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Case Report

Unmasking Guion-Almeida syndrome: clinical and genetic insights from a 3-year-old with EFTUD2 mutation

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ABSTRACT

Guion-Almeida–type mandibulofacial dysostosis is an uncommon craniofacial syndrome arising from EFTUD2 mutations. Because its clinical phenotype overlaps significantly with other forms of mandibulofacial dysostosis, genetic testing is often required to secure a definitive diagnosis. Herein this report describes a 3 year 5-month-old male child who exhibited characteristic craniofacial dysmorphism, a surgically corrected cleft palate, speech delay, recurrent respiratory tract infections, and bilateral conductive hearing loss. His growth indices were persistently below −3 SD. Whole-exome sequencing identified a heterozygous pathogenic EFTUD2 variant, thereby confirming the diagnosis of MFDGA. The child received supportive respiratory management, nutritional rehabilitation, and continued speech and hearing therapy. Follow-up evaluation demonstrated spontaneous closure of a previously noted muscular ventricular septal defect. Ongoing multidisciplinary care was recommended to comprehensively address craniofacial, developmental, and systemic concerns. This case underscores the pivotal role of molecular diagnostics in distinguishing MFDGA from phenotypically similar craniofacial disorders and highlights the importance of coordinated, long-term multidisciplinary management throughout childhood.

Keywords: Mandibulofacial dysostosis, EFTUD2 mutation, Craniofacial anomalies, Cleft palate, Developmental delay, Exome sequencing

INTRODUCTION

Guion-Almeida type mandibulofacial dysostosis is an uncommon genetic condition marked by craniofacial abnormalities such as underdeveloped mandible, micrognathia, palatal cleft and ear malformations. Affected children frequently present with feeding difficulties, recurrent respiratory infections, speech delay, and hearing impairment.[1]

Systemic manifestations include congenital heart disease, recurrent respiratory infections, esophageal atresia, vertebral segmentation defects, and short stature. Due to phenotypic overlap with conditions such as Treacher Collins syndrome and Pierre Robin sequence, diagnosis is often challenging without genetic confirmation. This case describes a 3-year-old boy with hallmark features of MFDGA confirmed by exome sequencing, emphasizing the role of molecular diagnosis and multidisciplinary care in such patients.

CASE REPORT

A 3-year 5-month-old boy presented with intermittent fever for one-week, productive cough, and increasing respiratory distress. He had a history of recurrent respiratory tract infections, including bronchopneumonia at 2 years. Perinatal history was unremarkable.

Developmentally, he had delayed language milestones with a developmental quotient of 58.5%. Gross motor delay was present until 18 months but normalized thereafter. He was receiving regular speech and occupational therapy. He underwent Veau–Wardill–Kilner pushback palatoplasty at 1 year of age for cleft palate. A congenital muscular ventricular septal defect diagnosed

during infancy had closed spontaneously. BERA demonstrated bilateral mild conductive hearing loss (peak wave V at 50 dB).

On examination, he was undernourished and stunted (weight 9.4 kg; height 88 cm; both < −3 SD; weight-for-height < −3 SD). Dysmorphic facies included micrognathia, retrognathia, dental crowding, surgically corrected cleft palate, low-set bat-like ears, a right preauricular sinus, and a left preauricular tag (Figure 1). A draining sinus tract was also noted in the neck.

Genetic analysis via whole exome sequencing revealed a heterozygous pathogenic variant in the EFTUD2 gene, establishing the diagnosis of Guion-Almeida type mandibulofacial dysostosis (Table 1).

Management and outcome

He received antibiotics and respiratory support for the current lower respiratory tract infection. Nutritional rehabilitation was initiated due to severe undernutrition. Hearing management and speech therapy were continued.

Cardiology review confirmed spontaneous closure of the VSD with no residual hemodynamic compromise. ENT follow-up was planned for ongoing conductive hearing loss and recurrent infections. The child improved clinically and was discharged with advice for long-term multidisciplinary follow-up involving ENT, cardiology, pulmonology, nutrition and genetic counselling.

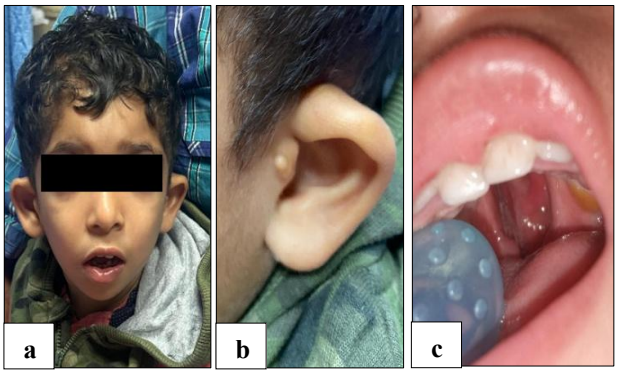

Figure 1: (a) Clinical photographs of the patient demonstrate micrognathia with low-set, bat-like ears, (b) a preauricular tag, and (c) a cleft palate prior to surgical repair.

Table 1: Whole-exome sequencing identified a heterozygous pathogenic variant in EFTUD2, confirming mandibulofacial dysostosis of the Guion-Almeida type.

Gene (transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
EFTUD2 (ENST00000426333.7)	Exon 16	c.1570A>G *(p.Ile524Val)*	Heterozygous	Mandibulofacial dysostosis, Guion-Almeida type (OMIM #610536)	Autosomal dominant	Uncertain significance (PM2)

DISCUSSION

Mandibulofacial dysostosis of the Guion-Almeida type (MFDGA), also called mandibulofacial dysostosis with microcephaly (MFDM), is a rare congenital disorder involving abnormalities of the craniofacial skeleton first described in 2006.[1] Advances in molecular genetics have identified EFTUD2 pathogenic mutations as the principal cause.[2] Recognition of the condition is clinically important, as its manifestations extend beyond the craniofacial region and require multidisciplinary management.

The most consistent clinical features of MFDGA are craniofacial anomalies, microcephaly, and developmental delay. Mandibular hypoplasia and retrognathia produce the typical facial profile, while cleft palate contributes to feeding problems, otitis media, and delayed speech development. External ear anomalies, such as microtia and preauricular tags, often cause conductive hearing loss.[1,3,5] In our patient, micrognathia, surgically repaired cleft palate, bilateral mild hearing loss, and dysmorphic ears closely reflected this phenotype. Microcephaly is an especially useful distinguishing feature, since it is not usually observed in clinically overlapping conditions like Treacher Collins syndrome.[3] Developmental impairments, especially speech delay, is common. Our patient had delayed language milestones and a developmental quotient below 60, consistent with previously reported cases.[2,4]

Systemic involvement varies between patients. Cardiac defects are among the most frequent extracranial findings, most commonly ventricular septal defects, although conotruncal anomalies have also been described.[6] Our patient had a muscular ventricular septal defect diagnosed in infancy, which closed spontaneously, illustrating the variable course of cardiac manifestations.

Recurrent respiratory infections are another important source of morbidity, often linked to palatal dysfunction or airway anomalies. This was also a major clinical problem for our patient, who required repeated admissions for lower respiratory tract infections. Growth restriction, present in this child, has been well documented in several case series.[5]

The molecular basis of MFDGA lies in EFTUD2 haploinsufficiency. The gene encodes a spliceosomal GTPase crucial for pre-mRNA splicing. Loss of one functional allele disrupts RNA processing, predominantly affecting neural crest–derived cells, which contribute to the development of craniofacial skeleton, ear structures, and cardiovascular system.[2,7] This explains the triad of mandibular hypoplasia, ear anomalies, and microcephaly, along with multisystem involvement. While most cases arise de novo, autosomal dominant transmission and cases of parental mosaicism have been observed in affected individuals.[2,3] This highlights the importance of genetic counselling for affected families, even when no family history is evident.

MFDGA shares several features with other craniofacial disorders. Treacher Collins syndrome has overlapping mandibular and auricular anomalies but typically lacks microcephaly and neurodevelopmental delay. Micrognathia and cleft palate define Pierre Robin sequence, which most often presents as an isolated defect without systemic involvement. Nager syndrome presents with mandibulofacial dysostosis but is distinguished by preaxial limb defects.[3,4] Hence, molecular confirmation of an EFTUD2 mutation is crucial for accurate diagnosis and counselling.

Treatment is supportive and requires a multidisciplinary approach. Early cleft repair is essential to improve feeding and speech development. Audiological interventions, including hearing aids or bone-conduction devices, should be initiated promptly to mitigate the impact of conductive hearing loss.[3,4] Nutritional support and close growth monitoring are critical in children with feeding difficulties or poor weight gain. Cardiology evaluation is warranted to identify and follow congenital heart disease, while ENT and pulmonology input are needed for recurrent respiratory infections or airway obstruction. Developmental therapies—speech, occupational, and physiotherapy—play a central role in improving long-term outcomes. Genetic counselling should be offered to families to explain recurrence risk and inheritance patterns.[2,3]

The outlook in MFDGA depends on the extent of systemic involvement. Children with milder craniofacial anomalies and limited systemic complications may achieve good developmental progress and independence. In contrast, those with severe cardiac disease, persistent respiratory problems, or significant neurodevelopmental impairment often face greater morbidity.[2,5,6] Nevertheless, early molecular diagnosis, coordinated multidisciplinary care, and proactive management of complications substantially improve quality of life.

CONCLUSION

MFDGA is a rare but clinically recognizable disorder characterized by craniofacial anomalies, microcephaly, cleft palate, ear malformations, and developmental delay. Most cases result from EFTUD2 mutations causing spliceosomal dysfunction. Recognition of its multisystem nature is essential for accurate diagnosis, prognosis, and management. Genetic confirmation distinguishes MFDGA from overlapping syndromes, provides recurrence-risk counselling, and facilitates coordinated multidisciplinary care throughout life.

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