also after successful strabismus surgery in some cases
- Surgical repositioning of the eyes and lids to help correct head position and alleviate secondary musculoskeletal complications from chronic head turn

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.

Testing of Relatives at Risk

CFEOM can often be diagnosed on clinical findings within the first months of life; early diagnosis can result in prevention of secondary complications.

Because of variable expression, examination of family members may provide early diagnosis of risk factors for amblyopia in mild cases that might otherwise go undetected.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

CFEOM1 and CFEOM3 are inherited in an autosomal dominant manner. CFEOM2 and Tukel syndrome are inherited in an autosomal recessive manner.

Risk to Family Members - Autosomal Dominant Inheritance (CFEOM1 and CFEOM3)

Parents of a proband

- Some individuals diagnosed with CFEOM1 or CFEOM3 have an affected parent.
- A proband with CFEOM1 may have the disorder as the result of a *de novo* gene mutation. In a study of 45 families and 13 simplex cases (i.e., a single occurrence of the CFEOM1 in a family), five and seven *de novo* mutations respectively were identified, suggesting that *de novo* mutations may be particularly common in simplex cases [Yamada et al 2003].
- A proband with CFEOM3 may have the disorder as the result of a *de novo* gene mutation. The proportion of cases caused by *de novo* mutations is not known.
- Recommendations for the evaluation of parents of a proband with CFEOM1 and an apparent *de novo* mutation include ophthalmologic examinations and consideration of molecular genetic testing for the *KIF21A* mutation if one has been identified in the proband.

Note: Although some individuals diagnosed with CFEOM3 have an affected parent, the family history may appear to be negative because of reduced penetrance in CFEOM3.

Sibs of a proband

- **CFEOM1**
  - The risk to sibs of a proband with CFEOM1 depends on the genetic status of the proband's parents.
  - If a parent of the proband is affected, the risk to each sib is 50%.
  - When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
  - If a disease-causing mutation cannot be detected in the DNA of either parent, two possible explanations are germline mosaicism in a parent or a *de novo*

mutation in the proband. Although no instances of germline mosaicism have been reported, it remains a possibility.

- **CFEOM3**
  - The risk to the sibs of a proband with CFEOM3 depends upon the clinical status of the proband's parents and the penetrance of the mutation.
  - If a parent of the proband is affected, the risk to each sib of inheriting the mutation is 50%. The penetrance in CFEOM3 appears to be approximately 90% [Doherty et al 1999].
  - When the parents are clinically unaffected, the risk to the sibs of a proband cannot be accurately determined.

Offspring of a proband. Each child of an individual with CFEOM1 or CFEOM3 has a 50% chance of inheriting the mutation.

Other family members of a proband. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Risk to Family Members - Autosomal Recessive Inheritance (CFEOM2 and Tukel syndrome)

This section is written from the perspective that molecular genetic testing for this disorder is available on a research basis only and results should not be used for clinical purposes. This perspective may not apply to families using custom mutation analysis. —ED.

Parents of a proband

- The parents of an individual with CFEOM2 or Tukel syndrome are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.
- One or two families with two-generation involvement have been reported. Referred to as pseudodominant inheritance, two-generation involvement can occur in autosomal recessive disorders when a parent (who has two disease-causing alleles) is affected and his/her reproductive partner is a carrier.

Sibs of a proband

- At conception, each sib of an individual with CFEOM2 or Tukel syndrome has 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.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with CFEOM2 or Tukel syndrome are obligate heterozygotes (carriers) for a disease-causing mutation.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier of a disease-causing mutation.

Carrier Detection

Carrier testing using molecular genetic techniques is not clinically available for either CFEOM3 or Tukel syndrome.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk is before pregnancy.

DNA banking. 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which molecular genetic testing is available on a research basis only or the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

No laboratories offering molecular genetic testing for prenatal diagnosis of other forms of CFEOM or Tukel syndrome are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutations have been identified in an affected family member in a research or clinical laboratory. For laboratories offering custom prenatal testing, see Testing.

Requests for prenatal testing for conditions such as CFEOM are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation(s) has/have been identified in an affected family member. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Congenital Fibrosis of the Extraocular Muscles

Locus Name	Gene Symbol	Chromosomal Locus	Protein Name
FEOM1	*KIF21A*	12q12	Kinesin family member 21A
FEOM2	*PHOX2A*	11q13.3-q13.4	Paired mesoderm homeobox protein 2A
FEOM3	Unknown	16q24.2-q24.3	Unknown
FEOM4	Unknown	13q12	Unknown
TUKLS	Unknown	21q22	Unknown

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Congenital Fibrosis of the Extraocular Muscles

135700	FIBROSIS OF EXTRAOCULAR MUSCLES, CONGENITAL, 1; CFEOM1
600638	FIBROSIS OF EXTRAOCULAR MUSCLES, CONGENITAL, TYPE 3; CFEOM3
602078	FIBROSIS OF EXTRAOCULAR MUSCLES, CONGENITAL, 2; CFEOM2
602753	ARISTALESS HOMEOBOX, DROSOPHILA, HOMOLOG OF; ARIX
608283	KINESIN FAMILY MEMBER 21A; KIF21A
609384	FIBROSIS OF EXTRAOCULAR MUSCLES, CONGENITAL, 3B; CFEOM3B
609428	TUKEL SYNDROME

Table C. Genomic Databases for Congenital Fibrosis of the Extraocular Muscles

Locus Name	Gene Symbol	Entrez Gene	HGMD
FEOM1	*KIF21A*	55605 (MIM No. 608283)	KIF21A
FEOM2	*PHOX2A*	401 (MIM No. 602753)	PHOX2A
FEOM3	Unknown	26176 (MIM No. 600638)	
FEOM4	Unknown		
TUKLS	Unknown	574049 (MIM No. 609428)	

For a description of the genomic databases listed, click here.

Molecular Genetic Pathogenesis

KIF21A. *KIF21A* is a member of the kinesin family of molecular motors and has a predicted structure similar to classic kinesin [Marszalek et al 1999] with an N-terminal motor domain that interacts with the microtubule track, a central coiled-coil stalk, and a C-terminal tail that loads or interacts with transported cargo. Among the 45 human and mouse kinesins, *KIF21A* is only one of two kinesins that contain a WD40 domain (known to assemble a stable platform that facilitates several protein interactions) at its C terminal tail. It is hypothesized that CFEOM1 results from mutations in *KIF21A* that affect either the dynamics of cargo binding or the ability of mutated *KIF21A* to deliver cargo necessary for oculomotor axonal, extraocular muscle, or neuromuscular junction development [Yamada et al 2003].

PHOX2A (ARIX). *PHOX2A* is a homeodomain transcription factor protein that plays a primary role in the oculomotor and trochlear alpha motor neuron development in mice and zebrafish [Pattyn et al 1997, Guo et al 1999]. It is predicted that CFEOM2 results from aberrant development of these motor nuclei [Nakano et al 2001]. Morin et al (1997) demonstrated that *Phox2a* -/- mice completely lacked a locus coeruleus, the main noradrenergic center of the brain. Furthermore, parasympathetic ganglia in the head are missing, and the superior cervical ganglion, as well as cranial sensory ganglia that normally express *Phox2a*, are severely affected. Homologous genes include *PHOX2B(PMX2B*). Mutations in *PHOX2B* cause congenital central hypoventilation syndrome (CCHS) [Amiel et al 2003].

***KIF21A*—Normal allelic variants:** The normal cDNA comprises 5,022 bp in 38 exons with alternative splicing of exon 12 and exons 29-31. Genomic length is approximately 150 kb [Yamada et al 2003].

Pathologic allelic variants: Seven different heterozygous missense mutations in three of the 38 exons of *KIF21A* have been identified in individuals with CFEOM1 [Yamada et al 2003, Ali et al 2004, Tiab et al 2004, Lin et al 2005, Shimizu et al 2005] and an eighth missense

mutation identified in one CFEOM3 pedigree [Yamada et al 2004]. Notably, 70% of the 56 probands have the identical mutation, a 2860C>T transition resulting in R954W. Seven of these *KIF21A* mutations alter only three amino-acid residues, each located in the 'a' position of a heptad repeat within an alpha helical coiled-coil region of the *KIF21A* stalk. The eighth mutation is located in the motor domain. Haplotype analysis demonstrated that five *de novo* mutations found in autosomal dominant CFEOM1 pedigrees all arose exclusively on the paternal allele [Yamada et al 2003].

Normal gene product: The predicted protein, kinesin family member 21A (KIF21A) is 1674 amino acids and comprises three domains (characteristic of the kinesin superfamily): an N-terminal head motor domain, a coiled-coil stalk region, and a C-terminal tail. The C terminal tail of KIF21A contains seven WD40 repeats that are found in only one other kinesin family member. It is suggested that KIF21A protein in humans is essential for delivery of cargo necessary for oculomotor axonal, extraocular muscle or neuromuscular junction development [Yamada et al 2003].

Northern and western blot analysis of *Kif21a* in mouse indicates that the mRNA and protein is expressed early during development and first detected around embryonic day E9.5. Expression analysis of *Kif21a* in adult mouse tissues indicates highest protein expression in the brain and moderate levels in the kidney, testes, and skeletal muscle [Marszalek et al 1999]. Kif21a protein is found in all regions of the adult CNS examined including the cortex, cerebellum, brain stem, olfactory bulb, and spinal cord [Marszalek et al 1999]. As opposed to the restricted dendritic expression of Kif21b, Kif21a protein is detected in the neuronal cell body, axon, and dendrites [Marszalek et al 1999]. Biochemical characterization of Kif21a has demonstrated that it can strongly bind microtubles in the presence of nonhydrolyzable ATP analogue and behaves as plus end-directed motor in in vitro mobility assays [Marszalek et al 1999]. In addition, differential centrifugation experiments demonstrated that Kif21a does not associate with membranous vesicles and is thought to interact with the insoluble cytoskeleton or a large protein complex [Marszalek et al 1999].

Abnormal gene product: The position and recurrence of *KIF21A* mutations suggests that the CFEOM1-causing mutations may have a dominant-negative effect by interfering with the interaction between *KIF21A* and its unidentified binding partners [Yamada et al 2003].

***PHOX2A*—Normal allelic variants:** The gene contains three exons. The genomic length is about 5 kb [Nakano et al 2001].

Pathologic allelic variants: Four different homozygous *PHOX2A* mutations have been identified in five families with CFEOM2. Two mutations are single base substitutions (one missense and one nonsense) and two are splice-site mutations [Nakano et al 2001, Yazdani et al 2003].

Normal gene product: The gene product is a transcription factor protein containing a homeodomain and brachyury-like motif. The protein is essential for development of the oculomotor and trochlear alpha motor neurons in mice and zebrafish.

Abnormal gene product: It is predicted that most mutations in *PHOX2A* lead to the truncation of the protein and are therefore thought to cause a lack of function.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current

as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Eye Simulator/Virtual Patient Simulator
This application provides an eye motion and pupil response simulator, animations to demonstrate neurological testing, and quizzes to test comprehension. It also provides a set of patient cases with various neurological pathologies.
http://cim.ucdavis.edu/EyeRelease/Interface/TopFrame.htm

AboutFace International
123 Edward Street Suite 1003
Toronto Ontario
Canada M5G 1E2
Phone: 800-665-FACE (800-665-3223)
Fax: 416-597-8494
Email: info@aboutfaceinternational.org
www.aboutfaceinternational.org

National Eye Institute
2020 Vision Place
Bethesda MD 20892-3655
Phone: 301-496-5248
Email: kcl@nei.nih.gov
www.nei.nih.gov

Prevent Blindness America
211 West Wacker Drive Suite 1700
Chicago Illinois 60606
Phone: 800-331-2020
Email: info@preventblindness.org
www.preventblindness.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Al-Baradie R, Yamada K, St Hilaire C, Chan WM, Andrews C, McIntosh N, Nakano M, Martonyi EJ, Raymond WR, Okumura S, Okihiro MM, Engle EC. Duane radial ray syndrome (Okihiro syndrome) maps to 20q13 and results from mutations in SALL4, a new member of the SAL family. Am J Hum Genet. 2002;71:1195–9. [PubMed: 12395297]

Ali M, Venkatesh C, Ragunath A, Kumar A. Mutation analysis of the KIF21A gene in an Indian family with CFEOM1: implication of CpG methylation for most frequent mutations. Ophthalmic Genet. 2004;25:247–55. [PubMed: 15621877]

Amiel J, Laudier B, Attie-Bitach T, Trang H, de Pontual L, Gener B, Trochet D, Etchevers H, Ray P, Simonneau M, Vekemans M, Munnich A, Gaultier C, Lyonnet S. Polyalanine expansion and frameshift mutations of the paired-like homeobox gene PHOX2B in congenital central hypoventilation syndrome. Nat Genet. 2003;33:459–61. [PubMed: 12640453]

Aubourg P, Krahn M, Bernard R, Nguyen K, Forzano O, Boccaccio I, Delague V, De Sandre-Giovannoli A, Pouget J, Depetris D, Mattei MG, Philip N, Levy N. Assignment of a new congenital fibrosis of extraocular muscles type 3 (CFEOM3) locus, FEOM4, based on a balanced translocation t(2;13)(q37.3;q12.11) and identification of candidate genes. J Med Genet. 2005;42:253–9. [PubMed: 15744040]

Bosley TM, Oystreck DT, Robertson RL, al Awad A, Abu-Amero K, Engle EC. Neurological features of congenital fibrosis of the extraocular muscles type 2 with mutations in PHOX2A. Brain. 2006;129:2363–74. [PubMed: 16815872]

Bosley TM, Salih MA, Jen JC, Lin DD, Oystreck D, Abu-Amero KK, MacDonald DB, al Zayed Z, al Dhalaan H, Kansu T, Stigsby B, Baloh RW. Neurologic features of horizontal gaze palsy and progressive scoliosis with mutations in ROBO3. Neurology. 2005;64:1196–203. [PubMed: 15824346]

Brodsky MC. Hereditary external ophthalmoplegia synergistic divergence, jaw winking, and oculocutaneous hypopigmentation: a congenital fibrosis syndrome caused by deficient innervation to extraocular muscles. Ophthalmology. 1998;105:717–25. [PubMed: 9544647]

Chan WM, Traboulsi EI, Arthur B, Friedman N, Andrews C, Engle EC. Horizontal gaze palsy with progressive scoliosis can result from compound heterozygous mutations in ROBO3. J Med Genet. 2006;43:e11. [PubMed: 16525029]

Demer JL, Clark RA, Engle EC. Magnetic resonance imaging evidence for widespread orbital dysinnervation in congenital fibrosis of extraocular muscles due to mutations in KIF21A. Invest Ophthalmol Vis Sci. 2005;46:530–9. [PubMed: 15671279]

Doherty EJ, Macy ME, Wang SM, Dykeman CP, Melanson MT, Engle EC. CFEOM3: a new extraocular congenital fibrosis syndrome that maps to 16q24.2-q24.3. Invest Ophthalmol Vis Sci. 1999;40:1687–94. [PubMed: 10393037]

Elgohary MA, Bradshaw P, Ahmad N. Anterior uveitis and congenital fibrosis of the extraocular muscles in a patient with Noonan syndrome. J Postgrad Med. 2005;51:319–21. [PubMed: 16388177]

Engle EC, Goumnerov BC, McKeown CA, Schatz M, Johns DR, Porter JD, Beggs AH. Oculomotor nerve and muscle abnormalities in congenital fibrosis of the extraocular muscles. Ann Neurol. 1997;41:314–25. [PubMed: 9066352]

Engle EC, McIntosh N, Yamada K, Lee BA, Johnson R, O'Keefe M, Letson R, London A, Ballard E, Ruttum M, Matsumoto N, Saito N, Collins M, Morris L, Monte M, Magli A, de Berardinis T. CFEOM1, the classic familial form of congenital fibrosis of the extraocular muscles, is genetically heterogeneous but does not result from mutations in ARIX. BMC Genet. 2002;3:3. [PubMed: 11882252]

Guo S, Brush J, Teraoka H, Goddard A, Wilson SW, Mullins MC, Rosenthal A. Development of noradrenergic neurons in the zebrafish hindbrain requires BMP, FGF8, and the homeodomain protein soulless/Phox2a. Neuron. 1999;24:555–66. [PubMed: 10595509]

Gutowski NJ, Bosley TM, Engle EC. 110th ENMC International Workshop: the congenital cranial dysinnervation disorders (CCDDs). Naarden, The Netherlands, 25-27 October, 2002. Neuromuscul Disord. 2003;13:573–8. [PubMed: 12921795]

Harissi-Dagher M, Dagher JH, Aroichane M. Congenital fibrosis of the extraocular muscles with brain-stem abnormalities: a novel finding. Can J Ophthalmol. 2004;39:540–5. [PubMed: 15491041]

Holve S, Friedman B, Hoyme HE, Tarby TJ, Johnstone SJ, Erickson RP, Clericuzio CL, Cunniff C. Athabascan brainstem dysgenesis syndrome. Am J Med Genet A. 2003;120:169–73. [PubMed: 12833395]

Iannaccone A, McIntosh N, Ciccarelli ML, Baldi A, Mutolo PA, Tedesco SA, Engle EC. Familial unilateral Brown syndrome. Ophthalmic Genet. 2002;23:175–84. [PubMed: 12324876]

Jen JC, Chan WM, Bosley TM, Wan J, Carr JR, Rub U, Shattuck D, Salamon G, Kudo LC, Ou J, Lin DD, Salih MA, Kansu T, Al Dhalaan H, Al Zayed Z, MacDonald DB, Stigsby B, Plaitakis A, Dretakis EK, Gottlob I, Pieh C, Traboulsi EI, Wang Q, Wang L, Andrews C, Yamada K, Demer JL, Karim S, Alger JR, Geschwind DH, Deller T, Sicotte NL, Nelson SF, Baloh RW, Engle EC. Mutations in a human ROBO gene disrupt hindbrain axon pathway crossing and morphogenesis. Science. 2004;304:1509–13. [PubMed: 15105459]

Kim JH, Hwang JM. Hypoplastic oculomotor nerve and absent abducens nerve in congenital fibrosis syndrome and synergistic divergence with magnetic resonance imaging. Ophthalmology. 2005;112:728–32. [PubMed: 15808269]

Kohlhase J, Heinrich M, Schubert L, Liebers M, Kispert A, Laccone F, Turnpenny P, Winter RM, Reardon W. Okihiro syndrome is caused by SALL4 mutations. Hum Mol Genet. 2002;11:2979–87. [PubMed: 12393809]

Lin LK, Chien YH, Wu JY, Wang AH, Chiang SC, Hwu WL. KIF21A gene c.2860C>T mutation in congenital fibrosis of extraocular muscles type 1 and 3. Mol Vis. 2005;11:245–8. [PubMed: 15827546]

Mackey DA, Chan WM, Chan C, Gillies WE, Brooks AM, O'Day J, Engle EC. Congenital fibrosis of the vertically acting extraocular muscles maps to the FEOM3 locus. Hum Genet. 2002;110:510–2. [PubMed: 12073023]

Marszalek JR, Weiner JA, Farlow SJ, Chun J, Goldstein LS. Novel dendritic kinesin sorting identified by different process targeting of two related kinesins: KIF21A and KIF21B. J Cell Biol. 1999;145:469–79. [PubMed: 10225949]

Morin X, Cremer H, Hirsch MR, Kapur RP, Goridis C, Brunet JF. Defects in sensory and autonomic ganglia and absence of locus coeruleus in mice deficient for the homeobox gene Phox2a. Neuron. 1997;18:411–23. [PubMed: 9115735]

Nakano M, Yamada K, Fain J, Sener EC, Selleck CJ, Awad AH, Zwaan J, Mullaney PB, Bosley TM, Engle EC. Homozygous mutations in ARIX(PHOX2A) result in congenital fibrosis of the extraocular muscles type 2. Nat Genet. 2001;29:315–20. [PubMed: 11600883]

Pattyn A, Morin X, Cremer H, Goridis C, Brunet JF. Expression and interactions of the two closely related homeobox genes Phox2a and Phox2b during neurogenesis. Development. 1997;124:4065–75. [PubMed: 9374403]

Pieh C, Goebel HH, Engle EC, Gottlob I. Congenital fibrosis syndrome associated with central nervous system abnormalities. Graefes Arch Clin Exp Ophthalmol. 2003;241:546–53. [PubMed: 12819981]

Reck AC, Manners R, Hatchwell E. Phenotypic heterogeneity may occur in congenital fibrosis of the extraocular muscles. Br J Ophthalmol. 1998;82:676–9. [PubMed: 9797671]

Shimizu S, Okinaga A, Maruo T. Recurrent mutation of the KIF21A gene in Japanese patients with congenital fibrosis of the extraocular muscles. Jpn J Ophthalmol. 2005;49:443–7. [PubMed: 16365788]

Tiab L, d'Alleves Manzi V, Borruat FX, Munier F, Schorderet D. Mutation analysis of KIF21A in congenital fibrosis of the extraocular muscles (CFEOM) patients. Ophthalmic Genet. 2004;25:241–6. [PubMed: 15621876]

Tischfield MA, Bosley TM, Salih MA, Alorainy IA, Sener EC, Nester MJ, Oystreck DT, Chan WM, Andrews C, Erickson RP, Engle EC. Homozygous HOXA1 mutations disrupt human brainstem, inner ear, cardiovascular and cognitive development. Nat Genet. 2005;37:1035–7. [PubMed: 16155570]

Traboulsi E, Engle E. Mutations in KIF21A are responsible for CFEOM1 worldwide. Ophthalmic Genet. 2004;25:237–9. [PubMed: 15621875]

Traboulsi EI, Lee BA, Mousawi A, Khamis AR, Engle EC. Evidence of genetic heterogeneity in autosomal recessive congenital fibrosis of the extraocular muscles. Am J Ophthalmol. 2000;129:658–62. [PubMed: 10844060]

Tukel T, Uzumcu A, Gezer A, Kayserili H, Yuksel-Apak M, Uyguner O, Gultekin SH, Hennies HC, Nurnberg P, Desnick RJ, Wollnik B. A new syndrome, congenital extraocular muscle fibrosis with ulnar hand anomalies, maps to chromosome 21qter. J Med Genet. 2005;42:408–15. [PubMed: 15863670]

Yamada K, Andrews C, Chan WM, McKeown CA, Magli A, de Berardinis T, Loewenstein A, Lazar M, O'Keefe M, Letson R, London A, Ruttum M, Matsumoto N, Saito N, Morris L, Del Monte M, Johnson RH, Uyama E, Houtman WA, de Vries B, Carlow TJ, Hart BL, Krawiecki N, Shoffner J, Vogel MC, Katowitz J, Goldstein SM, Levin AV, Sener EC, Ozturk BT, Akarsu AN, Brodsky MC, Hanisch F, Cruse RP, Zubcov AA, Robb RM, Roggenkaemper P, Gottlob I, Kowal L, Battu R, Traboulsi EI, Franceschini P, Newlin A, Demer JL, Engle EC. Heterozygous mutations of the kinesin KIF21A in

congenital fibrosis of the extraocular muscles type 1 (CFEOM1). Nat Genet. 2003;35:318–21. [PubMed: 14595441]

Yamada K, Chan WM, Andrews C, Bosley TM, Sener EC, Zwaan JT, Mullaney PB, Ozturk BT, Akarsu AN, Sabol LJ, Demer JL, Sullivan TJ, Gottlob I, Roggenkaemper P, Mackey DA, De Uzcategui CE, Uzcategui N, Ben-Zeev B, Traboulsi EI, Magli A, de Berardinis T, Gagliardi V, Awasthi-Patney S, Vogel MC, Rizzo JF III, Engle EC. Identification of KIF21A mutations as a rare cause of congenital fibrosis of the extraocular muscles type 3 (CFEOM3). Invest Ophthalmol Vis Sci. 2004;45:2218–23. [PubMed: 15223798]

Yamada K, Hunter DG, Andrews C, Engle EC. A novel KIF21A mutation in a patient with congenital fibrosis of the extraocular muscles and Marcus Gunn jaw-winking phenomenon. Arch Ophthalmol. 2005;123:1254–9. [PubMed: 16157808]

Yazdani A, Chung DC, Abbaszadegan MR, Al-Khayer K, Chan WM, Yazdani M, Ghodsi K, Engle EC, Traboulsi EI. A novel PHOX2A/ARIX mutation in an Iranian family with congenital fibrosis of extraocular muscles type 2 (CFEOM2). Am J Ophthalmol. 2003;136:861–5. [PubMed: 14597037]

Yazdani A, Traboulsi EI. Classification and surgical management of patients with familial and sporadic forms of congenital fibrosis of the extraocular muscles. Ophthalmology. 2004;111:1035–42. [PubMed: 15121385]

Zhao C, Lu SS, Li ND, Chen WY, Zhao KX. [The clinical manifestation and linkage analysis in one Chinese family with congenital fibrosis of extraocular muscles] Zhonghua Yan Ke Za Zhi. 2005;41:594–9. [PubMed: 16080892]

Suggested Readings

Traboulsi EI. Congenital abnormalities of cranial nerve development: overview, molecular mechanisms, and further evidence of heterogeneity and complexity of syndromes with congenital limitation of eye movements. Trans Am Ophthalmol Soc. 2004;102:373–89. [PubMed: 15747768]

Chapter Notes

Author Notes

Dr. Engle's Web sites:
www.childrenshospital.org/research/mrrc/index.htm
www.childrenshospital.org/research/mrrc/investigators/engle/index.html

Engle Laboratory
Division of Genetics, Children's Hospital Boston
Caroline Andrews, Research Study Coordinator
candrews@enders.tch.harvard.edu
www.childrenshospital.org/research/engle

Author History

Caroline Andrews, MSc (2004-present)
Jigar Desai, PhD (2006-present)
Elizabeth C Engle, MD (2004-present)
David G Hunter, MD, PhD (2006-present)
Koki Yamada, MD, PhD; Children's Hospital Boston (2004-2006)

Revision History

- 19 December 2006 (cd) Revision: prenatal diagnosis available for CFEOM1
- 22 September 2006 (me) Comprehensive update posted to live Web site
- 27 April 2004 (me) Review posted to live Web site
- 7 January 2004 (ee) Original submission