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Mandibulofacial Dysostosis with Microcephaly

Synonym: Mandibulofacial Dysostosis, Guion-Almeida Type (MFDGA), *EFTUD2*-Related Mandibulofacial Dysostosis with Microcephaly (Guion-Almeida Type)

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Summary

Clinical characteristics

Mandibulofacial dysostosis with microcephaly (MFDM) is characterized by malar and mandibular hypoplasia, microcephaly (congenital or postnatal onset), intellectual disability (mild, moderate, or severe), malformations of the external ear, and hearing loss that is typically conductive. Associated craniofacial malformations may include cleft palate, choanal atresia, zygomatic arch cleft (identified on cranial CT scan), and facial asymmetry. Other relatively common findings (present in 25%-35% of individuals) can include cardiac anomalies, thumb anomalies, esophageal atresia/tracheoesophageal fistula, short stature, spine anomalies, and epilepsy.

Diagnosis/testing

The diagnosis of MFDM is confirmed in a proband with typical clinical findings and a heterozygous pathogenic variant in *EFTUD2* identified by genetic testing.

Management

Treatment of manifestations: Individualized treatment of craniofacial manifestations is managed by a multidisciplinary team which may include: oromaxillofacial surgery, plastic surgery, otolaryngology, dentistry/orthodontics, and occupational and speech-language therapy. Newborn infants may have airway compromise at delivery due to choanal atresia and/or mandibular hypoplasia, requiring intubation and/or tracheostomy for initial stabilization. Esophageal atresia/tracheoesophageal fistula, cardiac defects, renal anomalies, and thumb anomalies are treated in a routine manner. Short stature is managed expectantly. Treatment of hearing loss is individualized, and may involve conventional hearing aid(s), bone-anchored hearing aid(s), and/or cochlear implant(s). Early individualized educational and therapy plans are devised as needed to optimize developmental outcome.

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Surveillance: Annual growth assessment and periodic developmental assessment with evaluation for obstructive sleep apnea and epilepsy as needed.

Genetic counseling

MFDM is an autosomal dominant disorder. Most individuals diagnosed with MFDM to date are presumed to have the disorder as the result of a *de novo EFTUD2* pathogenic variant; in some individuals, the causative pathogenic variant was inherited from a parent with a milder phenotypic presentation. If a parent of the proband has the pathogenic variant identified in the proband, the risk to sibs of the proband (at conception) is 50%. Once the causative *EFTUD2* pathogenic variant has been identified in an affected family member, prenatal testing and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Mandibulofacial dysostosis with microcephaly (MFDM) **should be suspected** in individuals with **mandibulofacial dysostosis** (a developmental disorder of the first and second branchial arches characterized by malar and maxillary hypoplasia) in the context of one or more additional features, including:

- **Microcephaly** (defined here as occipitofrontal circumference ≥2 SD below mean), which may be either primary (i.e., congenital; present a birth) or secondary (i.e., postnatal onset)
- **Intellectual disability,** which may be mild, moderate, or severe
- **Characteristic malformations of the external ear** (see Figure 1), which include microtia (grades I-III), deficiency of the superior helix and antihelix, preauricular tags, and auditory canal atresia/stenosis. The posterior-inferior margin of the lobule may have a right-angle ("squared-off") configuration.
- **Hearing loss,** typically conductive

Establishing the Diagnosis

The diagnosis of MFDM **is established** in a proband with typical clinical findings and a heterozygous pathogenic (or likely pathogenic) variant in *EFTUD2* identified by genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *EFTUD2* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the clinical phenotype of MFDM varies, individuals with highly characteristic clinical findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with an atypical or nonspecific clinical phenotype overlapping other inherited syndromes are more likely to be diagnosed using comprehensive genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of MFDM, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

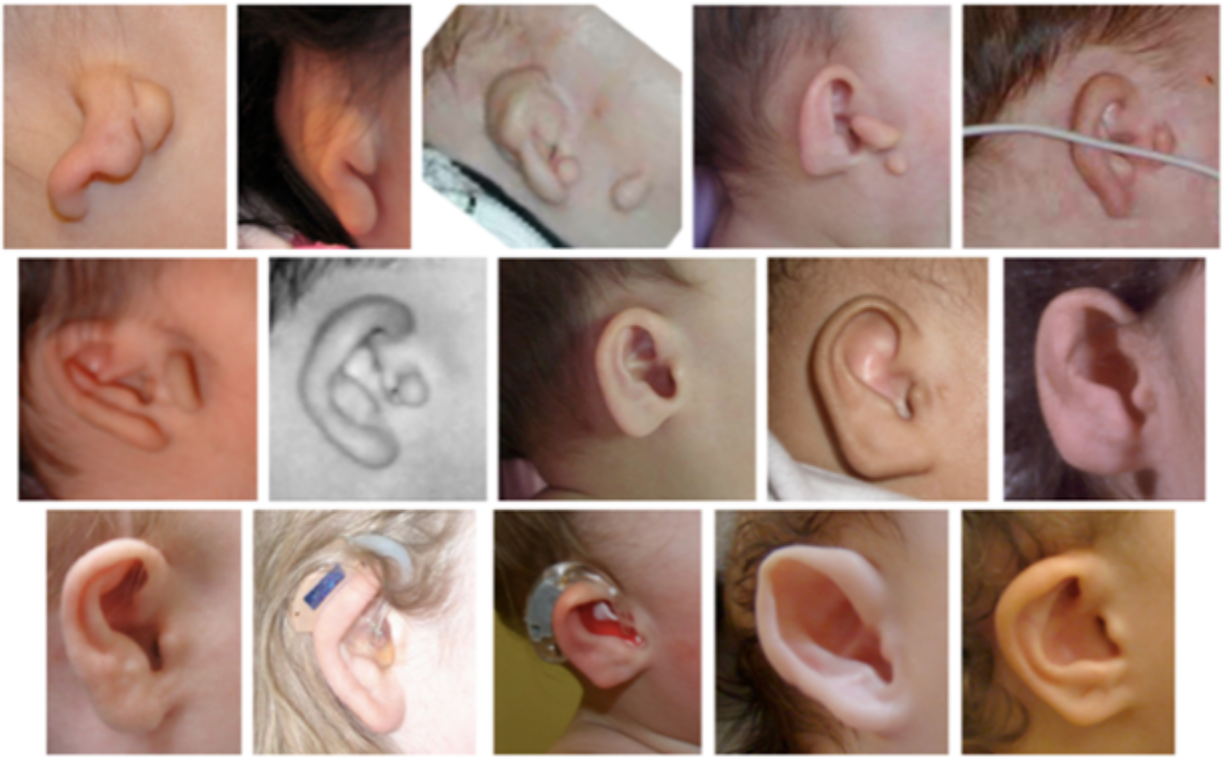

Figure 1. Range of external ear findings in MFDM. Microtia may be of any degree, and is frequently accompanied by preauricular tag(s) and/or auditory canal atresia/stenosis. The superior helix is relatively deficient. The posterior-inferior rim of the lobule may adopt a square configuration (e.g., see bottom right), which, if present, is suggestive.

- **Single-gene testing.** Sequence analysis of *EFTUD2* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **A multigene panel** that includes *EFTUD2* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder, a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited disorders with similar craniofacial features or is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, other techniques (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis (see Table 1).

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Mandibulofacial Dysostosis with Microcephaly

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
EFTUD2	Sequence analysis [3]	93% [4]
	Gene-targeted deletion/duplication analysis [5]	7% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Gordon et al [2012], Lines et al [2012], Need et al [2012], Luquetti et al [2013], Voigt et al [2013], Lehalle et al [2014], Deml et al [2015], Gandomi et al [2015], Sarkar et al [2015], Smigiel et al [2015], Huang et al [2016], Vincent et al [2016], Bick et al [2017], Matsuo et al [2017], McDermott et al [2017], Rengasamy Venugopalan et al [2017], Williams et al [2017], Paderova et al [2018], Yu et al [2018], Lacour et al [2019], Silva et al [2019], Wu et al [2019]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

Mandibulofacial dysostosis with microcephaly (MFDM) is a multiple malformation syndrome comprising craniofacial skeletal anomalies, microcephaly, developmental delay / intellectual disability, abnormalities of the ears and hearing, and, in some instances, extracranial malformations (esophageal atresia, congenital heart defects, thumb anomalies), and/or short stature.

To date, 126 individuals have been identified with a pathogenic variant in *EFTUD2* [Gordon et al 2012, Lines et al 2012, Need et al 2012, Luquetti et al 2013, Voigt et al 2013, Lehalle et al 2014, Deml et al 2015, Gandomi et al 2015, Sarkar et al 2015, Smigiel et al 2015, Huang et al 2016, Vincent et al 2016, Bick et al 2017, Matsuo et al 2017, McDermott et al 2017, Rengasamy Venugopalan et al 2017, Williams et al 2017, Paderova et al 2018, Yu et al 2018, Lacour et al 2019, Silva et al 2019, Wu et al 2019]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Mandibulofacial Dysostosis with Microcephaly: Frequency of Select Features

Feature		% of Persons w/Feature	Comment
Facial structural differences	Malar hypoplasia	92%	
	Micrognathia / Mandibular hypoplasia	93%	
	Cleft palate	43%	
	Choanal atresia	30%	
	Facial asymmetry	58%	
Microcephaly		87%	Occipitofrontal circumference ≥2 SD below mean
Developmental delay / Intellectual disability		97%	Severity varies (may be mild, moderate, or severe; critical sequelae (e.g. neonatal airway compromise, cardiac anomalies) may affect developmental outcome.
Ear malformations & hearing loss	Microtia / Dysplastic pinna(e)	97%	
	Auditory canal atresia or stenosis	68%	
	Preauricular tag	50%	
	Hearing loss	83%	
Other findings	Cardiac anomalies	35%	Typically atrial &/or ventricular septal defect
	Thumb anomalies	34%	Typically proximally placed; uncommonly, preaxial polydactyly or hypoplasia
	Esophageal atresia / Tracheoesophageal fistula	33%	
	Short stature	30%	
	Spine anomalies	28%	Incl scoliosis, kyphosis, hemivertebrae, & cervical segmentation anomalies
	Epilepsy	26%	

Mandibulofacial dysostosis is characterized by malar and maxillary hypoplasia.

Accompanying findings in MFDM include micrognathia/mandibular hypoplasia, cleft palate, and/or choanal abnormality.

Cleft palate in MFDM occurs as a Pierre Robin sequence, characterized by a midline bony defect without accompanying cleft lip. Submucous cleft has also been described. Choanal atresia is generally osseous, being either unilateral or bilateral; choanal stenosis is also frequent.

Zygomatic arch cleft has been identified in ten of 19 individuals assessed (best done with cranial CT with 3-D reconstruction).

Characteristic dysmorphic features (Figure 2), distinct from those seen in the other mandibulofacial and acrofacial dysostoses (see Differential Diagnosis), are recognizable by early childhood. In addition to malar and maxillary hypoplasia, microcephaly, and the typical ear anomalies described in this section, features include metopic ridge, prominent glabella, broad nasal bridge with prominent ridge and bulbous tip, large oral aperture, everted lower lip, and/or (frequently) facial asymmetry.

Microcephaly is present in about 87% of reported individuals (n=33; median -3.5 SD; range -0.2 SD to -6.5 SD) [Huang et al 2016]. Cephalic growth curves for MFDM are published [Huang et al 2016]. In some instances,

individuals have exhibited apparent cephalic "catch-up" growth, resulting in a normal adult occipitofrontal circumference despite microcephaly in childhood. Individuals whose head circumference falls within the normal range have also been reported to have intellectual disability [Luquetti et al 2013, Lehalle et al 2014].

Developmental delay and/or intellectual disability are present in almost all individuals. Among 30 persons on whom data are available, the degree of intellectual disability was reported as "mild" (~40%), "moderate" (~50%), or "severe" (~10%) [Gordon et al 2012, Lines et al 2012, Luquetti et al 2013, Voigt et al 2013].

Affected children are ambulatory but show delayed motor development, taking first steps at a median age of 26 months (n=38; range 13-60 months) [Huang et al 2016].

Among those who are verbal, the median reported age at first words is 27 months (n=32; range 12 months to 5.6 years); some affected persons remain nonverbal into adult life [Huang et al 2016]. Assessment of language skills may be confounded by the presence of hearing loss and/or cleft palate.

To date there have been no detailed or cross-sectional studies of long-term neuropsychological outcomes in MFDM. Developmental data in the few affected adults identified to date suggest a broad range of outcomes, with some affected persons achieving semi-independent living with paid employment [Huang et al 2016], whereas others are nonverbal and require extensive assistance with daily activities [Authors, unpublished data].

Ear malformations and hearing loss

- **External ear malformations.** External ears are anomalous in virtually all affected individuals. Typical findings (see Figure 2) include microtia (grades I-III), deficiency of the superior helix and antihelix, preauricular tags, and auditory canal atresia/stenosis. The posterior-inferior margin of the lobule may have a right-angle ("squared-off") configuration.
- **Middle/inner ear malformations.** Ear structures (ossicles, semicircular canals) are absent and/or malformed in some individuals; this is best assessed by temporal bone CT [Gordon et al 2012, Luquetti et al 2013, Voigt et al 2013].
- **Hearing loss.** Hearing loss is typically conductive (~60%) as opposed to sensorineural or mixed, and is likely to result from malformation or absence of the middle ear ossicles, auditory canal atresia, or both.

Other relatively common findings

- **Cardiac anomalies** are present in 35% of individuals. Hemodynamically insignificant atrial and ventricular septal defects are the most common; tetralogy of Fallot, patent ductus arteriosus, and aortic arch abnormalities (e.g., coarctation) have also been reported [Need et al 2012, Lehalle et al 2014].
- **Thumb anomalies** (proximally placed, duplicated, or hypoplastic thumbs) are seen in about 35% of individuals.
- **Esophageal atresia / tracheoesophageal fistula** (EA/TEF) is present in about 35% of affected individuals. EA/TEF is typically type C (the most common type), in which the upper esophageal pouch ends blindly and the lower esophageal pouch connects abnormally to the trachea (distal tracheoesophageal fistula). Laryngotracheal anomalies (tracheomalacia, posterior laryngotracheoesophageal clefts) may be seen in association with EA/TEF. It may be suspected antenatally because of polyhydramnios or absent stomach echolucency, or neonatally in the context of unexplained respiratory distress and/or failed nasogastric tube placement.
- **Short stature** is present in 30% of individuals. Height growth curves for MFDM are published [Huang et al 2016].
- **Spine anomalies** include scoliosis, kyphosis, hemivertebrae, and cervical segmentation anomalies.
- **Epilepsy** is present in 26% of individuals. Detailed clinical data regarding the type of epilepsy have not been specifically reported. Matsuo et al [2017] report one individual with recurrent seizures for which EEG demonstrated occasional spike discharges originating from the right frontal area.

Additional malformations (low frequency)

- **Other CNS abnormalities.** Although brain MRI imaging data is limited, in most cases individuals have a structurally normal brain (apart from microcephaly). The CNS malformations reported on rare occasion have included undergyration, cerebral atrophy, cerebellar and pontine hypoplasia, olfactory bulb agenesis, and (in 1 individual) exencephaly [Lines et al 2012, Lehalle et al 2014, Huang et al 2016, Matsuo et al 2017, Lacour et al 2019, Silva et al 2019].
- **Renal anomalies** include unilateral renal agenesis, vesicoureteric reflux, and ureteropelvic junction obstruction.
- **Other.** Cryptorchidism, lacrimal system abnormalities, and epidermal dermoid have each been reported in one or a few individuals [Lines et al 2012, Luquetti et al 2013, Lehalle et al 2014].

Genotype-Phenotype Correlations

No genotype-phenotype correlations for *EFTUD2* have been identified.

Individuals with microdeletions encompassing *EFTUD2* and contiguous genes may have additional features or more severe intellectual disability [Lines et al 2012, Gandomi et al 2015].

Penetrance

MFDM is highly penetrant but variably expressive. Features may be subclinical in some affected individuals, as in the case of two non-mosaic, intellectually normal mothers – each with two affected children – in whom the only reported clinical findings were unilateral zygomatic cleft and facial asymmetry [Voigt et al 2013] and mild facial asymmetry and a preauricular tag [McDermott et al 2017].

Nomenclature

The descriptive term "mandibulofacial dysostosis with microcephaly" is synonymous with the eponym "mandibulofacial dysostosis, Guion-Almeida type" [Guion-Almeida et al 2009].

Some have suggested that MFDM be classified as an acrofacial dysostosis rather than a mandibulofacial dysostosis [Voigt et al 2013]. This is predominantly a clinical (rather than pathophysiologic) distinction based on the presence of limb anomalies in the former category, and their absence in the latter.

In the 2023 revision of the Nosology of Genetic Skeletal Disorders [Unger et al 2023], MFDM is referred to as *EFTUD2*-related mandibulofacial dysostosis with microcephaly (Guion-Almeida type) and included in the craniofacial dysostoses group.

Prevalence

The prevalence of MFDM has not been established. At least 126 cases caused by mutation of *EFTUD2* have been reported to date (see Table 2 and references cited in Clinical Description).

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *EFTUD2*.

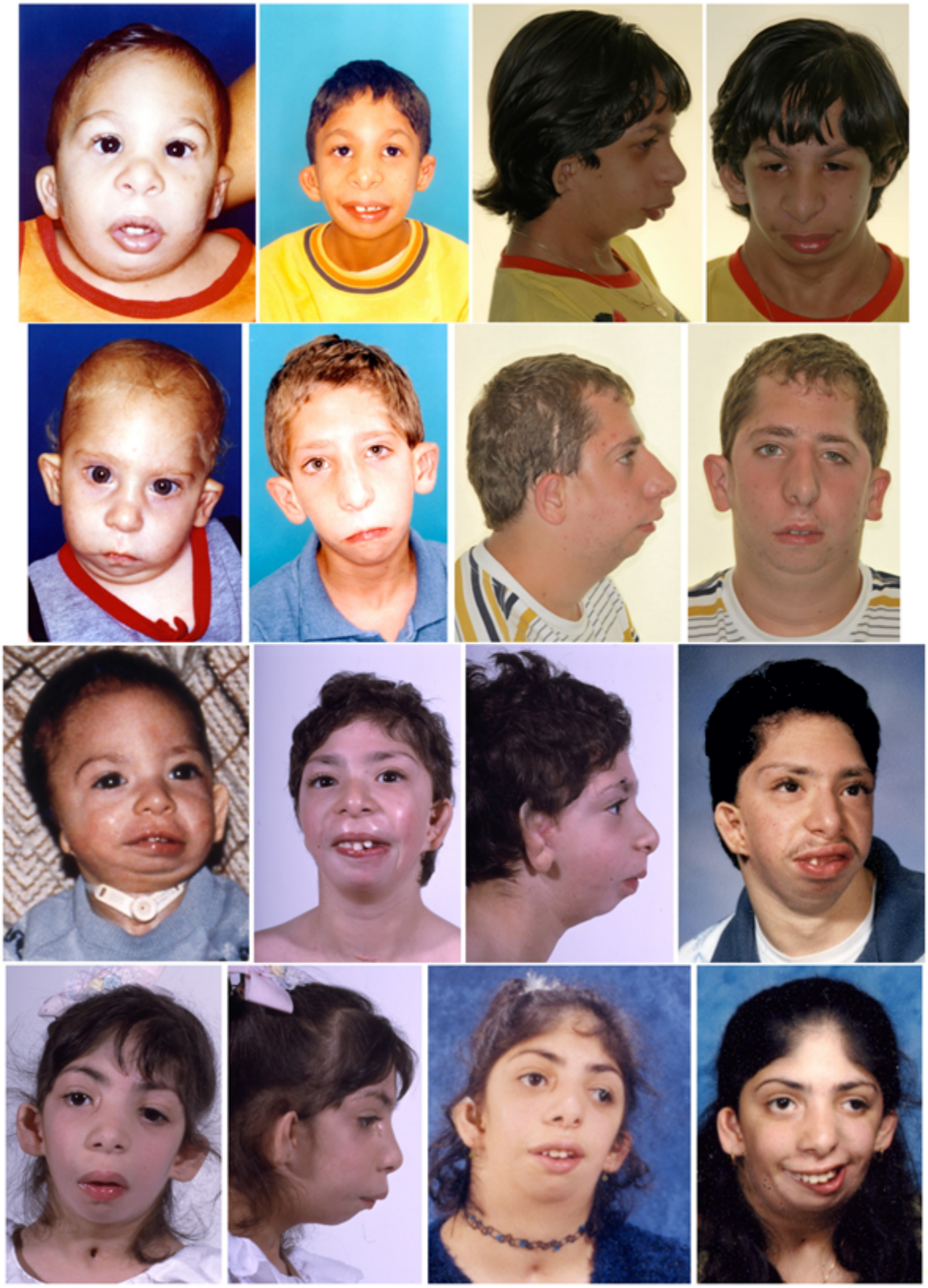

Figure 2. Typical craniofacial features of MFDM. These include micrognathia, malar hypoplasia, a relatively high nasal root with prominent ridge, everted lower lip, and (frequently) facial asymmetry. Characteristic ear malformations, present in essentially all individuals, are depicted in more detail in Figure 1. A recognizable gestalt, which is most easily appreciated in young children, can nonetheless be discerned well into adulthood.

Differential Diagnosis

Mandibulofacial Dysostosis

Table 3. Genes of Interest in the Differential Diagnosis of Mandibulofacial Dysostosis with Microcephaly

Gene(s)	DiffDx Disorder	MOI	Clinical Characteristics of DiffDx Disorder Overlapping w/MFDM	Distinguishing Features
CHD7 [1]	CHARGE syndrome (See *CHD7* Disorder.)	AD	Microcephaly, ear anomalies, choanal atresia, TEF, CHD	Ocular coloboma & Mondini malformation are present in CHARGE but not in MFDM.
DHODH	Miller acrofacial dysostosis (OMIM 263750)	AR	MFD w/postaxial limb defects ± other extracranial malformations	OFC & intelligence are typically normal in Miller acrofacial dysostosis.
POLR1C *POLR1D* *TCOF1*	Treacher Collins syndrome (TCS)	AD AR	• MFD (may resemble MFD in MFDM) • Malformations occur in 1st & 2nd branchial arch-derived structures. • ID (w/o microcephaly) is not common but may be present in some persons. [2] • Lower lid clefts, absent eyelashes, & lacrimal system anomalies may be present.	• Cardiac & esophageal malformations are not assoc w/TCS. • Intellect & OFC are usually in average range in TCS. • Unlike TCS, palpebral fissures are not consistently downslanting in MFDM.
RPL5 *RPL11* *RPL35A* *RPS10* *RPS17* *RPS19* *RPS24* *RPS26* [3]	Diamond-Blackfan anemia (DBA)	AD (XL [4])	~1/3 of persons exhibit MFD-like craniofacial anomalies ± cleft palate, anomalous thumbs, cardiac anomalies, &/or growth restriction.	Moderate-to-severe anemia in DBA
SF3B4	Nager acrofacial dysostosis (OMIM 154400)	AD	MFD w/preaxial (typically upper) limb defects, ± other extracranial malformations	OFC & intelligence typically normal in Nager acrofacial dysostosis

AD = autosomal dominant; AR = autosomal recessive; CHD = congenital heart defect; DiffDx = differential diagnosis; ID = intellectual disability; MFD = mandibulofacial dysostosis; MFDM = mandibulofacial dysostosis with microcephaly; MOI = mode of inheritance; OFC = occipitofrontal circumference; TEF = tracheoesophageal fistula; XL = X-linked

1. The finding of a *CHD7* pathogenic variant is not equivalent to a diagnosis of CHARGE syndrome; the phenotypic spectrum of heterozygous *CHD7* pathogenic variants encompasses CHARGE syndrome as well as subsets of features that comprise the CHARGE syndrome phenotype.

2. Intellectual disability (without microcephaly) may be present in individuals with either (a) a history of neonatal airway compromise or (b) microdeletions encompassing *TCOF1* and adjacent genes [Vincent et al 2016].

3. Listed genes represent the most common genetic causes of Diamond-Blackfan anemia (DBA); more than 20 genes are known to be associated with DBA (see Diamond-Blackfan anemia).

4. DBA is most often inherited in an autosomal dominant manner; *GATA1*- and *TSR2*-DBA are inherited in an X-linked manner (*GATA1* and *TSR2* are less common genetic causes of DBA and are not included in the table).

Craniofacial Microsomia

Craniofacial microsomia (CFM) is a first- and second-arch malformation spectrum encompassing several phenotypes, including oculo-auriculo-vertebral (OAV) syndrome and Goldenhar syndrome (OMIM 164210).

CFM most frequently occurs as a simplex case (i.e., in a single individual in a family) with unknown etiology; recurrence risks are empiric.

CFM shares several major features with mandibulofacial dysostosis with microcephaly (MFDM), including preauricular tags, microtia, aural atresia, hearing loss, and – notably – facial asymmetry, present in approximately 65% of persons with CFM and also a frequent finding in MFDM (58%).

The spectrum of orofacial clefting differs between the two conditions: midline cleft palate is typical of MFDM, while CFM can be associated with any type of orofacial cleft, including lateral oral clefts. Although various extracranial anomalies may occur in either condition, vertebral anomalies in particular should suggest CFM.

At least two persons with an *EFTUD2* pathogenic variant were diagnosed with "bilateral OAV syndrome" prior to the recognition of MFDM as a distinct syndrome [Authors, personal observation].

Tracheoesophageal Fistula

Tracheoesophageal fistula is a feature of several other recognized conditions, including Feingold syndrome and VACTERL association (OMIM 192350); clinical differentiation is generally straightforward.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with mandibulofacial dysostosis with microcephaly (MFDM), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Mandibulofacial Dysostosis with Microcephaly

System/Concern	Evaluation	Comment
MFD	• Airway assessment for evidence of upper-airway obstruction w/or w/o choanal atresia • Exam for midline cleft palate & referral to multidisciplinary cleft palate team as required	Important in newborns w/disorder
DD/ID	Developmental assessment	Incl adaptive, cognitive, & speech-language evals
Hearing loss	Audiologic eval	Assess for hearing loss.
EA/TEF	Urgent eval in newborns, esp in those w/history of polyhydramnios, unexplained respiratory distress, &/or failed nasogastric tube placement	
Cardiac anomaly	Echocardiogram & cardiologist eval	
Renal anomaly	Renal ultrasound	
Skeletal anomaly	Radiograph to assess for scoliosis, rib or thumb malformation as clinically indicated	
Short stature	Assess w/growth charts.	Height growth curves for MFDM are published. [1]
Genetic counseling	By genetics professionals [2]	To inform affected persons & families re nature, MOI, & implications of MFDM to facilitate medical & personal decision making

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

DD/ID = developmental delay / intellectual disability; EA/TF = esophageal atresia / tracheoesophageal fistula; MFD = mandibulofacial dysostosis; MFDM = mandibulofacial dysostosis with microcephaly; MOI = mode of inheritance
1. Huang et al [2016]
2. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

There are no published management guidelines to date for MFDM.

Esophageal atresia / tracheoesophageal fistula, cardiac defects, renal anomalies, and thumb anomalies are treated in a routine manner. Short stature is managed expectantly. Of note, the response to human growth hormone has not been specifically reported.

Table 5. Treatment of Manifestations in Individuals with MFDM

Manifestation/Concern	Treatment	Considerations/Other
Mandibulofacial dysostosis	• Neonates w/airway compromise at delivery may require intubation &/or tracheostomy for initial stabilization. • Treatment of craniofacial manifestations is individualized & managed by a multidisciplinary team incl oromaxillofacial surgery, plastic surgery, otolaryngology, dentistry/orthodontics, & occupational & speech-language therapy.	
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	To optimize developmental outcome
Hearing loss	Treatment is individualized & may involve conventional hearing aid(s), bone-anchored hearing aid(s), &/or cochlear implant(s).	Community hearing services through early intervention or school district

DD/ID = developmental delay / intellectual disability

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, antiparkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation

can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Table 6. Recommended Surveillance for Individuals with MFDM

System/Concern	Evaluation	Frequency
Mandibulofacial dysotosis	Evaluate for obstructive sleep apnea.	As needed
Developmental delay / Intellectual disability	Developmental assessment & psychoeducational testing for children	Periodically throughout childhood
Short stature	Growth parameters	Annually throughout childhood & adolescence
Epilepsy	Neurologic eval w/EEG &/or brain imaging if appropriate	As needed

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Mandibulofacial dysostosis with microcephaly (MFDM) is an autosomal dominant disorder often caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- More than 80% of individuals diagnosed with MFDM to date are presumed to have the disorder as the result of a *de novo EFTUD2* pathogenic variant [Huang et al 2016].
- In 12 of 64 individuals diagnosed with MFDM, the causative pathogenic variant was inherited from a parent with a milder phenotypic presentation [Gordon et al 2012, Voigt et al 2013, Lehalle et al 2014, Huang et al 2016].
- Molecular genetic testing and clinical evaluation are recommended for the parents of a proband with an apparent *de novo EFTUD2* pathogenic variant (i.e., the proband is the only family member known to have MFDM).
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. The incidence of parental germline mosaicism in MFDM is 6% [Huang et al 2016]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism.
- The family history of some individuals diagnosed with MFDM may appear to be negative because of a failure to recognize the disorder in family members because of milder manifestations of the disorder in a heterozygous parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to sibs of the proband (at conception) is 50%. Although MFDM is thought to be highly penetrant, intrafamilial clinical variability is observed, and a sib who inherits an *EFTUD2* pathogenic variant may be more or less severely affected than the proband [Huang et al 2016].
- If the proband has a known MFDM-related pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is greater than that of the general population because of the possibility of parental germline mosaicism.
- If the parents have not been tested for the *EFTUD2* pathogenic variant but are clinically unaffected, sibs are still presumed to be at increased risk for MFDM because of the possibility of subclinical manifestations of the disorder in a heterozygous parent or the possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with MFDM has a 50% chance of inheriting the *EFTUD2* pathogenic variant.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has the *EFTUD2* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to parents of affected individuals, as well as to young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *EFTUD2* pathogenic variant has been identified in an affected family member, prenatal testing and preimplantation genetic testing are possible. The phenotype of affected offspring cannot be accurately predicted based on the results of prenatal molecular genetic testing (see Penetrance).

Fetal ultrasound examination. Because the sensitivity of prenatal ultrasound for detection of MFDM has not been assessed, molecular genetic testing is the recommended mode of prenatal diagnosis. Many of the characteristic findings in MFDM have a low probability of detection by antenatal ultrasound.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Cleft Palate-Craniofacial Association**
  Phone: 919-933-9044
  acpa-cpf.org
- **Children's Craniofacial Association**
  Phone: 800-535-3643
  Email: contactCCA@ccakids.com
  www.ccakids.org
- **FACES: National Craniofacial Association**
  Phone: 800-332-2373; 423-266-1632
  Email: info@faces-cranio.org
  www.faces-cranio.org
- **National Institute of Dental and Craniofacial Research (NIDCR)**
  Bethesda MD 20892-2190
  Phone: 866-232-4528 (toll-free); 301-496-4261
  Fax: 301-480-4098
  Email: nidcrinfo@mail.nih.gov
  www.nidcr.nih.gov
- **World Craniofacial Foundation**
  7777 Forest Lane
  Suite C-616
  Dallas TX 75230
  Phone: 800-533-3315

Fax: 972-566-3850
Email: info@worldcf.org
www.worldcf.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Mandibulofacial Dysostosis with Microcephaly: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
EFTUD2	17q21.31	116 kDa U5 small nuclear ribonucleoprotein component	EFTUD2 @ LOVD	EFTUD2	EFTUD2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Mandibulofacial Dysostosis with Microcephaly (View All in OMIM)

603892	ELONGATION FACTOR Tu GTP-BINDING DOMAIN-CONTAINING 2; EFTUD2
610536	MANDIBULOFACIAL DYSOSTOSIS, GUION-ALMEIDA TYPE; MFDGA

Molecular Pathogenesis

EFTUD2 encodes a small GTPase that is one of several subunits belonging to the U5 small nuclear ribonucleoprotein particle (snRNP) [Fabrizio et al 1997]. The U5 snRNP is a component of the major and minor spliceosomes, two large macromolecular machines that mediate canonic (U2-dependent) and minor (U12-introns) intron splicing [Wahl et al 2009]. The *Saccharomyces cerevisiae* homolog of *EFTUD2*, Snu114p, is essential for (1) the dissociation of the U4 and U6 RNAs during pre-spliceosomal activation and (2) subunit disassembly and recycling after catalytic splicing is complete [Fabrizio et al 1997, Bartels et al 2002, Small et al 2006]. An *EFTUD2* haploinsufficient zebrafish model displayed abnormal brain development with neuronal apoptosis. No other systems were affected. RNA sequencing and functional analyses demonstrated RNA splicing deficiency which led to inadequate nonsense-mediated RNA decay and activation of the p53 pathway [Lei et al 2017].

Mechanism of disease causation. Reported *EFTUD2* pathogenic variants include missense, nonsense, frameshift, and splice site variants, as well as whole- or partial-gene deletions, consistent with haploinsufficiency as the underlying mechanism [Lines et al 2012].

Chapter Notes

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Revision History

- 6 April 2023 (sw) Revision: "*EFTUD2*-Related Mandibulofacial Dysostosis with Microcephaly (Guion-Almeida Type)" added as a synonym; Nosology of Genetic Skeletal Disorders: 2023 Revision [Unger et al 2023] added to Nomenclature
- 12 November 2020 (ha) Comprehensive update posted live
- 3 July 2014 (me) Review posted live
- 21 January 2014 (ml) Original submission

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