R.C.P.U. NEWSLETTER

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EFTUD2-related Mandibulofacial Dysostosis with Microcephaly

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Mandibulofacial dysostosis with microcephaly (MFDM), also referred to mandibulofacial dysostosis Guion-Almeida type, is an autosomal dominant disorder characterized by various craniofacial malformations, malar and mandibular hypoplasia, microcephaly, intellectual disability, external ear malformations, and hearing loss[1]. MFDM was first described in four, unrelated individuals by Guion-Almeida et al. in the late 1990s and early 2000s[2,3]. The causative gene, EFTUD2, was first identified in 2012 by Lines et al. through whole exome sequencing of a series of twelve patients presenting with the classic MFDM phenotype[4]. Since then, nearly 130 patients have been reported with pathogenic EFTUD2 variants and this number continues to grow as both awareness of MFDM increases and access to genetic testing is improved[1].

Located at 17q21.31, EFTUD2 is a highly conserved spliceosomal GTPase that is critical for proper neural crest and craniofacial development[1,4,5]. EFTUD2 encodes the U5-116kD protein, which is a component of the U5 small nuclear ribonucleoprotein (snRNP)[5,6]. U5, in combination with U1, U2, and U4/U6 snRNPs comprise the major spliceosome complex, which is responsible for regulating and preforming 99% of RNA splicing reactions within the human body[6]. RNA splicing is a critical process in which the protein-coding regions, known as exons, of pre-mRNA transcripts are joined together while the non-coding regions, known as introns, that separate the exons are removed[6,7]. Research involving mouse models have demonstrated that mutations in EFTUD2 result in improper splicing function, leading to an increase in exon skipping and alternatively spliced MDM2[6]. MDM2 is a critical regulator of cell division and apoptosis via regulation of the p53 gene[6]. Alternative slicing, caused by EFTUD2 mutations, results in a shortened protein product that is unable to bind effectively to its co-regulators, leading to increased stabilization and upregulation of P53[6]. With this upregulation of p53, Beauchamp et al. observed higher expression of P53-target genes and increased cell death, ultimately resulting in craniofacial defects in their mouse models[6]. This increase in P53 activity is responsible for early cell depletion of neural crest progenitors, resulting in abnormal neural crest cell migration and development of the first and second pharyngeal arches and their derivatives, including craniofacial structures[5,6]. It still remains largely unknown why disruption of EFTUD2 and its role in splicing, a ubiquitous reaction active in all cell types, results in abnormalities largely restricted to the craniofacial region[5].

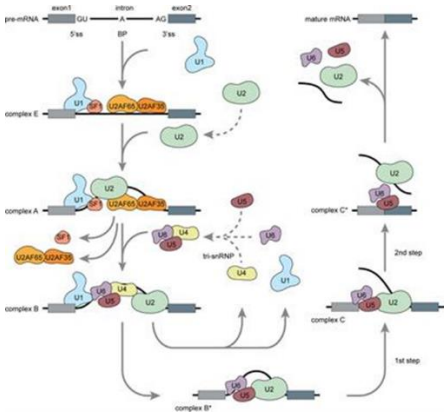

Figure 1. Diagram depicting RNA splicing; adapted from Ren et al., 2021

The MFDM phenotype is relatively broad, but core features are facial structural differences, microcephaly, developmental delay (DD)/intellectual disability (ID), ear malformations, and hearing loss[1]. Facial differences most commonly include malar and/or mandibular hypoplasia, facial asymmetry, cleft palate, and choanal atresia1. Microcephaly is reported in 87% of individuals diagnosed with MFDM[1]. The severity of DD/ID seen can vary between individuals on a range from mild to critical sequelae[1]. Hearing loss is typically conductive, secondary to malformations of the middle and inner ear, while external ear malformations, including microtia and preauricular tags are also common features[1]. Other findings, including cardiac abnormalities, digit abnormalities, short stature, esophageal atresia, spine abnormalities, and epilepsy, have been reported[1].

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%	

Table 1: Clinical findings with EFTUD2 Ref: Genereviews.org

The majority (~80%) of MFDM cases are due to a de novo EFTUD2 pathogenic variant, although parent to child transmission has been reported[1,8]. The molecular basis of EFTUD2 pathogenic variants include missense, nonsense, frameshift, splice site variants, and whole- or partial-gene deletions[1]. Microdeletions of the 17q21.31 region encompassing EFTUD2 have also been reported in conjunction with features beyond the typical MFDM spectrum[9]. To date, no genotype-phenotype correlations have been made, likely due largely in part to the limited number of MFDM patients with molecular confirmation[1]. This is limited by not only the relatively small number of patients with the condition, but also the fact that EFTUD2 is a more recently described genetic etiology. Given the inherent bias towards more “classic” MFDM cases reported in clinical literature and of clinical interest, it has been suggested that the full phenotypic spectrum of MFDM, especially the possibility of milder cases, has yet to be elucidated[8].

Treatment for MFDM hinges primarily on management of manifestations, rather than truly therapeutic or curative treatments[1]. Management of craniofacial presentations is dependent on the individual and best handled by a specialized, multidisciplinary craniofacial team. Individuals may require and/or benefit from specialized learning plans throughout schooling depending on the level of DD/ID along with therapies such as speech, physical, and

occupational[1]. Individuals with other findings such as short stature or epilepsy also need to follow with and be managed by appropriate specialists[1]. No formal management guidelines for MFDM are published, so management is currently patient-dependant[1].

MFDM is a relatively recently described syndrome with much to still be uncovered regarding the nature of EFTUD2 mutations. Compilation and addition of new cases and patients will continue to shed light on emerging phenotypes and provide insight into more comprehensive management and anticipatory guidance. As clinical knowledge expands, our molecular understanding of the mechanism by which EFTUD2 disruptions will also deepen, potentially providing information on pathways for targeted treatments and improved management for patients.

Family Resources:

American Cleft Palate-Craniofacial Association
Phone: 919-933-9044
Fax: 919-933-9604
Email: info@acpa-cpf.org
www.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

Facebook groups:

- Mandibuolofacial Dysostosis with Microcephaly
- Famille MFDM – EFTUD2

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About the RCPU:

The Raymond C. Philips Research and Education Unit began in 1978 when the legislature established section 393.20, F.S., of what is now known as the "prevention" legislation. It is named after Raymond C. Philips, who was the Superintendent of Gainesville's Tacachale (formerly Sunland) Center for 38 years, and was an acknowledged state and national leader in services for mentally retarded persons. The Unit is located on the Tacachale campus and is funded through a contract with the Department of Children and Families and the Department of Health.

The purpose of the R.C.P.U. is to treat, prevent, and/or ameliorate disorders of intellectual disability through medical evaluations, education and research. The unit provides direct evaluations and counseling to families and promotes service, education, and prevention projects. Some of the conditions currently under study at the RCPU involve Angelman, Velo-Cardio-Facial, Prader-Willi, Fragile X, Williams and Smith-Lemli-Opitz syndromes.

The R.C. Philips Unit is a resource for all Floridians interested in the diagnosis, treatment and prevention of mental retardation. Staff members are available for consultation and for educational programs for health.

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