Fibrosis of Extraocular Muscles, Congenital, 1

Alternative Names
CFEOM1
Ophthalmoplegia, Congenital
Blepharoptosis with Absent Eye Movements
FEOM1 Locus
Fibrosis of Extraocular Muscles, Congenital, 3B
CFEOM3B

Record Category
Disease phenotype

WHO-ICD
Diseases of the eye and adnexa > Disorders of ocular muscles, binocular movement, accommodation and refraction

Incidence per 100,000 Live Births
0-1

OMIM Number
135700

Mode of Inheritance
Autosomal dominant

Gene Map Locus
12q12

Description
Congenital fibrosis of the extraocular muscles (CFEOM) is a heterogeneous non-progressive eye movement disorder, which results from the dysfunction of all or part of the oculomotor nerve (cranial nerve III) and/or the muscles this cranial nerve innervates. CFEOM is characterized by a variable restrictive external ophthalmoplegia, ptosis and eyes that are fixed in an abnormal position. The classification of CFEOM is based on clinical manifestations and genetic classification is based on molecular analysis. To date, there are seven forms and four genetic loci for CFEOM. CFEOM1, CFEOM2, CFEOM3 and Tukel syndrome have been mapped, and mutations in KIF21A and PHOX2A have been found to cause CFEOM1 and CFEOM2, respectively.

CFEOM1 is the most common form of the condition affecting at least 1 in 230,000 people worldwide. It is inherited as an autosomal dominant pattern, characterized by bilateral ptosis, ophthalmoplegia, and hypotropic eyes with chin up position. Affected patients may require a stepwise surgical approach to correct strabismus and eyelid position.

Molecular Genetics
CFEOM1 has been found to be due to mutation in the KIF21A gene, which encodes a kinesin motor protein involved in the anterograde transport of cargo along the cellular cytoskeleton of microtubules, and is likely to be essential in the normal development of cranial nerve III, which emerges from the brain and controls muscles that raise the eyes and eyelids.

Epidemiology in the Arab World
Saudi Arabia
Khan et al. (2008) reported two unrelated Saudi families with congenital fibrosis of the extraocular muscles type 1. All affected patients (one child from family A and four adults from family B) had ptosis, hypotropia, and virtually complete ophthalmoplegia. The two families were not consanguineous, but there was endogamy in family B. The affected child from family A developed a moderate esotropia. All patients from family B had high astigmatism, and two sons developed mild esotropia with attempted upgaze. Later, Khan et al. (2010) analyzed a family that had familial congenital fibrosis of the extraocular muscles (CFEOM) with apparent autosomal recessive inheritance. The family consisted of two affected siblings, three asymptomatic siblings, and their two asymptomatic parents. The two affected siblings had large-angle exotropia, moderate bilateral hypotropia, moderate bilateral ptosis, sluggish pupils, and almost complete ophthalmoloplegia with some abnormal synkinesis. The asymptomatic parents were not related and had unremarkable ophthalmic examinations. Four other siblings were normal by history; three underwent venous blood sampling for confirmatory testing. Sequencing of

the KIF21A gene revealed heterozygous p.R954L in both affected individuals, but not in their parents or three asymptomatic siblings, consistent with parental germline mosaicism. Haplotype analysis suggested paternal inheritance but was not conclusive. Khan et al. (2010) noted that parental germline mosaicism can mimic recessive inheritance in CFEOM and likely is underrecognized. They also recommended that ophthalmologists should be aware of this phenomenon when counseling parents of children with apparent recessive (or *de novo*) hereditary eye disease. In 2011, Khan et al. sequenced the KIF21A gene in five probands with classic CFEOM1. None of the probands had mutations in KIF21A. Khan et al. (2011) speculated that the lack of KIF21A mutations in CFEOM1 patients exclusively from consanguineous families, most of whom had siblings with CFEOM, is strong evidence for a recessive form of CFEOM1.

References

Khan AO, Khalil DS, Al Sharif LJ, Al-Ghadhfan FE, Al Tassan NA. Germline Mosaicism for KIF21A Mutation (p.R954L) Mimicking Recessive Inheritance for Congenital Fibrosis of the Extraocular Muscles. Ophthalmology. 2010; 117(1):154-8. PMID: 19896199 [AB]

Khan AO, Khalil DS, Al-Tassan NA. Congential fibrosis of the extraocular muscles type I (CFEOM1) on the Arabian Peninsula. Ophthalmic Genet. 2008; 29(1):25-8. PMID: 18363169 [FT]

Khan AO, Shinwari J, Omar A, Al-Sharif L, Khalil DS, Alanazi M, Al-Amri A, Al Tassan N. Lack of KIF21A mutations in congenital fibrosis of the extraocular muscles type I patients from consanguineous Saudi Arabian families. Mol Vis. 2011; 17:218-24. PMID: 21264235 [AB]

Related CTGA Records

Kinesin Family Member 21A

External Links

http://ghr.nlm.nih.gov/condition/congenital-fibrosis-of-the-extraocular-muscles

http://www.ncbi.nlm.nih.gov/books/NBK1348/

Contributors

Ghazi O. Tadmouri: 11.1.2015

Nada Assaf: 26.12.2014