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ORIGINAL RESEARCH
Pediatric Cardiology

Clinical and molecular characterizations of four patients diagnosed with mandibulofacial dysostosis, Guion-Almeida type

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ABSTRACT

Objective: Mandibulofacial dysostosis, Guion-Almeida type (MFDGA), is a rare autosomal dominant disorder caused by pathogenic variants in the *EFTUD2* gene, which encodes a component of the spliceosome complex. MFDGA is characterized by microcephaly, dysmorphic facial features, neuromotor developmental delay, intellectual disability, hearing loss, and other systemic abnormalities.

Material and Methods: We present four patients diagnosed with MFDGA in light of clinical and molecular findings using whole-exome sequencing (WES). Variant segregation was confirmed in all families, and all variants occurred *de novo*.

Results: We identified four distinct *EFTUD2* variants in our patients, including three novel variants: one splice-site variant (c.1414-1G>C) and two frameshift variants (*p.Val834Glufs24*) and (*p.Met957Valfs59*). All patients had severe microcephaly, neuromotor developmental delay, intellectual disability, and speech delay. The most frequently recognized dysmorphic facial features were epicanthus, upturned nose, anteverted nares, micrognathia, malar hypoplasia, and dysplastic ears. Common clinical findings included conductive hearing loss, feeding problems, and congenital heart anomalies, such as ventricular septal defect and secundum atrial septal defect. Novel findings included unilateral partial cutaneous syndactyly between the third and fourth fingers, autism spectrum disorder, and poor sleep.

Conclusion: This study broadens the mutational landscape of *EFTUD2* and enhances our understanding of genotype–phenotype correlations in MFDGA. The identification of three novel variants underscores the importance of molecular diagnostics in patients with syndromic craniofacial dysostoses and provides valuable data for genetic counseling and future functional studies. It also emphasizes the importance of molecular testing in accurate diagnosis and management.

Keywords: *EFTUD2*; Mandibulofacial dysostosis; Guion-Almeida type; microcephaly; neurodevelopmental delay; speech delay; whole-exome sequencing.

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Guion-Almeida tipi mandibulofasiyal disostoz tanısı konulan dört hastanın klinik ve moleküler özellikleri

ÖZET

Amaç: Mandibulofasiyal disostoz, Guion-Almeida tipi (MFDGA), spliceozom kompleksinin bir bileşenini kodlayan EFTUD2 genindeki patojenik varyantların neden olduğu nadir bir otozomal dominant hastalıktır. MFDGA; mikrosefali, dismorfik yüz özellikleri, nöromotor gelişimsel gecikme, zihinsel yetersizlik, işitme kaybı ve diğer sistemik anormalliklerle karakterizedir.

Gereç ve Yöntemler: Tüm ekzom dizilemesi (TED) kullanılarak elde edilen klinik ve moleküler bulgular ışığında MFDGA tanısı konulan dört hastayı sunuyoruz. Varyant segregasyonu tüm ailelerde doğrulandı ve tüm varyantlar *de novo* olarak meydana geldi.

Bulgular: Hastalarımızda üçü yeni olmak üzere dört farklı EFTUD2 varyantı tanımladık: bir intronik varyant (c.1414-1G>C) ve iki çerçeve kayması varyantı (*p.Val834Glufs24*) ve (*p.Met957Valfs59*). Tüm hastalarda şiddetli mikrosefali, nöromotor gelişimsel gecikme, zihinsel yetersizlik ve konuşma gecikmesi mevcuttu. En sık tanımlanan dismorfik yüz özellikleri epikantus, yukarı kalkık burun, antevert burun delikleri, mikrognati, malar hipoplazi ve displastik kulaklardı. Yaygın klinik bulgular arasında iletim tipi işitme kaybı, beslenme sorunları ve ventriküler septal defekt ile sekundum atriyal septal defekt dâhil konjenital kalp anomalileri yer alıyordu. Yeni bulgular arasında tek taraflı üçüncü ve dördüncü parmaklar arasında kısmi kutanöz sindaktili, otizm spektrum bozukluğu ve uyku bozukluğu bulunuyordu.

Tartışma: Bu çalışma, EFTUD2 varyantlarının mutasyonel spektrumunu genişletmekte ve MFDGA'daki genotip-fenotip korelasyonlarına katkı sağlamaktadır. Üç yeni varyantın tanımlanması, sendromik kraniyofasiyal disostozlu hastalarda moleküler tanılamanın önemini vurgulamakta; genetik danışmanlık ve gelecekteki fonksiyonel çalışmalar için değerli veriler sunmaktadır. Ayrıca, doğru tanı ve tedavide moleküler testlerin önemini bir kez daha ortaya koymaktadır.

Anahtar Kelimeler: EFTUD2; konuşma gecikmesi; Mandibulofasiyal disostoz; Guion-Almeida tipi; mikrosefali; nörogelişimsel gecikme; tüm ekzom dizilemesi.

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INTRODUCTION

Mandibulofacial dysostosis, Guion-Almeida type (MFDGA, MIM #610536; also known as mandibulofacial dysostosis with microcephaly), is a rare autosomal dominant craniofacial dysostosis that exhibits broad clinical variability, characterized by microcephaly, dysmorphic facial features, neuromotor developmental delay, severe speech impairment, and intellectual disability. The exact prevalence of the condition remains unknown. MFDGA is included in Group 35 of the 2023 Nosology for genetic skeletal disorders, under the category of craniofacial dysostoses, together with other well-known conditions such as Treacher Collins syndrome, Miller syndrome, and frontonasal dysplasias (1). The most characteristic facial features of MFDGA are downslanting palpebral fissures, epicanthus, malar hypoplasia, upturned nose, anteverted nares, micrognathia, dysplastic ears, and preauricular skin tags. Almost all patients with MFDGA exhibit mild to moderate, and occasionally severe, intellectual disability. In addition, short stature, choanal atresia, cleft palate, tracheoesophageal fistula (TEF)/esophageal atresia (EA), congenital heart diseases, conductive hearing loss, epilepsy, and growth retardation can be observed.

In 2006, Guion-Almeida et al. (2) first reported four patients with an unknown etiology of trigonocephaly, microcephaly, growth retardation, cleft palate, unusual ears with skin tags, intellectual disability, and severe speech delay. Later, in 2012, Lines et al. (3) identified Elongation Factor Tu GTP Binding Domain Containing 2 (*EFTUD2*) as the gene responsible for the disease in a study involving 12 patients, including two of Guion-Almeida's patients. Heterozygous single-nucleotide variants resulting in haploinsufficiency in the *EFTUD2* gene are responsible for approximately 90% of the patients, while the remaining cases are attributed to deletions and duplications of the gene. MFDGA demonstrates high penetrance and significant variability in clinical expression. Clinical manifestations in affected patients range from subtle, subclinical features that

complicate definitive diagnosis to severe, multisystem lethal anomalies (4). To date, approximately 150 patients with confirmed *EFTUD2* heterozygous variants have been reported (5). Expanding the clinical and molecular features of this genetic disorder is crucial for a better understanding of its pathogenesis.

In this study, we aimed to evaluate the clinical and molecular characteristics of four MFDGA patients with three novel *EFTUD2* variants, diagnosed through whole-exome sequencing (WES), providing new insights into the molecular and clinical diversity of the syndrome.

MATERIAL AND METHODS

Four patients from different families were included in this study. All patients exhibited microcephaly, neuromotor developmental delay, intellectual disability, severe speech delay, and dysmorphic facial features. Chromosome analysis, microarray, and CGG trinucleotide repeat testing for Fragile X syndrome were performed on peripheral blood samples from all patients. Subsequently, all patients underwent whole-exome sequencing (WES). Relevant clinical and laboratory findings were retrieved from past medical records. Written informed consent for genetic testing, as well as for the publication of clinical data, patient photographs, and genetic findings, was obtained from the parents of each patient. The study adhered to the Declaration of Helsinki and was approved by the Ethical Committee of Ümraniye Education and Research Hospital (approval number: B.10.1.TKH.4.34.H.GP.0.01/145, date: 09/05/2025).

Genomic DNA extraction from peripheral blood was performed using the DNA Blood 500 µl Kit according to established protocols. The Twist Human Core Exome V2 Kit was used for whole-exome capture and sequencing. Variant calling was performed from FASTQ files using the Sophia DDM platform, which also facilitated variant annotation and analysis. Sequence alignment and variant identification were conducted with the Pepper basic algorithm using the hg19 human genome reference.

Variants with a minor allele frequency exceeding 1% were excluded using data from the Genome Aggregation Database (gnomAD) (https://gnomad.broadinstitute.org), the 1000 Genomes Project (http://www.1000genomes.org/), and the Exome Aggregation Consortium (ExAC) (http://exac.broadinstitute.org/). Genes relevant to the patients' phenotype, particularly those involved in microcephaly, were prioritized for analysis. Variants with substantial impacts on the protein, including nonsense, frameshift, and canonical splice-site variants, were initially assessed. Candidate variants were evaluated using the ClinVar (https://www.ncbi.nlm.nih.gov/clinvar), LOVD (https://www.lovd.nl), and HGMD (http://www.hgmd.cf.ac.uk) databases, in conjunction with relevant publications. The variants were classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines (6). Segregation analysis of all variants within the families was performed using Sanger sequencing.

Statistical Analysis

Descriptive statistics of the clinical and laboratory findings are expressed as mean±standard deviation, numbers, or percentages. Comparative statistics were not performed because the number of patients was limited and not homogeneously distributed.

RESULTS

Clinical Features

Patient 1: A 2-year-8-month-old boy was referred to our pediatric genetics clinic presenting with distinctive facial traits. He was preterm, born at 35 weeks to healthy parents with no consanguinity. His birth weight was 2000 g (10^{th}–50^{th} centile), while height and head circumference were unknown. He underwent surgery due to choanal atresia. Neuromotor development was delayed, with independent sitting at 1 year of age and walking at 18 months. His speech development was significantly delayed, and he used only 1–2 words. At the age of three, his latest physical assessment revealed weight, height, and head circumference of 11 kg (-2.66 SDS), 89 cm (-2.19 SDS), and 44 cm (-4.02 SDS), respectively. Notable dysmorphic facial features included midface hypoplasia, hypertelorism, epicanthus, downslanting palpebral fissures, depressed nasal bridge, upturned nose with anteverted nares, long philtrum, micrognathia, low-set ears, preauricular skin tag, and second-degree microtia. Additionally, he had conductive hearing loss. His mother reported poor sleep. Echocardiogram findings were normal.

Patient 2: A 4-year-5-month-old boy with microcephaly and trigonocephaly was referred to our pediatric genetics clinic for assessment of a potential genetic condition. He was the second child of healthy, non-consanguineous parents with no significant family history. He was born at 36 weeks of gestation with a birth weight of 2250 g (10^{th}–50^{th} centile), a length of 46 cm (10^{th}–50^{th} centile), and a head circumference of 33 cm (50^{th}–90^{th} centile). He had a history of seizures at the age of one. Motor development was globally delayed, and he began walking at the age of 2. He was receiving treatment for mild autism spectrum disorder. At 4 years 7 months of age, anthropometric measurements revealed a weight of 16 kg (-0.7 SDS), height of 105 cm (-0.87 SDS), and occipitofrontal circumference of 45.5 cm (-3.99 SDS). His dysmorphic facial features included a prominent metopic ridge, synophrys, downslanting palpebral fissures, epicanthus, telecanthus, upturned nose, anteverted nares, prominent philtrum, micrognathia, and low-set ears. Additionally, bilateral cutaneous syndactyly of the second and third toes was observed. He had severe chewing difficulty and mild conductive hearing loss. Biochemical tests revealed a very low LDL level. Echocardiographic evaluation identified a ventricular septal defect (VSD).

Patient 3: A 5-year-old boy, the third child of healthy consanguineous parents, was born at 38 weeks of gestation. His birth weight was 3100 g (10^{th}–50^{th} centile), height 50 cm (50^{th}–90^{th} centile), and head size 33 cm (10^{th}–50^{th} centile). After

birth, he required a 3-month stay in the neonatal intensive care unit (NICU) due to respiratory distress. He underwent surgery for choanal atresia at the age of 2. Motor milestones were delayed. He was able to form simple sentences, but his speech was unclear. He had his first seizure at the age of 2. At 5.5 years, anthropometric measurements showed a weight of 16 kg (-1.63 SDS), height of 112.5 cm (-0.27 SDS), and occipitofrontal circumference of 44.5 cm (-4.98 SDS). Malar hypoplasia and dysplastic ears were noted among dysmorphic facial features. Additionally, cutaneous syndactyly was present between the third and fourth fingers of the hands and between the second and third toes of the feet. Hearing examination was normal. He had severe chewing difficulty. Echocardiography revealed a secundum atrial septal defect (ASD).

Patient 4: The boy, the second child of healthy unrelated parents, was born at 37 weeks of gestation. His birth weight was 2760 g (10^{th}–50^{th} centile), while height and head circumference were unknown. He spent six days in the neonatal intensive care unit for respiratory distress. Motor development was delayed, with walking achieved at 18 months. He had been receiving antiepileptic treatment for seizure management since the age of 1.5 years. He underwent surgery for incomplete cleft palate at the age of one. At 8 years 11 months, his weight was 27 kg (-0.31 SDS), height 121 cm (-1.93 SDS), and head size 46 cm (-4.87 SDS). His dysmorphic facial features included a prominent metopic ridge, upslanting palpebral fissures, epicanthus, and first-degree microtia. Hearing examination was compatible with conductive hearing loss. His echocardiogram was normal.

Common Findings

All patients had severe microcephaly, neuromotor developmental delay, and mild to moderate intellectual disability. Chromosome and microarray analyses were normal. CGG trinucleotide repeats for Fragile X syndrome were within the normal range. Metabolic screening–including calcium, phosphorus, and thyroid hormone levels–as well as biochemical tests assessing liver and kidney function, were normal in all four patients. All patients underwent normal abdominal ultrasonography and ophthalmologic examination. Cranial magnetic resonance imaging performed on Patients 2, 3, and 4 was normal. The clinical features of the patients are summarized in Table 1, and their photographs are shown in Figure 1.

EFTUD2 Variants

We conducted WES and detected four different heterozygous variants in the *EFTUD2* gene among the four patients. Variant classification was carried out in accordance with ACMG recommendations. Two of the variants were frameshift, while the others were nonsense and splicing variants. Three of the variants have not been previously reported in the literature. The nonsense variant c.1732C>T (p.Arg578*) in Patient 1 had been previously reported. This variant has been classified as pathogenic according to the ACMG guidelines (PVS1, PM2, PP5). In Patient 2, molecular analysis revealed a splicing variant, c.1414-1G>C. Frameshift variants c.2501del (*p.Val834Glufs24*) and c.2869_2870del (*p.Met957Valfs59*) were detected in Patient 3 and Patient 4, respectively. These novel variants have been considered likely pathogenic according to the ACMG criteria (PVS1, PM2). Segregation analysis revealed that all patients inherited the variants *de novo*. Figure 2 depicts the pedigrees of patients carrying *EFTUD2* variants.

DISCUSSION

MFDGA is a rare single-gene disorder characterized by microcephaly, neuromotor developmental delay, intellectual disability, and distinctive dysmorphological features. Characteristic facial features, such as mandibular hypoplasia and dysplastic ears, provide the primary clues for recognizing the syndrome. The *EFTUD2* gene is located on chromosome 17q21.31 and, according to the common transcript (NM_004247.3), consists of 28 exons. It encodes a highly conserved spliceosomal GTPase composed of 972 amino acids, which serves as a core unit of U5 small nuclear ribonucleoproteins and plays a pivotal role in the splicing process (7).

So far, the HGMD (Professional 2024.4, April 2025) has documented nearly 160 pathogenic mutations in the *EFTUD2* gene in affected individuals. Among these, 28% were frameshift, 26% were splicing, 19% were missense, 14% were nonsense, 10% were large deletions, and the remainder were complex rearrangements. To the best of our knowledge, no hotspot region of the *EFTUD2* gene has been identified in association with MFDGA. However, exons 16, 18, and 26 were found to harbor a higher frequency of pathogenic variants among MFDM patients compared to other exons (8). None of the patients in our cohort were found to harbor variants in these exons.

The majority of the mutations are anticipated to lead to haploinsufficiency of *EFTUD2*. It has been reported that 75% of patients were sporadic, arising from *de novo* mutations, while 19% were familial cases following an autosomal dominant inheritance pattern. Mildly affected parents may remain undiagnosed until their child is identified with MFDM. The remainder were caused by germline mosaicism (4).

To date, no definitive genotype–phenotype correlation has been established in MFDGA due to limited available data. Cardiac abnormalities observed in patients with canonical splice-site variants have been suggested as a contributing factor in determining the severity of MFDM (8). Additionally, the rate of cardiac anomalies was significantly higher in patients with frameshift variants (8). Two of our patients were diagnosed with congenital heart disease; one carried an intronic variant, while the other had a frameshift variant. In rare cases, individuals with large deletions involving *EFTUD2* may present with severe intellectual disability (9). Cleft palate has been observed more frequently in patients carrying intronic variants than in those with exonic variants (8). One of our patients had a cleft palate and carried a previously unreported frameshift variant.

In MFDGA, approximately 59% of reported patients are male (10). Notably, all patients in our cohort were male. Microcephaly is observed in a significant number of patients,

Table 1. Distribution of admission symptoms

	P1	P2	P3	P4	Total data (%)
EFTUD2 heterozy-gous variant (NM_004247.3)	*c.1732C>T* (*p.Arg578**)	*c.1414-1G>C*	*c.2501* del (*p.Val834Glufs*24*)	*c.2869_2870* del (*p.Met957Valfs*59*)	
Variant type	Nonsense	Intronic	Frameshift	Frameshift	
Novel variant	-	+	+	+	
Inheritance	*de novo*	*de novo*	*de novo*	*de novo*	
Gender	M	M	M	M	
Age	3 y	4 y 7 m	5.5 y	8 y 11 m	
Height SDS	-2.19	-0.87	-0.27	-1.93	
Weight SDS	-2.66	-0.7	-1.63	-0.31	
Head circumferen-ce SDS	-4.02	-3.99	-4.98	-4.87	
Prematurity	+	+	-	+	75
Short stature	+	-	-	-	25
Microcephaly	+	+	+	+	100
Trigonocephaly	-	+	-	+	25
Facial asymmetry	+	-	-	-	25
Midface hypopla-sia	+	-	-	-	25
Upslanting pal-pebral fissures	-	-	-	+	25
Downslanting pal-pebral fissures	+	+	-	-	75
Epicanthus	+	+	-	+	75
Choanal atresia	+	-	+	-	50
Upturned nose	+	+	-	-	50
Short nose	+	-	-	-	25
Anteverted nares	+	+	-	-	50
Malar hypoplasia	+	+	+	+	100
Prominent philtrum	+	+	-	-	50
Cleft palate	-	-	-	+	25
Mandibular hypop-lasia	+	+	+	+	100
Micrognathia	+	+	-	+	100
Microtia	+	-	-	+	50
Preauricular skin tags	+	-	-	-	25
Dysplastic ears	+	+	+	+	100
Low-set ears	+	+	-	+	75
Conductive hearing loss	+	+	-	+	75
Chewing difficulties	-	+	+	-	50
Cardiac involvement	-	Ventricular septal defect	Secundum atrial septal defect	-	50
Cutaneous syndactyly on 2nd–3rd toes of the foot	-	+	+	-	50
Proximally placed thumbs	-	+	+	-	50
Delayed motor mi-lestones	+	+	+	+	100
Intellectual disabi-lity	+	+	+	+	100
Speech delay	+	+	+	+	100
Seizure	-	+	+	+	75
Other anomalies	Poor sleep	Low LDL levels, autism spectrum	Cutaneous syndactyly disorder on 3rd–4th fingers of the hand	Dysplastic uvula	

EFTUD2: Elongation factor tu gtp binding domain containing 2; SDS: Standard deviation score; LDL: Low-density lipoprotein; Y: Years; M: Months.

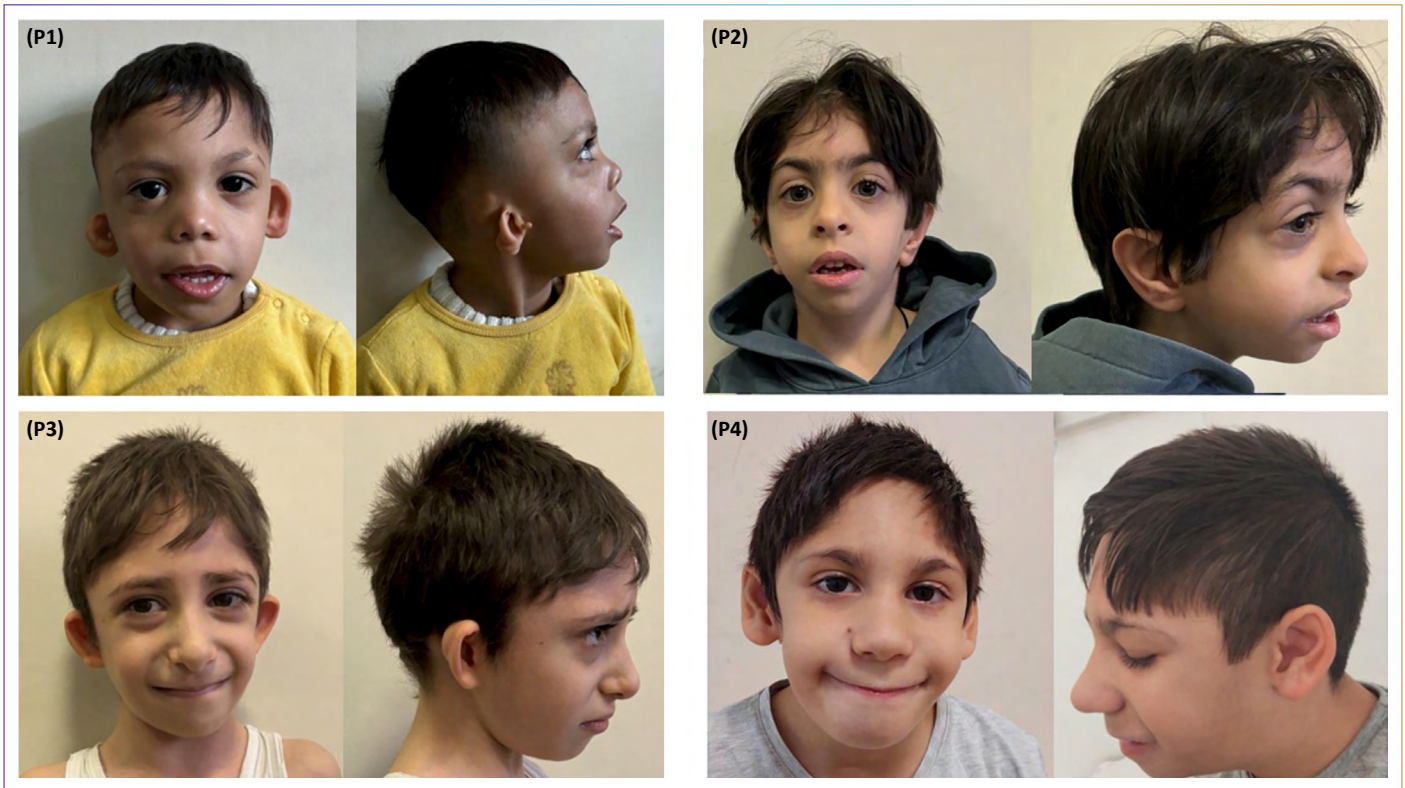

Figure 1. Dysmorphic facial features of the patients. All patients exhibited micrognathia, which was especially prominent in lateral view photographs. **(P1)** Epicanthus, hypertelorism, downslanting palpebral fissures, depressed nasal bridge, upturned nose with anteverted nares, low set ears, pre-auricular skin tag on the right ear, and microtia. **(P2)** Trigonocephaly, synorphysis, downslanting palpebral fissures, telecanthus, and low set ears. **(P3)** Malar hypoplasia, dysplastic and protrude ears. **(P4)** Trigonocephaly, hypertelorism, upslanting palpebral fissures, and microtia.

tends to be severe, and may have either a prenatal or postnatal onset (3, 11). The head circumference at birth was documented for two of our patients, and both measurements were within the normal range for their gestational age. However, all had severe microcephaly at their latest examinations, with a mean head circumference of -4.46 SDS. In some studies, none of the patients exhibited microcephaly, underscoring the clinical heterogeneity of the disease (5, 12).

In MFDGA, all patients exhibit varying degrees of neuromotor developmental delay, speech delay, and intellectual disability. Expressive language skills are more delayed compared to other motor milestones. The average age at which patients spoke their first words ranged from 20 to 30 months (3). Central nervous system (CNS) anomalies are infrequently observed in patients with MFDGA and may include cerebral atrophy, delayed myelination, exencephaly, cerebellar and pontine hypoplasia, as well as olfactory bulb agenesis (4, 11, 13). Matsuo et al. (14) reported that approximately 21.2% of individuals with MFDGA experience seizures, which may be linked to brain degeneration. Three of our four patients had a history of seizures, and cranial MRI findings were unremarkable. This discrepancy from previously reported data may be attributed to the limited sample size in our cohort.

Mandibular hypoplasia is observed in nearly all patients and, in some individuals, may be associated with cleft palate,

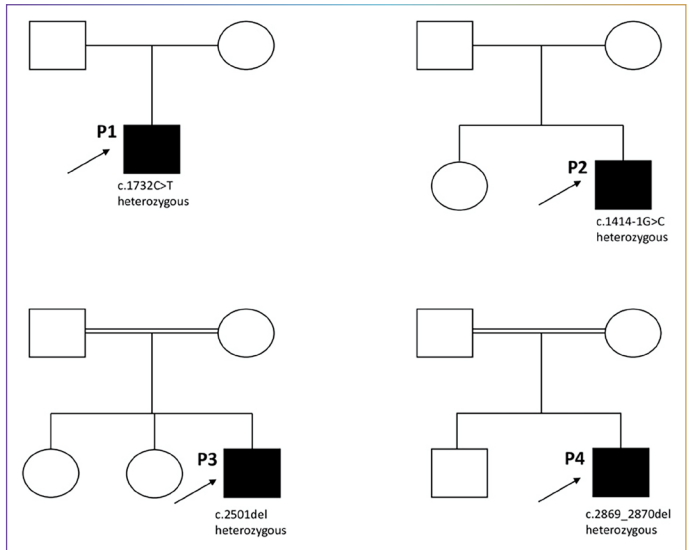

Figure 2. Pedigrees of the patients with *de novo EFTUD2* variants.

constituting Pierre Robin sequence. This condition can lead to glossoptosis and cause feeding difficulties, requiring tube feeding or gastrostomy. Additionally, patients with severe respiratory distress necessitating tracheostomy have been reported as well (10, 15). None of our patients had severe mandibular hypoplasia leading to feeding difficulties or significant respiratory distress.

Choanal atresia or stenosis occurs in approximately 33% of patients with MFDGA (4). Two of our patients had choanal atresia. Short stature has been reported in approximately 30% of patients with MFDGA, although severe growth impairment is typically not observed (4). In line with previous reports, short stature was observed in 25% of our patients.

Another common major feature of MFDGA is congenital cardiac anomalies, observed in more than half of patients—primarily ASD, but also including VSD, patent ductus arteriosus (PDA), peripheral pulmonary stenosis, aortic coarctation, and tricuspid insufficiency (3, 4, 11, 16). In our study, consistent with the literature, two patients had secundum ASD and VSD as cardiac malformations.

Gastrointestinal issues were seen in 27–33% of patients, such as TEF and EA (4, 11, 17). Two of our patients experienced severe chewing difficulties, but none had a history of EA or TEF. Ophthalmologic involvement is observed in approximately 30% of patients and includes conditions such as astigmatism, myopia, hypermetropia, strabismus, and lacrimal duct stenosis (11). None of these manifestations were present in our patients.

Approximately 71% of patients with MFDGA experience hearing loss, the majority of which is conductive in nature. Abnormalities of the middle and inner ear, including malformation or absence of the middle ear ossicles, auditory canal stenosis or atresia, or both, can be observed (4, 5, 11). Similar to the literature, conductive hearing loss was detected in 75% of our patients; however, none underwent imaging to investigate the underlying etiology.

Malformations of the urogenital system, such as cryptorchidism, small scrotum, unilateral renal agenesis, and vesicoureteral reflux, have been reported rarely (3, 11). No urogenital anomalies were identified in any of our patients. Kyphosis, scoliosis, fifth finger clinodactyly, brachydactyly, camptodactyly, pectus carinatum, hemivertebrae, zygomatic cleft, absent ribs, and supernumerary ribs are skeletal anomalies that are infrequently observed (4, 11, 12, 15). All of our patients underwent radiographic evaluation for skeletal involvement. No scoliosis or costal anomalies were identified; only brachydactyly and clinodactyly were detected, each in two patients.

Cutaneous syndactyly of the second and third toes is a rare finding (11). Interestingly, this anomaly was identified in two of our patients. Additionally, one of these patients exhibited unilateral partial cutaneous syndactyly between the third and fourth fingers, a feature not previously reported in the literature to date. In the literature, only one 8-year-old male patient carrying the *de novo* c.994+5G>A *EFTUD2* variant has been reported with a possible diagnosis of autism spectrum disorder (18). In our patient cohort, a patient harboring the c.1414-1G>C variant was also diagnosed with mild autism spectrum disorder. One of our patients exhibited sleep disturbances, a finding that has not been previously reported in the literature. These findings appear to be novel, although a coincidental occurrence cannot be ruled out. The limited number of patients included in our study represents a restricting factor for drawing definitive conclusions.

CONCLUSION

The diagnosis and genetic counseling of patients with microcephaly, intellectual disability, and speech delay, who lack significant systemic involvement, are especially important for future generations. WES is a highly effective molecular diagnostic tool for identifying causative genes in numerous rare disorders, particularly in unrelated sporadic cases. We report novel pathogenic variants in the *EFTUD2* gene and emphasize unique clinical features of MFDGA, such as hypocholesterolemia, autism spectrum disorder, cutaneous syndactyly of the fingers, and sleep disturbances. The identification of these novel characteristics underscores the need for updated management recommendations. Furthermore, accurate identification of the underlying genetic disorder is essential for providing effective genetic counseling. Given the considerable risk of recurrence, patients should be offered preimplantation genetic testing.

Ethics Committee Approval: The Ümraniye Education and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 09/05/2025, number: B.10.1.TKH.4.34.H.GP.0.01/145).

Informed Consent: Written informed consent for genetic testing, as well as for the publication of clinical data, patient photographs, and genetic findings, was obtained from the parents of each patient.

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Hasta Onamı: Genetik testler, klinik verilerin, hasta fotoğraflarının ve genetik bulguların yayınlanması için her hastanın ebeveynlerinden yazılı bilgilendirilmiş onam alındı.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

Yazma Yardımı için Yapay Zeka Kullanımı: Beyan edilmedi.

Yazarlık Katkıları: Fikir – BY, YKD, ZYY; Tasarım – GK, ÖAD, AS; Denetlemeler – YKD, ZYY; Kaynaklar – BY, GK, ÖAD, TK; Malzemeler – SÖ, TK, AS; Veri Toplama ve/veya İşleme – BY, SÖ, EU, TK; Analiz ve/veya Yorumlama – BY, EU, YKD; Literatür Araştırması – EU, TK; Yazım – BY, GK, ZYY; Eleştirel İncelemeler – SÖ, AS, ÖAD.

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REFERENCES

1. Unger S, Ferreira CR, Mortier GR, Ali H, Bertola DR, Calder A, et al. Nosology of genetic skeletal disorders: 2023 revision. Am J Med Genet A 2023;191:1164–209.
2. Guion-Almeida ML, Zechi-Ceide RM, Vendramini S, Ju Nior AT. A new syndrome with growth and mental retardation, mandibulofacial dysostosis, microcephaly, and cleft palate. Clin Dysmorphol 2006;15:171–4.
3. Lines MA, Huang L, Schwartzentruber J, Douglas SL, Lynch DC, Beaulieu C, et al. Haploinsufficiency of a spliceosomal GTPase encoded by *EFTUD2* causes mandibulofacial dysostosis with microcephaly. Am J Hum Genet 2012;90:369–77.
4. Huang L, Vanstone MR, Hartley T, Osmond M, Barrowman N, Allanson J, et al. Mandibulofacial dysostosis with microcephaly: mutation and database update. Hum Mutat 2016;37:148–54.
5. Chen Y, Yang R, Chen X, Lin N, Li C, Fu Y, et al. Atypical mandibulofacial dysostosis with microcephaly diagnosed through the identification of a novel pathogenic mutation in *EFTUD2*. Mol Genet Genomic Med 2024;12:e2426.
6. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405–24.
7. Beauchamp MC, Alam SS, Kumar S, Jerome-Majewska LA. Spliceosomopathies and neurocristopathies: Two sides of the same coin? Dev Dyn 2020;249:924–45.
8. Ulhaq ZS, Soraya GV, Istifiani LA, Pamungkas SA, Arisanti D, Dini B, et al. A brief analysis on clinical severity of mandibulofacial dysostosis guion-almeida type. Cleft Palate Craniofac J 2024;61:688–96.
9. Zarate YA, Bell C, Schaefer GB. Radioulnar synostosis and brain abnormalities in a patient with 17q21.31 microdeletion involving *EFTUD2*. Cleft Palate Craniofac J 2015;52:237–9.
10. Abell K, Hopkin RJ, Bender PL, Jackson F, Smallwood K, Sullivan B, et al. Mandibulofacial dysostosis with microcephaly: An expansion of the phenotype via parental survey. Am J Med Genet A 2021;185:413–23.
11. Lehalle D, Gordon CT, Oufadem M, Goudefroye G, Boutaud L, Alessandri JL, et al. Delineation of *EFTUD2* haploinsufficiency-related phenotypes through a series of 36 patients. Hum Mutat 2014;35:478–85.
12. Luquetti DV, Hing AV, Rieder MJ, Nickerson DA, Turner EH, Smith J, et al. "Mandibulofacial dysostosis with microcephaly" caused by *EFTUD2* mutations: expanding the phenotype. Am J Med Genet A 2013;161A:108–13.
13. Silva JB, Soares D, Leão M, Santos H. Mandibulofacial dysostosis with microcephaly: a syndrome to remember. BMJ Case Rep 2019;12:e229831.
14. Matsuo M, Yamauchi A, Ito Y, Sakauchi M, Yamamoto T, Okamoto N, et al. Mandibulofacial dysostosis with microcephaly: A case presenting with seizures. Brain Dev 2017;39:177–81.
15. Smigiel R, Bezniakow N, Jakubiak A, Błoch M, Patkowski D, Obersztyn E, et al. Phenotype analysis of Polish patients with mandibulofacial dysostosis type Guion-Almeida associated with esophageal atresia and choanal atresia caused by *EFTUD2* gene mutations. J Appl Genet 2015;56:199–204.
16. Kim SY, Lee DH, Han JH, Choi BY. Novel splice site pathogenic variant of *EFTUD2* Is associated with mandibulofacial dysostosis with microcephaly and extracranial symptoms in Korea. Diagnostics (Basel) 2020;10:296.
17. Kohailan M, Al-Saei O, Padmajeya S, Aamer W, Elbashir N, Al-Shabeeb Akil et al. A *de novo* start-loss in *EFTUD2* associated with mandibulofacial dysostosis with microcephaly: case report. Cold Spring Harb Mol Case Stud 2022;8:a006206.
18. Need AC, Shashi V, Hitomi Y, Schoch K, Shianna KV, McDonald MT, et al. Clinical application of exome sequencing in undiagnosed genetic conditions. J Med Genet 2012;49:353–61.