First and second branchial arch involvement in mandibulofacial dysostosis Guion-Almeida type

V. Quinzi1°, C. De Luca2°, F. Giovannetti3, A. Splendiani4, D. Cocciadiferro5, R. Capolino5, F. Brancati3,#, G. Marzo1*.

1 Department of Life, Health and Environmental Sciences, Postgraduate School of Orthodontics, University of L’Aquila, Italy
2 Human Genetics Laboratory, Department of Life, Health and Environmental Sciences, University of L’Aquila, Italy
3 Maxillofacial Surgery, Department of Life, Health and Environmental Sciences, University of L’Aquila, Italy
4 Radiology Unit, Department of Biotechnological and Applied Clinical Sciences, University of L’Aquila, Italy
5 Medical Genetics, Bambino Gesù Children’s Hospital, IRCCS, 00165 Rome, Italy
# San Raffaele Roma IRCCS, Rome, Italy

Introduction

Mandibulofacial dysostoses are genetically heterogeneous disorders characterised by the core triad of malar and maxillary hypoplasia associated with dysplastic ears, resulting from abnormal development of the first and second branchial arches [Lehalle et al. 2014]. One rare autosomal dominant form is Mandibulofacial Dysostosis Guion-Almeida type (MFDGA; OMIM#610536), caused by heterozygous variants in the EFTUD2 gene. MFDGA also features microcephaly, intellectual disability and (conductive) hearing loss. Other craniofacial malformations may include cleft palate, choanal atresia, zygomatic arch cleft and facial asymmetry. Extra-craniofacial findings such as cardiac anomalies, thumb anomalies, esophageal atresia or tracheoesophageal fistula, short stature, spine anomalies and epilepsy may also be present [Lines et al. 2014].

Although mandibulofacial dysostosis is a distinctive feature of MFDA, the wide phenotypic spectrum greatly overlaps with other known craniofacial dysostoses such as oculo-auriculo-vertebral spectrum (or Goldenhar), Nager, Feingold or atypical CHARGE syndrome [Lehalle et al. 2014; 2015]. In some cases, differential diagnosis can be challenging, while getting to an early genetic diagnosis is extremely useful, not only for the correct management of cranial malformations, but also for the early diagnosis and treatment of the comorbidities associated with the disease [Luquet et al. 2013; Lacour et al. 2019].

MFDGA is an autosomal dominant disorder, with a 50% risk of transmission from an affected individual. De novo occurrence of EFTUD2 pathogenic variants is a frequently observed mechanism, with most patients born to unaffected parents. Intrafamilial clinical variability is observed with some individuals having inherited the disease from a parent with a milder phenotypic presentation. For this reason, molecular genetic testing and clinical evaluation are recommended for the parents of each proband with a molecularly confirmed EFTUD2 pathogenic variant. If the parents are negative for the specific variant, the recurrence risk for future pregnancies is very low, but still increased as compared to the general population for the rare possibility of a germline mosaicism. In case of a new pregnancy, prenatal invasive testing can be offered to these couples to rule out this risk. EFTUD2 encodes a core component of the major spliceosome in humans, a large ribonucleoprotein complex that carry out mRNA processing through removing the introns from pre-mRNA transcripts [Lehalle et al. 2015]. The disease is caused by haploinsufficiency of EFTUD2, with point mutations such as missense, nonsense, frameshift or splice site variants, but also partial or whole gene deletions being reported [Lines et al. 2012]. Because clinical variability is observed in MFDM, genetic testing is relevant for differential diagnosis: genetic testing strategies include direct sequencing of the EFTUD2 gene or multigene panel testing by next-generation sequencing or, finally, exome sequencing. In case no mutation is detected by sequencing analysis identified, other techniques (such as MLPA or quantitative PCR) are needed to detect single or multi-exon gene deletions or duplications.

Clinical description

The patient is a 11-year-old girl born at 38 weeks g.a. to non-consanguineous healthy parents. Pregnancy was characterised by intrauterine growth retardation. At birth she presented with microcephaly (OFC 31 cm, <3° ct), weight 2,510 g (10° ct) and length 48 cm (10–25° ct). Apgar was 10 (1’) and echocardiogram, renal and transfontanellar ultrasound were normal.

Her development was characterised by speech delay, and at 4 years of age she was diagnosed with congenital malformation of the external and middle ear with bilateral stenosis of the external auditory canal and bilateral conductive hearing loss, treated with bone conduction hearing devices. Brain MRI was normal.

At the last evaluation she presented with mild intellectual disability, microcephaly (OFC 50 cm, <3° ct), facial asymmetry, hypertelorism, entropion of inferior eyelid, prominent columella, large mouth, micrognazia, dysmorphic auricles, convex profile, lip incompetence, skeletal class II, hyperdver-
FIG. 1 Extra-oral examination - Facial asymmetry, Convex profile, Lip incompetence
gent, short vertical ramus (Fig. 1), severe space deficiency in both arches (Fig. 2), anterior open bite, good oral hygiene (Fig. 3), bilateral 2°-3° toe syndactyly and dysmorphic and proximally placed thumb (Fig. 4).

Genetic testing including karyotype and CGH-array both resulted normal. Given the phenotype, highly suggestive for mandibular dysostosis with macrocephaly, sequencing of the EFTUD2 gene (NM_004247.3) was performed, detecting the heterozygous pathogenic variant c.2032delA (p. Thr678Argfs*10) in the patient. The following segregation of the variant in parents disclosed its de novo origin.

Conclusion

First and second branchial arches involvement is typical of MFDGA, due to the loss of function of the EFTUD2 gene, impairing the regulation of gene expression and cell proliferation performed by the spliceosome complex during embryo development. The function of the spliceosome complex is ubiquitous, but its dysfunction may affect specific regions of the developing embryo depending on the specific spliceosome component involved. The pattern of the EFTUD2 gene expression has indeed been demonstrated to involve specific tissues such as the mesenchyme of the mandibula, the limb and the lung buds, the epithelium of the otic vesicle, the trachea and the oesophagus and the neuroepithelium of the forebrain, which correlates very well with several of the developmental regions affected in MFDGA patients [Gordon et al., 2012].

For this reason, after a diagnosis of MFDGA a thorough clinical evaluation is recommended to establish the extent of the disease and to ensure early treatment. Developmental delay is one of the most common features in individuals with MFDGA with variable grade of severity, ranging from mild to severe. Consultation with a paediatric neurologist is recommended to ensure an early intervention program for access to occupational, physical, speech, and feeding therapy. Conductive hearing loss is also very frequent, as a result of malformations or absence of the middle ear ossicles or auditory canal atresia (or both). Treatment is individualised and may involve hearing aids or cochlear implants.

Other less common manifestations, described in around one third of the patients, include cardiac anomalies, typically atrial or ventricular septal defects, for which an echocardiogram and a cardiologist evaluation is recommended; esophageal atresia and/or tracheoesophageal fistula, which may be suspected antenatally because of polyhydramnios, or neonatally in the context of unexplained respiratory distress or failed nasogastric tube placement, and require an urgent otolaryngologist evaluation; short stature, which should be assessed annually throughout childhood and adolescence following specific height growth charts [Huang et al. 2016], and spine anomalies, including scoliosis, kyphosis, hemiver-
tebrae, and cervical segmentation anomalies, evaluated by radiograph.

Epilepsy is reported in one fourth of affected subjects, therefore, a neurologic evaluation with EEG is recommended, followed by brain imaging if needed. Renal anomalies such as unilateral renal agenesis, vesicoureteral reflux, and ureteropelvic junction obstruction have also rarely been reported, so renal ultrasound might be considered.

The dental-orthodontic evaluation is essential to establish the right timing of intervention. Often these patients need maxillary expansions and the procedure of serial extractions due to the severe of space deficiency in one or both arches. Skeletal Class II cannot be corrected with functional devices due to the peculiar aspect of the jaw. The aesthetic aspect deserves more in-depth consideration at the end of growth, when an orthodontic-surgical choice can be decided together with the patient.

References