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Research Paper

An Autosomal Dominant *TUBB3* Mutation Associated With Congenital Fibrosis of the Extraocular Muscles Type 3 in an Iranian Family

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ABSTRACT

Introduction: Congenital fibrosis of the extraocular muscles type 3 (CFEOM3) is a congenital cranial dysinnervation disorder (CCDD) marked by variable ophthalmoplegia and ptosis with considerable phenotypic heterogeneity. We report a large multigenerational Iranian family with autosomal dominant CFEOM3.

Methods: Affected individuals underwent a comprehensive ophthalmologic evaluation. Whole-exome sequencing (WES) in the proband, followed by Sanger sequencing in 10 affected and 4 unaffected relatives, identified a heterozygous missense variant, c.784C>T (p.Arg262Cys), in exon 4 of *TUBB3* (16q24.3), which cosegregated with the disease phenotype.

Results: Cranial magnetic resonance imaging in 2 affected individuals revealed asymmetric basal ganglia morphology, predominantly affecting the caudate nuclei and putamen. At the level of the anterior commissure, the bilateral CFEOM3 patient lacked a visible commissure, whereas the unilateral patient exhibited a thin but identifiable structure. Midline sagittal imaging demonstrated corpus callosum dysgenesis in both individuals, with slightly greater involvement of the corpus callosum body in the unilateral case, though this difference was not radiologically significant. Despite differences in ocular phenotype, overall cerebral involvement was largely comparable.

Conclusion: These findings confirm the pathogenic role of the *TUBB3* p.Arg262Cys variant in CFEOM3A and extend the spectrum of ophthalmologic and neuroimaging abnormalities within an extended family. The results highlight the complex genotype–phenotype relationships in *TUBB3*-related disease and underscore the importance of integrated clinical and molecular evaluation for precise diagnosis.

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Highlights

- *TUBB3* R262C segregates with CFEOM3A in a large Iranian family.
- Brain MRI shows asymmetric basal ganglia and corpus callosum dysgenesis.
- The anterior commissure is absent in bilateral cases, thin but visible in unilateral cases.
- Ophthalmoplegia severity varies among affected individuals.
- Our findings expand the genotype–phenotype spectrum of TUBB3-related CFEOM3A.

Plain Language Summary

Some people are born with a condition called congenital fibrosis of the extraocular muscles type 3 (CFEOM3), which limits eye movement and may cause drooping eyelids. The severity of eye problems can differ even among family members. We studied a large Iranian family with several members affected by CFEOM3A. Medical exams, eye tests, brain imaging, and DNA analysis were performed. We identified a specific change in the *TUBB3* gene, c.784C>T, present in all affected members but absent in healthy relatives. This change likely disrupts normal eye and nerve development, explaining the observed eye problems. Brain imaging showed that this gene change can also alter brain structures, including the basal ganglia and connections between the brain's two hemispheres. Family members with more severe eye problems had more noticeable brain changes, helping explain the variability in symptoms. These findings improve understanding of how a single genetic change can affect both eye and brain development. This knowledge can aid diagnosis, guide families, and may eventually help develop better strategies to manage congenital eye movement disorders.

Introduction

Congenital fibrosis of the extraocular muscles (CFEOM) is a congenital cranial dysinnervation disorder (CCDD) characterized by non-progressive ophthalmoplegia and ptosis resulting from abnormal development of the oculomotor or trochlear nerves (Wang et al., 1998; Yamada et al., 2004). Among the CFEOM phenotypes, CFEOM type 3 (CFEOM3) is a rare, dominantly inherited form of congenital restrictive ophthalmoplegia. CFEOM3 represents a clinically prominent and genetically heterogeneous form, notable for marked phenotypic variability and asymmetric neurological and anatomical involvement, which complicates clinical classification (Engle et al., 2002; Traboulsi, et al., 2000; Yamada et al., 2003). In some pedigrees, the phenotype segregates with full penetrance (Mackey et al., 2002), whereas in others it may show probable incomplete penetrance (Doherty et al., 1999).

Early clinical descriptions emphasized congenital limitation of eye movements associated with variable ptosis, frequent interocular asymmetry, and relative preservation of horizontal gaze in some affected individuals (Gillies, et al., 1995). Linkage studies subsequently mapped the disease locus to chromosome 16q24.3 (Doherty et al., 1999; Mackey et al., 2002). Subsequent molecular studies of CFEOM3A identified mutations in *TUBB3*, which encodes the neuron-specific β-tubulin isotype III, a critical component of microtubules involved in axon guidance, neuronal connectivity, and cranial nerve development (Chew et al., 2013; Tischfield et al., 2010). Neuroimaging and experimental investigations subsequently revealed abnormalities of oculomotor nerve development and broader axon guidance defects, placing CFEOM3 within the wider group of CCDDs rather than a purely ocular motility disorder (Tischfield et al., 2010).

Pathogenic *TUBB3* variants are associated with a wide phenotypic spectrum, ranging from isolated congenital ophthalmoplegia to combined ocular and neurodevelopmental abnormalities with variable neuroimaging findings. Notably, base substitutions affecting conserved residues, including p.Arg62Gln, p.Arg262Cys, p.Ala302Thr, and p.Asp417Asn, produce distinct yet overlapping clinical manifestations, underscoring the variable genotype–phenotype correlations characteristic of *TUBB3*-related CFEOM3 (Chew et al., 2013; Tischfield et al., 2010).

In this study, we report an Iranian family with autosomal dominant CFEOM3A in which a heterozygous *TUBB3* missense variant, c.784C>T (p.Arg262Cys, R262C), was identified and demonstrated to cosegregate with the disease phenotype. This report, to our knowledge, provides the first detailed clinical, genetic, and neuroimaging characterization of a *TUBB3*-related CFEOM3 family from Iran, confirming the phenotypic spectrum associated with the c.784C >T variant.

Materials and Methods

Subjects and clinical assessment

A large multigenerational family originating from the central region of Iran, exhibiting a hereditary disorder of extraocular eye movement, was ascertained for this study. In total, 28 family members demonstrated clinical manifestations of the condition. Both affected individuals and available unaffected relatives from each generation were enrolled, and demographic information, including age, sex, and detailed clinical features, was systematically documented.

The study was conducted in accordance with the principles of the Declaration of Helsinki and received approval from the Ethics Committee of the Neuroscience Research Center. Written informed consent was obtained from all participants before their inclusion. Comprehensive ophthalmologic assessments were performed at Shahid Labbafi Nedjad Educational Hospital. In contrast, genetic analyses and related investigations were carried out at the Neuroscience and Cognitive Sciences Research Center, Shahid Beheshti University of Medical Sciences.

Ophthalmologic and neuroimaging evaluation

Comprehensive ophthalmologic examinations were performed in all affected family members. These evaluations included assessment of refractive errors, amblyopia, eyelid position and function, pupillary light reflexes, extraocular muscle motility, and the type and severity of strabismus. Forced duction testing was conducted to assess mechanical restriction, and levator palpebrae superioris muscle function was specifically evaluated in individuals presenting with ptosis. Ptosis was observed in all affected participants.

Cranial magnetic resonance imaging (MRI) was obtained for two affected individuals, one with bilateral CFEOM3A and one with unilateral CFEOM3A, to characterize associated neuroanatomical features further. MRI protocols included acquisition of coronal and axial T1-weighted sequences and axial T2-weighted images, enabling detailed assessment of the basal ganglia, commissural pathways, and midline brain anatomy. Due to logistical constraints, additional family members were not imaged.

All MRI studies were conducted at the National Brain Mapping Laboratory (NBML) on a 3-Tesla MRI scanner using standardized clinical imaging protocols. Neuroimaging evaluation focused on the morphology of the basal ganglia, visualization of the anterior commissure at its expected anatomical level, and assessment of corpus callosum development. Comparative analyses were performed between the 2 imaged individuals to evaluate inter-individual variability in neuroanatomical findings in relation to unilateral versus bilateral CFEOM involvement.

Genetic analysis

Peripheral blood samples were collected in EDTA (ethylenediaminetetraacetic acid)-containing tubes, and genomic DNA was extracted from leukocytes using the standard salting-out method (Miller et al., 1988). Whole-exome sequencing (WES) was performed on genomic DNA obtained from the proband using the Illumina HiSeq 2500 platform (Illumina, San Diego, CA, USA).

Bioinformatic analysis focused on chromosomal regions and genes previously implicated in CCDDs, identified c.784C>T (R262C) in exon 4 of *TUBB3* (reference transcript NM_006086).

The candidate variant was validated by polymerase chain reaction (PCR) amplification followed by Sanger sequencing using specific primers (forward: 5′-GGAGTCACCACCTCCTTGC-3′; reverse: 5′-CCATCATGTTCTTGGCATCG-3′). Segregation analysis was performed in available family members to assess cosegregation of the variant with the disease phenotype.

Results

Clinical findings

Comprehensive ophthalmologic evaluation of affected family members revealed common characteristics of CFEOMs, including ptosis (unilateral in some individuals and bilateral in others), hypotropia with restricted upgaze, chin-up posture, and exotropia with restricted horizontal gaze. Affected individuals were unable to elevate one or both eyes above the horizontal midline and

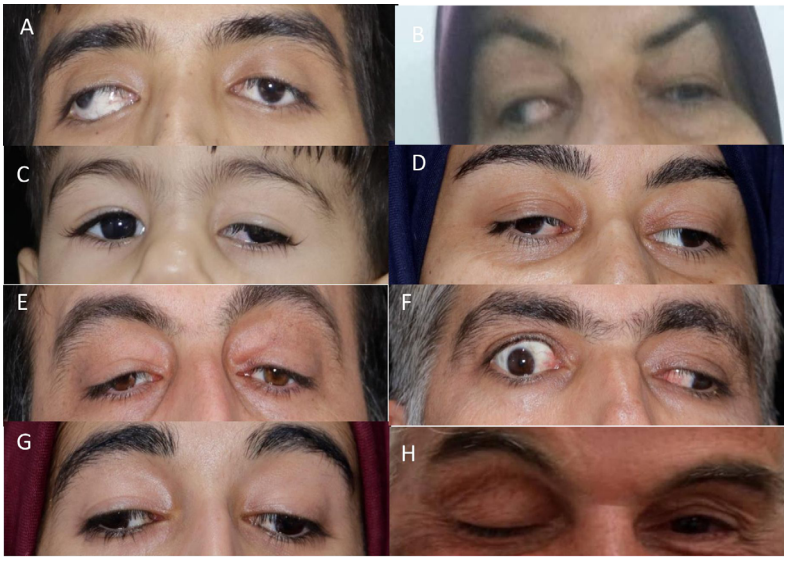

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Figure 1. Clinical photographs of affected family members with the c.784C>T variant demonstrating the phenotypic spectrum of CFEOM3A

Note: The c.784C>T variant can cause bilateral ptosis and severe CFEOM3A with an infraducted and abducted resting eye position. (A, B, D, F), moderate unilateral CFEOM3A (C, H) and mild CFEOM3A (E, G) images demonstrate congenital ptosis and ophthalmoplegia, with variable severity across individuals, consistent with a congenital, non-progressive phenotype. All photographs were obtained in primary gaze.

exhibited limited function of the lateral and inferior rectus muscles (Figure 1).

Based on ophthalmologic findings alone, the clinical presentation showed substantial overlap between clinical features traditionally attributed to CFEOM1 and CFEOM3, making a reliable clinical distinction between these subtypes challenging. However, limited supraduction movement observed in some patients is compatible with CFEOM3. None of the patients reported any progressive worsening of ocular manifestations.

Genetic analysis

Pedigree analysis demonstrated an autosomal dominant inheritance pattern for the disease phenotype (Figure 2). WES of the proband identified a heterozygous missense variant, c.784C>T (R262C), in exon 4 of the *TUBB3* gene on chromosome 16q24.3, corresponding to the known CFEOM3A locus. Segregation analysis using Sanger sequencing confirmed the presence of this variant in all affected family members and its absence in all tested unaffected family members (Figure 3).

Neuroimaging findings

Brain MRI was performed in 2 closely related affected individuals: patient 1 with bilateral CFEOM3A and patient 2 with unilateral CFEOM3A, revealing variable but largely overlapping neuroanatomical findings.

Both patients demonstrated asymmetric basal ganglia morphology, predominantly involving the caudate nucleus and putamen. These alterations were bilateral and more pronounced in the left hemisphere in both patients (Figures 4A1, 4B1, 4C1, 4A2, 4B2, and 4C2).

Evaluation at the expected anatomical level of the anterior commissure showed the absence of a visible anterior commissure in the bilateral CFEOM3A case. In contrast, a thin but identifiable anterior commissure was present in the unilateral CFEOM3A case (Figures 4D1, 4E14, 4D2, and 4E2).

Midline sagittal imaging revealed corpus callosum dysgenesis in both patients. The unilateral CFEOM3A patient showed slightly greater involvement of the body of the corpus callosum than the bilateral case; however, this difference was not radiologically significant. Notably, despite the differences in ocular phenotype, no meaningful differences in overall cerebral involvement were observed (Figures 4F1 and 4F2).

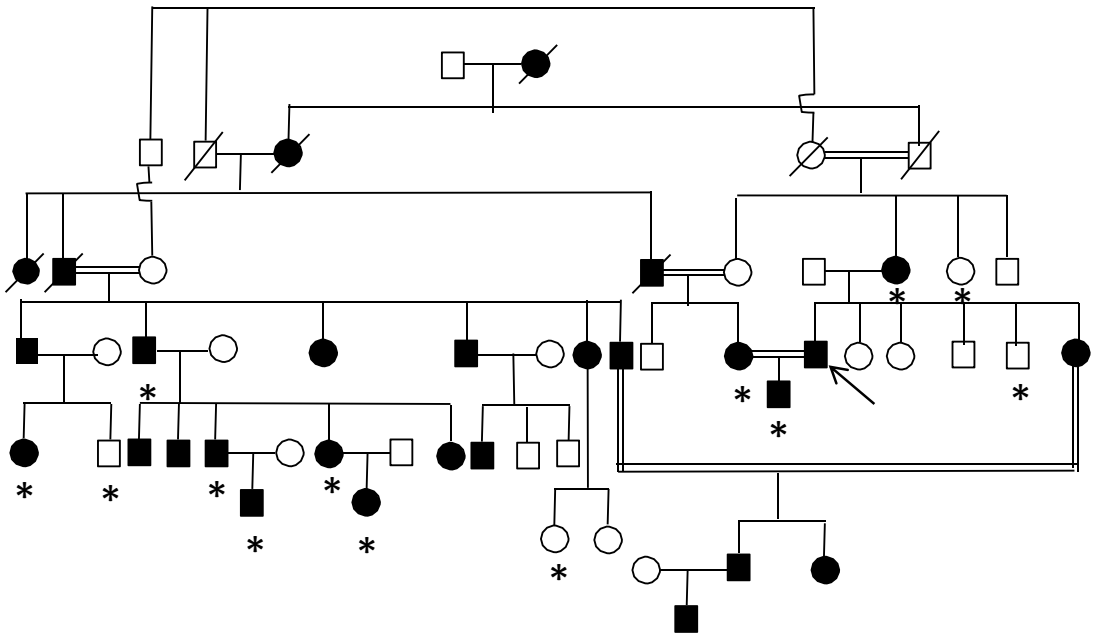

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Figure 2. Pedigree of the family affected by CFEOM3A

Note: Pedigree analysis suggested an autosomal dominant pattern of inheritance, characterized by vertical transmission from one generation to the next. The arrow marks the proband subjected to WES, and asterisks (*) indicate individuals analyzed by Sanger sequencing.

Discussion

CFEOM type 3 (CFEOM3) is a genetically and phenotypically heterogeneous form of CCDD most commonly associated with heterozygous missense variants in the *TUBB3* gene, which encodes the neuron-specific β-tubulin isotype III (Tischfield et al., 2010). βIII-tubulin plays a critical role in microtubule assembly and dynamics, axon guidance, and neuronal migration during neurodevelopment (Tischfield et al., 2010). Pathogenic *TUBB3* variants disrupt microtubule function, occasionally impair interactions with kinesin motor proteins, and result in abnormal cranial nerve development and defective extraocular muscle innervation (Tischfield et al., 2010).

In the present study, we identified a heterozygous *TUBB3* variant, c.784C>T (R262C), segregating with disease in an autosomal dominant manner across multiple generations in a large Iranian family. Clinically, affected individuals exhibited congenital ptosis, severe vertical gaze limitation, and variable involvement ranging from unilateral to bilateral CFEOM3A, consistent with the broad phenotypic spectrum previously reported for *TUBB3*-related CFEOM3 (Ceylan et al., 2017; Chew et al., 2013; Tischfield et al., 2010).

The penetrance of the disease allele could not be formally evaluated due to the lack of systematic assessment of all unaffected family members. However, the biochemical consequences of replacing arginine at position 262 (p.Arg262Cys) with cysteine are expected to disrupt the electrostatic and structural properties of βIII-tubulin, potentially impairing microtubule dynamics and axon guidance, and contributing to the observed disease phenotype. This interpretation is supported by the loss of a positively charged arginine residue and the introduction of a reactive thiol group by cysteine, changes predicted to affect tubulin folding and function adversely. Collectively, these considerations suggest that the c.784C>T (R262C) variant is likely to exhibit high, and possibly complete, penetrance.

Neuroimaging in our cohort further supported the diagnosis of CFEOM3A and demonstrated variable central nervous system involvement. In both unilateral and bilateral patients examined by neuroimaging, basal ganglia involvement was observed, and abnormalities of the anterior commissure were present despite differences in ocular phenotype. These largely overlapping neuroanatomical findings suggest that central nervous system perturbations are a consistent feature of *TUBB3*-related CFEOM3A. Such observations are in line with prior reports describing corpus callosum dysgenesis, basal gan-

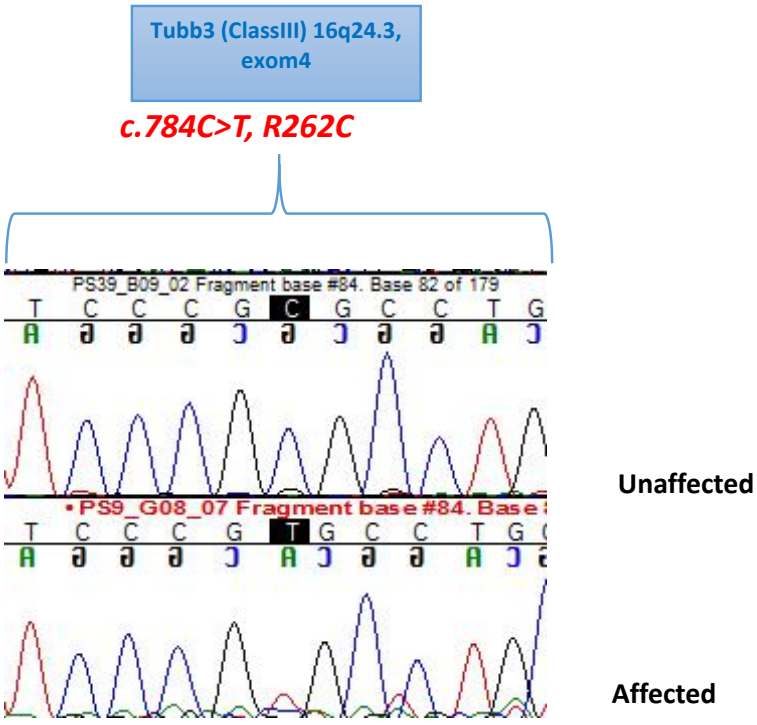

Figure 3. Sanger sequencing confirmation of the *TUBB3* variant

Note: Electropherograms show a heterozygous c.784C>T (p.Arg262Cys) variant in exon 4 of the *TUBB3* gene (16q24.3) in affected individuals. Overlapping C/T peaks indicate the variant, consistent with a heterozygous state. This variant segregated with the disease phenotype and was absent in unaffected family members.

glia abnormalities, and commissural defects in *TUBB3*-associated disorders (Chew et al., 2013; Poirier et al., 2010; Tischfield et al., 2010; Tischfield & Engle, 2010), and further support the concept of variable expressivity in this condition.

Conclusion

Taken together, our findings expand the phenotypic and neuroimaging spectrum associated with the *TUBB3* variant (c.784C>T, R262C) and highlight the variable expressivity observed in CFEOM3A. This study underscores the critical value of integrating detailed molecular genetic analysis with comprehensive clinical and neuroimaging assessments to achieve accurate diagnosis and inform effective genetic counseling in families affected by CCDDs.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Research Ethics Committee of the Neuroscience Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran (Code: IR.SBMU.PHNS.REC.1400.172). Written informed consent was obtained from all participants before their inclusion.

Data availability

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declaration of generative AI and AI-assisted technologies in the writing process

No AI tool influenced the scientific content, data analysis, or conclusions of this work.

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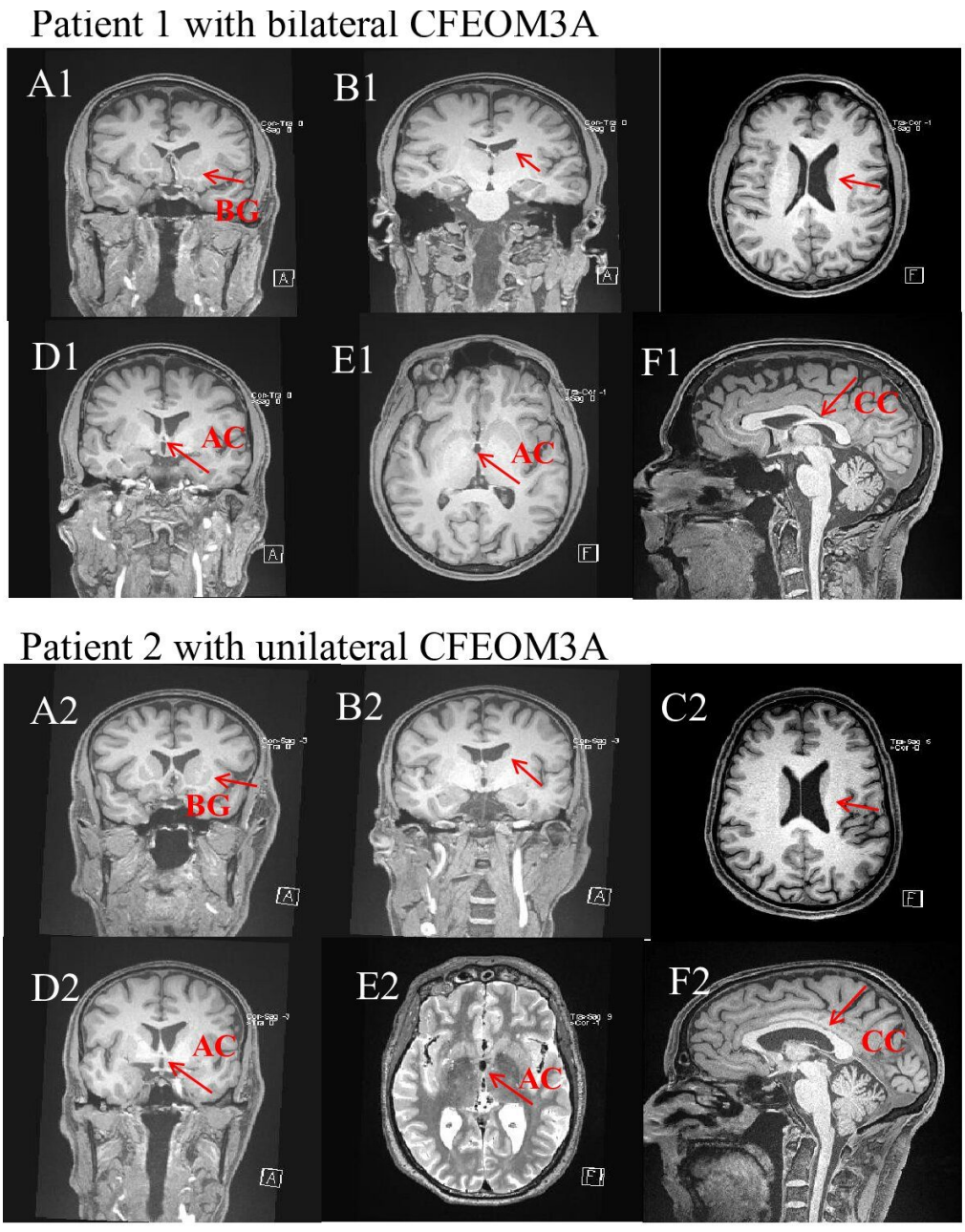

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Figure 4. Brain MRI findings in 2 patients with TUBB3-associated CFEOM3A, including 1 patient with bilateral CFEOM3A and 1 patient with unilateral CFEOM3A

A1–C1) Coronal and axial T1-weighted images of the patient with bilateral CFEOM3A show asymmetric involvement of the basal ganglia bilaterally, predominantly affecting the caudate nuclei and putamen (arrows); A2–C2) Coronal and axial T1-weighted images of the patient with unilateral CFEOM3A demonstrate unilateral, less pronounced asymmetry of the basal ganglia, primarily involving the left caudate nucleus and putamen (arrows); D1, E1) Coronal and axial T1-weighted images at the expected anatomical level of the anterior commissure in the bilateral CFEOM3A patient reveal the absence of a visible anterior commissure, with arrows indicating the anticipated location; D2, E2) Coronal T1-weighted and axial T2-weighted images of the unilateral CFEOM3A patient depict a thin but clearly identifiable anterior commissure (arrows); F1, F2) Midline sagittal T1-weighted images demonstrate corpus callosum dysgenesis in both patients; involvement of the body of the corpus callosum is slightly more pronounced in the unilateral CFEOM3A patient (L), although this difference is not considered radiologically significant.

Note: T1, T1-weighted; T2, T2-weighted.

Authors' contributions

Conceptualization: Noor M Ghiasvand and Fatemeh Sadat Rashidi; Methodology: Fatemeh Sadat Rashidi, Ehsan Ahmadipour, Afagh Alavi, Hamed Javadian, Abbas Bagheri, Motahhareh Sadeghi, and Setareh Shomali; Investigation: Fatemeh Sadat Rashidi, Ehsan Ahmadipour, Afagh Alavi, Hamed Javadian, and Parisa Azimi; Writing the original draft: Fatemeh Sadat Rashidi and Noor M Ghiasvand; Review, and editing: Noor M Ghiasvand and Parisa Azimi; Funding acquisition: Nader Maghsoudi and Fatemeh Sadat Rashidi; Resources: Fatemeh Sadat Rashidi, Motahhareh Sadeghi, and Hamed Javadian; Supervision: Noor M Ghiasvand.

Conflict of interest

The authors declared no conflict of interest.

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