Case report of a 17q21.31 microdeletion associated with EFTUD2 mandibulofacial dysostosis with microcephaly identified by comparative genomic hybridization

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Abstract:

Mandibulofacial dysostosis with microcephaly (MFDM) is a rare, sporadic malformation syndrome manifesting with severe craniofacial abnormalities, microcephaly, developmental delay, and additional dysmorphic features. Although most cases of clinically diagnosed MFDM remain genetically unexplained, recent sequencing studies have linked this condition to heterozygous EFTUD2 mutations in 15 probands in the literature. In this case report, we present a previously undescribed dizygotic female twin proband (Twin A) born at 36 weeks gestation with severe microcephaly, microcrania, cleft palate, severe retrognathia, oral and pharyngeal dysphagia, bilateral proximal radioulnar synostosis, 11 thoracic ribs, abnormal MRI findings, highpitched cry due to unilateral vocal cord paralysis, and additional dysmorphic features. Newborn screening and a series of additional biochemical investigations were diagnostically negative. The proband's twin sister (Twin B) was born healthy and shows no phenotypic similarities. Family history is unremarkable for any known genetic syndromes, and the twins' parents are both reportedly in good health. Array comparative genomic hybridization (aCGH)+SNP analysis was performed on Twin A to assess for chromosome rearrangements and regions of homozygosity. Results of this assay identified a small de novo pathogenic deletion on chromosome 17q21.31, encompassing the EFTUD2 gene. The deleted region also included 13 additional genes considered unlikely to be responsible for the proband's phenotype. No regions of homozygosity were identified in the 400K array, which would also confirm a non-consanguineous family history. Of the total 15 reported MFDM-associated EFTUD2 mutations described to date, all alterations resulted in genetic haploinsufficiency, consistent with our proband's microdeletion pathomechanism. In addition, our proband's phenotypic features both overlap and expand on the clinical features of previously reported probands in the literature. As a result, we encourage continued genetic investigation and reporting of other individuals with EFTUD2 mutations and clinical MFDM to better delineate genotype-phenotype correlations for more accurate diagnosis of this complex condition.