Resumo

Introdução: Fibrose congénita dos músculos extra-oculares (FCMEO) constitui um grupo raro de patologias caracterizadas por oftalmoplegia congénita, não progressiva e restritiva dos músculos extra-oculares, com ou sem ptose palpebral. FCMEO está associada a desenvolvimento anormal da totalidade ou parte dos nervos óculo-motor (III) e troclear (IV) e da consequente inervação aberrante dos músculos extra-oculares e/ou músculo elevador palpebral.

Objectivos: Realizar uma completa caracterização fenotípica de doze pacientes Portugueses, realizar um estudo genético para os "hotspot" das mutações da FCMEO no gene *KIF21A* por sequenciação directa (em nove pacientes de seis famílias independentes) e estabelecer potenciais correlações genótipo-fenótipo.

Métodos: Avaliação clínica e análise mutacional do gene *KIF21A* em doze pacientes portugueses com FCMEO.

Resultados: Fibrose congénita dos músculos extra-oculares foi demonstrada em todos os casos. Identificamos dez pacientes com FCMEO do tipo 1 e dois pacientes com provável FCMEO do tipo 3. Todos os pacientes têm ptose bilateral com posição anómala da cabeça compensatória com o queixo levantado, 92% têm ambliopia, 42% têm inervação aberrante, 42% têm patologias sistémicas associadas (tais como atraso mental em 25% e polidactilia em 8,3%). A maioria dos pacientes têm oftalmoplegia com os olhos fixos em infradução (sendo incapazes de elevar os olhos acima da linha média vertical), estrabismo horizontal com exotropia variável e movimentos oculares bruscos. Os resultados da análise mutacional estão pendentes.

Conclusão: Caracterizamos, de um ponto de vista clínico e genético, o primeiro grupo de famílias portuguesas com FCMEO. Um conhecimento profundo deste grupo de patologias é inestimável para o adequado tratamento e aconselhamento destes pacientes.

Abstract

Introduction: Congenital fibrosis of the extraocular muscles (CFEOM) describes a group of rare congenital non-progressive, restrictive ophthalmoplegia of the extraocular muscles with or without ptosis. They are associated with abnormal development of all or part of the oculomotor (III) and the trochlear (IV) nerves and resultant aberrant innervations of extraocular muscles and/or levator.

Objective: To perform a complete phenotypical characterization of twelve affected Portuguese individual, a genetic evaluation searching for the "hotspot" CFEOM mutations in *KIF21A* by direct sequencing (in nine patients of six independent families) and to establish a potential genotype-phenotype correlations.

Methods: Clinical evaluation and mutation analyses of the *KIF21A* gene in twelve Portuguese patients with CFEOM.

Results: Congenital fibrosis of the extraocular muscles was demonstrated in all cases. We identified ten patients with CFEOM type 1 and two patients with probable CFEOM type 3. All patients have bilateral ptosis with a compensatory chin up head posture, 92% have amblyopia, 42% neural misdirection, 42% have associated systemic features (such as intellectual development delay in 25% and polydactyly in 8,3%). Most patients have ophthalmoplegia with the eyes fixed in infraducted position (with the inability to elevate the eyes above the vertical midline), horizontal strabismus with variable exotropia and jerky eye movements. Mutational analysis results are pending.

Conclusions: We characterize, from a clinical and genetic standpoint, the first group of portuguese families with CFEOM. In-depth knowledge of this group of conditions is invaluable for appropriate treatment and counseling of these patients.

Keywords:

CFEOM, extraocular muscles, *KIF21A* gene, oculomotor nerve, ophthalmoplegia, ptosis, strabismus, trochlear nerve.

Introduction

Congenital fibrosis of the extraocular muscles (CFEOM) is a rare congenital incomitant strabismus syndrome that is included in the congenital cranial dysinnervation disorders (CCDDs). CCDDs are due to neurogenic disturbances of brainstem or cranial nerve development. They are characterized by abnormal eye, eyelid, and/or facial movement and includes CFEOM, Duane retraction syndrome, HOX A1 spectrum, horizontal gaze palsy and progressive scoliosis, hereditary congenital facial palsy and hereditary congenital ptosis (1).

CFEOM includes four strabismus syndromes: 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) and Tukel Syndrome (2-6). Overall, CFEOM is characterized by congenital non-progressive, restrictive ophthalmoplegia of the extraocular muscles with or without blepharoptosis (7). In general, affected individuals have severe limitation of vertical gaze and variable limitation of horizontal gaze. Individuals with CFEOM frequently compensate for the ophthalmoplegia by maintaining abnormal head positions and by moving their heads rather than their eyes to track objects (7).

CFEOM affects 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 (superior oblique). Magnetic resonance imaging (MRI) suggests that the abducens nerve and innervated muscle (the lateral rectus) may also be affected, as well as the optic nerve (8). Neuropathology, neuroimaging and genetic studies nowadays have clarified that myopathic changes are secondary to aberrant innervation of the extraocular muscles (9). Usually, CFEOM patients show normal cognitive and physical development; However, there

are many cases with delayed psycho-motor development and central nervous system malformations (10-12).

CFEOM1 is the "classic" and most common form of CFEOM. It's characterized by bilateral ptosis and ophthalmoplegia with the eyes fixed in an infraducted position and with the inability to elevate the eyes above the horizontal midline (13, 4). Patients characteristically assume a compensatory "chin up" head posture (14). There is a heterogeneous involvement of the horizontal extraocular muscles (15) and horizontal strabismus may be present with an increased incidence of exotropia (14). Strabismic and deprivational amblyopia are frequent consequences (14). Aberrant eye movements are common (especially both eyes turning inward on attempted upgaze and synkinetic eye movements including synergistic divergence) (15, 16). Marcus Gunn jaw-winking have been observed (16-18). Forced duction test is positive for restriction. Autopsy and MRI demonstrated: absent or severely hypoplastic superior division of the oculomotor nerve; abnormality of the caudal alpha motor neurons of the oculomotor nucleus; hypoplasia of the oculomotor nerve as it exited in the brain stem and replacement of the normal superior rectus muscle and levator palpebrae superioris with atrophic, fibrotic tissue (8, 13). There are absent or hypoplastic motor nerves to all of the extraocular muscles, further supporting aberrant innervations as an underlying pathological process in CFEOM (8, 13, 14).

CFEOM1 is inherited in an autosomal dominant manner with complete penetrance. A patient with CFEOM1 may have inherited the disease-causing mutation or have a *de novo* gene mutation. The gene is on FEOM1 locus on chromosome 12cen (19). *KIF21A* mutations are associated with most familial cases of CFEOM1 that map to FEOM1 locus and with most simplex cases of CFEOM1 (4, 17, 20-23). 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 (7). The *KIF21A* gene encodes a kinesin microtubule-associated motor protein that is associated with anterograde organelle transport in neuronal cells (24). Seven different heterozygous missense mutations in three of the 38 exons of the *KIF21A* gene have been identified in individuals with CFEOM1 (4, 20, 22, 23). Mutations may affect structural morphology of the protein, thereby limiting its function (9). It is suggested that KIF21A protein in humans is essential for delivery of cargo necessary for oculomotor axonal, extraocular muscle or neuromuscular junction development (4).

CFEOM2 is characterized by congenital non-progressive bilateral ptosis (of variable severity) and a partially or completely fixed large angle exotropia (rarely fixed in an orthotropic position). Vertical and horizontal eye movements are severely restricted. Patients characteristically undertake compensatory strategies such as a "chin up" posture or manual lid elevation to fixate on objects. There is phenotypic heterogeneity about the vertical misalignment (25). Several patients had anomalous eye movements, such as mild vertical movements of an eye during abduction, convergence or blinking; abduction of an eye on attempted down gaze; and globe retraction (25). Often, pupils are small and pupillary light and near reflexes are not presents; however, pupils are reactive to topical pharmacological stimulation (25-27). Amblyopia from both deprivation and strabismus are features of this disease (26). Forced ductions test is positive for restriction. Autopsy, surgery and MRI demonstrated: anatomically absent cranial nerves III and IV; extraocular muscles innervated by both cranial nerve III (i.e. levator palpebrae superioris, superior rectus, inferior rectus, medial rectus, inferior oblique) and cranial nerve IV (superior oblique) were atrophic, tight and thin or absent (25). Associated systemic abnormalities have not been reported in genetically defined CFEOM2 patients (25).

CFEOM2 is inherited in an autosomal recessive manner with complete penetrance. CFEOM2 has been found, to date, only in consanguineous pedigrees (14). The gene for CFEOM2 has been mapped to the FEOM2 locus on chromosome 11q13 (27). *PHOX2A (ARIX*) is the only gene known to be associated with the CFEOM2 phenotype (3). To date, four homozygous mutations have been identified: two splice site mutations, one missense mutation, and one nonsense mutation (3, 26). CFEOM2-causing mutations in *PHOX2A* all likely result in complete loss of function of paired mesoderm homeobox protein 2A. There is no correlation between specific *PHOX2A* mutations and the CFEOM2 phenotoype (3, 25). *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) and is involved in the determination of the noradrenergic neuronal phenotype (28, 29). The findings from animal models provide support that CFEOM2 results from aberrant development of the oculomotor and trochlear alpha motor nuclei and absent innervation of the extraocular muscles by cranial nerves III and IV (3, 14).

CFEOM3 is characterized by a variable phenotypic presentation in which the individual does not meet the clinical criteria for classic CFEOM1 or CFEOM2 (7). Affected individuals may have bilateral or unilateral disease. Congenital non-progressive unilateral or bilateral ptosis may be present. The vertical eye movements have variable restriction with presence or absence of upgaze above the midline; the horizontal eye movements can be normal to severely restricted. The patient may be orthotropic in primary position, and will adopt compensatory head postures depending upon the severity of the clinical phenotype (2, 5, 30). Forced ductions test is positive for restriction. Aberrant eye movements may be present and the pupils are normal (2).

CFEOM3 is inherited in an autosomal dominant manner with incomplete penetrance and variable expressivity. According new researches the genetic basis of CFEOM consists in two mutations: in the TUBB3 (gene encoding component of microtubules, a neuronal specific tubulin) (CFEOM3A) (31) and rarely KIF21A (CFEOM3B) (32). CFEOM due to TUBB3 mutations can be associated with intellectual and behavioral impairments, facial paralysis, and/or later-onset axonal sensorimotor polyneuropathy (31). A CFEOM3C variant has been recognized in 3 generations of a single family, where all affected members carry a chromosomal translocation t(2;13)(q37.3;q12.11) (5).

Tukel syndrome (or CFEOM-U) is a congenital fibrosis of extraocular muscles with ulnar hand anomalies (postaxial oligodactyly/oligosyndactyly of the hands). It affects primarily the right eye and right hand. It appears to be very rare (only in one large Turkish family). The inheritance is autosomal recessive and the locus was mapped to a 1.5-Mb region on the chromosome 21qter (6).

In this paper we propose to perform a complete phenotypical characterization of twelve affected Portuguese individual, a genetic evaluation searching for the “hotspot” CFEOM mutations in the *KIF21A* gene by PCR amplification followed by direct sequencing (in nine patients of six independent families) and to establish a potential genotype-phenotype correlations.

Methods

Patient and Pedigree Collection

All probands (fig. 1) were examined and met the diagnostic criteria for Congenital Fibrosis of the Extraocular Muscles (7).

The probands and their family members were also clinically examined according to ophthalmological data collection form from Children's Hospital Boston Center for Strabismus Research (33). Thus they underwent complete ophthalmic examination of visual acuity, refraction status and general ocular examination, anomalous head posture, lid position, ocular alignment, ocular motility and were evaluated for associated systemic features. [Table 1]

Table 1 – Clinical assessment protocol

1. Age	11. Alignment with abnormal head posture
2. Preliminary diagnosis	12. Ocular motility
3. Cycloplegic refraction	13. Globe retraction
4. Best corrected visual acuity	14. Aberrant movement
5. Pupils (size/shape and reaction to light/near)	15. Nystagmus
6. Anterior segment exam	16. Quality of eye movement (smooth/jerky)
7. Fundus exam	17. Bell's phenomenon
8. Head Posture	18. Forced duction test
9. Ptosis measurements	19. Inheritance
10. Primary position alignment	20. Other associated features

Blood samples were collected from nine representative patients followed at University Hospital of Coimbra.

All affected individuals and family members gave written informed consent in accordance with institutional guidelines defined by the ethics committee of the University Hospital of Coimbra. All research procedures were in accordance with the Declaration of Helsinki.

Mutation Analysis

Blood samples were collected from probands, and genomic DNA was extracted using an automated DNA extractor (BioRobot EZ1, Qiagen, Hilden, Germany).

Mutation detection was conducted by PCR amplification of exons 8, 20, and 21 of the *KIF21A* gene and flanking intron-exon boundaries from genomic DNA of each proband in six families and 3 related (nine patients). The analysed exons of the *KIF21A* gene were PCR-amplified using previously described primers and conditions by the research group at Children's Hospital Boston Center for Strabismus Research Boston, USA.

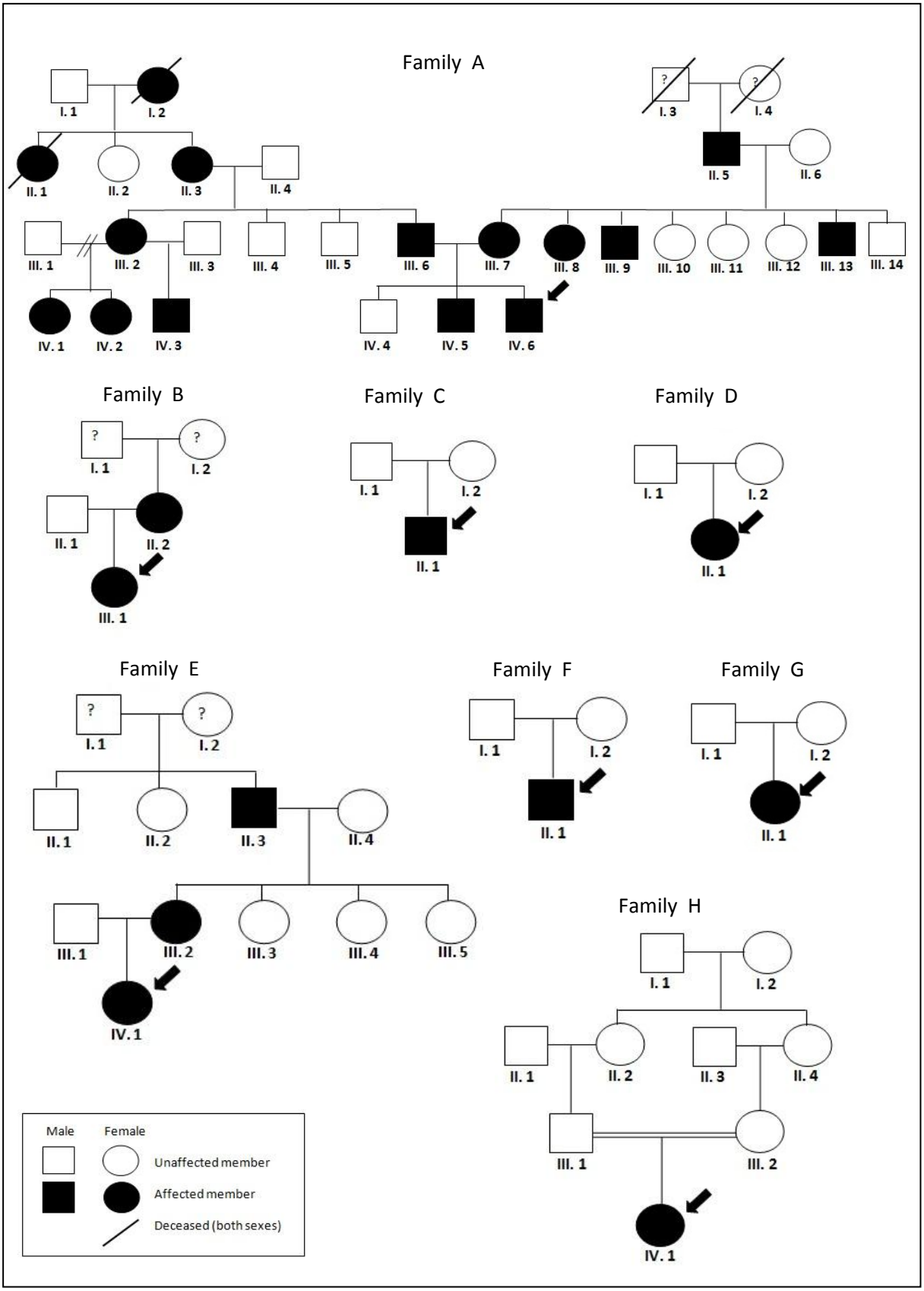

Fig. 1. Pedigrees of families with congenital fibrosis of the extraocular muscles (CFEOM).

Arrows indicate the proband in each family.

Results

We identified three CFEOM1 pedigrees (families A, B and E), three sporadic CFEOM1 individuals (from families D, F and G) and two probable sporadic CFEOM3 individuals (from families C and H). (fig. 1)

The findings in families A, B, D, E, F, G (table II and III, fig. 2) are consistent with CFEOM type 1 phenotype. All patients have bilateral ptosis with a compensatory chin up head posture. All patients have congenital non-progressive ophthalmoplegia with the eyes fixed in infraducted position (except family B and patient E.IV.1 that have an orthophoric primary position alignment) with the inability to elevate the eyes above the vertical midline. There is a heterogeneous involvement of the horizontal extraocular muscles (most patients have horizontal eye movements but patients A IV.3, A IV.6 and G II.1 have involvement of the horizontal extraocular muscles). The most patients have horizontal strabismus with variable exotropia and jerky eye movements. All patients have amblyopia (with a best corrected visual acuity varying between OU: 0,4 and OU:0,9). Four patients (A IV.3, A IV.6, D II.1 and G II.1) have aberrant eye movements. Nystagmus is common (four in ten patients). No patient has globe retraction. These patients' inheritance is autosomal dominant (with complete penetrance) in the families A, B and E or unknown (*de novo* gene mutation?) in families D, F and G. It is expectable that mutation analysis leads to the identification of mutations in the *KIF21A* gene (in the exons 8, 20 or 21).

The patients C II.1 and H IV.1 (table II and III) have an unknown inheritance and due to their atypical phenotype, they fit the criteria of CFEOM3.

Patient C II.1 has multiple systemic features, including intellectual and motor development delay, low implantation ears, polydactyly (of the right foot) and cryptorchidism.

He has a marked chin up, head tilt to the left shoulder posture, with marked and bilateral ptosis and severe amblyopia. About the alignment, the right eye has variable exotropia and the left eye has a hypotropic and exotropic position. There is no elevation above vertical midline.

Patient H IV.1 has bilateral aberrant innervations of the levator palpebrae superioris (jaw-wink-like), moderated chin up and an orthophoric primary position alignment. There is no amblyopia. There is no elevation above vertical midline and adducts only to horizontal midline. There is synergistic divergence.

Five patients (42%) have associated systemic features. Three patients (C II.1, D II.1 and F II.1) [25%] have intellectual development delay.

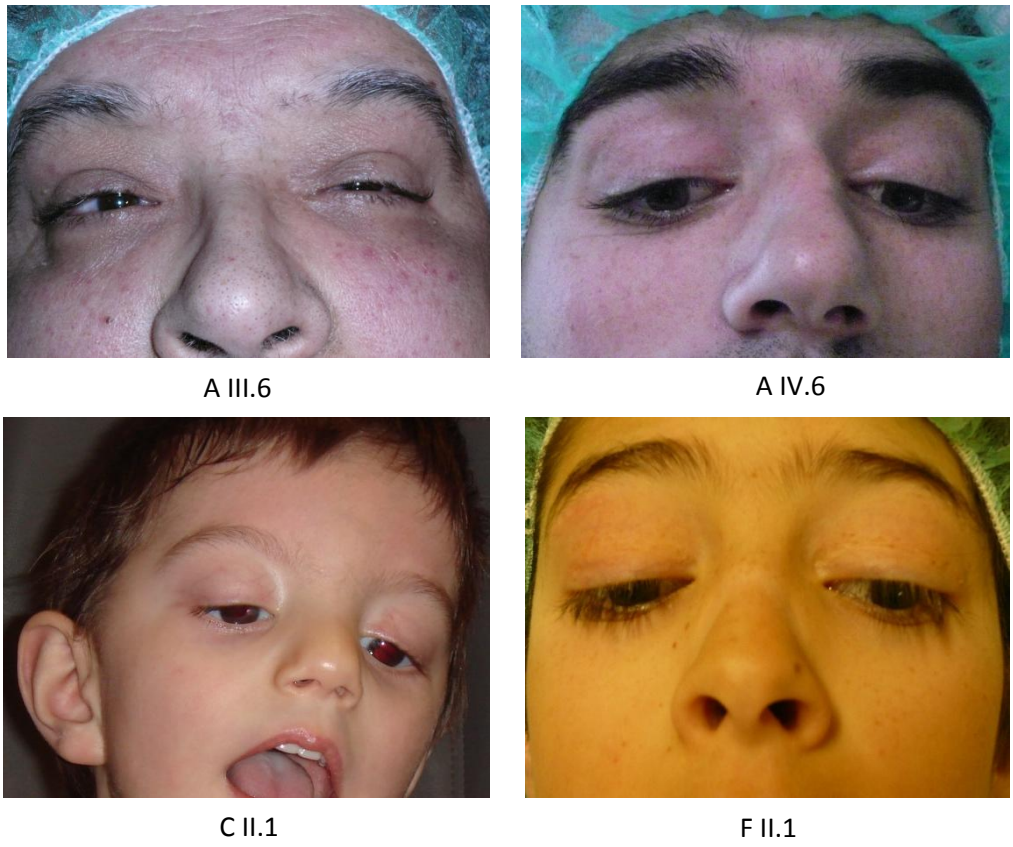

Fig. 2 – Photographs showing three CFEOM1 patients (A III.6, A IV.6, F II.1) and one probable CFEOM3 patient (C II.1).

Table II. Clinical features and basic eye exam

Patient	Age	Inheritance	Systemic features	BCVA	C. Refraction	Pupils	ASE	Fundus
A III.6	55	AD	FAP, glaucoma, arrhythmia	OU: 0,5	N.A. (no spectacle correction)	PERRLA	Amyloid deposits	C/D 0,5 RE C/D 1,0 LE Droop out NFL
A III.7	50	AD	None	OU: 06	N.A. (no spectacle correction)	PERRLA	Normal	Normal
A IV.3	9	AD	Renal cyst (in the right kidney); Blepharophimosis and epicanthus	OU: 0,5	OD: +2,5 +0,5x90 OS: +1,25	PERRLA	Normal	Normal
A IV.6	22	AD	None	OU: 0,4	OD: 0,0 OS: 0,0	PERRLA	Normal	Normal
B II.2	32	AD	None	OU: 0,6	OD: 0,0 OS: 0,0	PERRLA	Normal	Normal
B III.1	7	AD	None	OU: 0,6	OD: +1,00 OS: + 1,00	PERRLA	Normal	Normal
C II.1	6	Unknown	Intellectual and motor development delay, low implantation ears, polydactyly of the right foot, cryptorchidism (unilateral)	OU: 0,1	N.A. (difficult assessment due to photophobia)	PERRLA	Normal	Normal
D II.1	5	Unknown	Intellectual development delay	OU: 0,5	OD: +1,5 x 100; OS: +1,5x80	PERRLA	Normal	Normal
E IV.1	5	AD	None	OU: 0,5	OD: 0,0 OS: 0,0	PERRLA	Normal	Normal
F II.1	14	Unknown	Intellectual development delay, hyperactivity, dermoid cyst on the eyebrow, left ventricular hypertrophy and anteroseptal myocardial ischemia.	OU: 0,5	OD: - 8,00 +1,00x80; OS: -7,00 + 1,00x75	PERRLA	Normal	Normal
G II.1	10	Unknown	None	OU: 0,9	OD: +4,5 OS: +5,0	PERRLA	Normal	Normal
H IV.1	8	Unknown	None	OU: 1,0	N.A.	PERRLA	Normal	Normal

Legend: AD - Autosomal Dominant; AR – Autosomal Recessive; ASE - Anterior segment exam; BCVA – Best corrected visual acuity; C. Refraction – Cycloplegic refraction; FAP - Familial Amyloid Polyneuropathy; N.A. – Not available; NFL – Nerve fiber layer; OU – Both eyes; OD - Right eye; OS- Left eye; PERRLA - Pupils equal, round, reactive to light and accommodation

Table III. Ocular motility and eyelid functional assessment

Patient	**Head Posture**	**Ptosis**	**Primary position alignment**	**Alignment with AHP**	**Ocular motility**	**GR**	**Aberrant movement**	**Nystagmus**	**Quality of eye movement**
A III.6	Marked chin up	Bilateral and marked	Hypotropic position (infraducted)	Exotropia in downgaze	No elevation; unable to reach vertical midline. Horizontal eye movements.	No	No	Yes	Jerky
A III.7	Marked chin up	Bilateral and marked	Hypotropic position (infraducted)	Exotropia in downgaze	No elevation; unable to reach vertical midline. Horizontal eye movements.	No	No	Yes	Jerky
A IV.3	Marked chin up	Bilateral and marked	Esotropic and hypotropic position	Esotropia	No elevation. Abducts only to horizontal midline but not beyond.	No	Yes (synergistic convergence)	Yes	Jerky
A IV.6	Marked chin up	Bilateral and marked	Hypotropic position (infraducted)	Hypotropic position; Alternate fixation with OD/OS.	No elevation, neither adduction, neither abduction. In attempted downgaze - large angle exotropia; In attempted supraduction – variable esotropia; In attempted levo-dextroversion – small angle esotropia.	No	Yes	No	Jerky
B II.2	Moderated chin up	Bilateral but asymmetric; moderated	Orthophoric	Orthophoric	No elevation above vertical midline	No	No	No	Smooth (except on attempted elevation: jerky)
B III.1	Moderated chin up	Bilateral but asymmetric; moderated	Orthophoric	Orthophoric	No elevation above vertical midline	No	No	No	Smooth (except on attempted elevation: jerky)
C II.1	Marked chin up, head tilt to the left shoulder	Bilateral and marked	OD: Variable exotropia OS: hypotropic and exotropic position	OS: hypotropic position (variable)	No elevation above vertical midline	No	No	Yes	Jerky

D II.1	Small chin up position	Bilateral, moderated	OU: Variable exotropia. OD: Hypotropic and exotropic position	Orthophoric – exotropia variable	No elevation above vertical midline	No	Yes (synergistic divergence)	No	Smooth (rapid saccades induce jerk)
E IV.1	Marked chin up	Bilateral and marked	Orthophoric – variable exotropia, intermittent	Orthophoric	No elevation above vertical midline	No	No	No	Jerky
F II.1	Marked chin up	Bilateral and moderated	Hypotropic position	Orthophoric	No elevation above vertical midline	No	No	Yes	Jerky
G II.1	Moderate chin up	Bilateral but asymmetric; moderated	Hypotropic position	Orthophoric	No elevation above vertical midline. On attempted adduction – upshoot; on attempted abduction – downshoot	No	Upshoots and downshoots	No	Jerky
H IV.1	Moderated chin up	Bilateral aberrant innervation jaw-wink-like	Orthophoria	Variable exotropia	Adducts only to horizontal midline but not beyond. No elevation above vertical midline.	No	Yes (synergistic divergence)	No	Smooth; occasionally jerky

Legend: AHP – Abnormal Head Posture; GR – Globe retraction; OU – Both eyes; OD – Right eye; OS – Left eye

Table IV. Mutation analyses – pending

	KIF21A mutations	
Patient	**Allele 1**	**Allele 2**
A III.6	Pending	Pending
A III.7	Pending	Pending
A IV.6	Pending	Pending
B II.2	Pending	Pending
B III.1	Pending	Pending
C II.1	Pending	Pending
D II.1	Pending	Pending
E IV.1	Pending	Pending
F II.1	Pending	Pending

Discussion

CFEOM is a very rare, congenital and non progressive disorder with multiple extra ocular muscles restrictions. The diagnosis and classification of CFEOM is defined by clinical characteristics and genetics. We have ten patients with the diagnosis of CFEOM type 1 and two patients with the probable diagnosis of CFEOM type 3. Due to the overlap in the clinical features between different CFEOM groups, genetic evaluation is important to confirm the diagnosis.

Numerous ocular and systemic associations have been described in patients with CFEOM: refractive errors and amblyopia, neural misdirection, optic nerve dysplasia or hypoplasia, chorioretinal coloboma, Marcus Gunn jaw-winking phenomenon, other cranial nerve anormalies (V and VII), facial dysmorphism and neurodevelopmental defects.

We found amblyopia in eleven patients (91,7%), neural misdirection in five patients (41,7%) intellectual and motor development delay in three patients (25%), blepharophimosis and epicantus in one patient (8,3%), polydactyly, low implantation of ears and unilateral cryptorchidism in one patient (8,3%), dermoid cyst, left ventricular hypertrophy and anteroseptal myocardial ischemia in one patient (8,3%). Seven patients (58,3%) have no systemic associated features.

In individuals with CFEOM1 seven different heterozygous missense mutations in three of the 38 exons of the *KIF21A* gene have been identified (4, 20, 22, 23); in individuals with CFEOM2 four homozygous mutations of *PHOX2A* have been identified (3, 26). Individuals with CFEOM3 phenotype are genetically heterogeneous: in individuals with CFEOM3A eight different heterozygous mutations in the TUBB3 gene have been identified (31), in individuals with CFEOM3B an heterozygous mutation in the

KIF21A gene (32), in individuals with CFEOM3C a translocation t(2;13)(q37.3;q12.11) (33).

The genetic evaluation always begins searching for the "hotspot" CFEOM mutations in *KIF21A* by PCR amplification followed by direct sequencing of exons 8, 20, and 21 of the *KIF21A* gene and flanking intron-exon boundaries from genomic DNA. However, recent studies reveal that although *KIF21A* is the only gene associated with CFEOM1 to date, up to 40% of sporadic CFEOM1 cases do not have identifiable mutations in *KIF21A* (34) and a study of CFEOM1 patients from consanguineous Saudi Arabian families confirmed the lack of *KIF21A* mutations, evidencing a recessive form of CFEOM1 (35). These studies confirm the genetic heterogeneity of the CFEOM1 clinical phenotype and how it is particularly useful for appropriate genetic counseling of sporadic *KIF21A*-negative patients.

In the Portuguese patients, KIF21A mutations (in the three "hotspots") are expected to be identified. However, due to the geographic isolation and genetic uniqueness of our population and the relatively high consanguinity level is possible that we will identify new mutations and/or find KIF21A-negative patients.

The results of genetic evaluation are important for:

1. Confirmation of the diagnosis;
2. Clarification of genotype-phenotype correlations;
3. To assess the impact of different mutations in the clinical severity;
4. To plan the best timing for surgical intervention;
5. Appropriate genetic counseling and prenatal diagnosis.

The surgical correction of strabismus and ptosis in CFEOM is challenging. Strabismus surgery is always attempted before ptosis correction. The expectations of

strabismus surgery should be realistic and parents and patient should be well informed about these expectations.

Presently, it is possible to provide genetic testing and counseling for affected individuals. The recent findings about physiopathology and genetics of CFEOM may lead to improved care for affected individuals because the more the specific disorders are understood, the easier it will be to develop targeted therapies for these disorders.

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