PrgmNr 2565 - Biallelic frameshift variant in the TBC1D2B gene in two siblings with progressive cognitive impairment, gingival overgrowth, limb tremor, and fibrous dysplasia of face

Author Block: G. ROLDÃO CORREIA COSTA¹, N. de Leeuw², R. Pfundt², I. Cristina Sgardioli¹, A. dos Santos¹, V. Gil-da-Silva-Lopes¹, T. Paiva Vieira¹; ¹Sch. of Med. Sci., Univ. of Campinas, Campinas, Brazil, ²Radboud Univ. Med. Ctr., Nijmegen, Netherlands

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The TBC1D2B gene is a GTPase-activating protein involved in membrane trafficking that interacts with the early endosomal marker proteins RAB5. Biallelic loss-of-function variants in this gene were first reported in 2020 as a cause for a neurodevelopmental disorder with seizures and gingival overgrowth in individuals from three unrelated families. Here we report two male siblings, with similar clinical characteristics, born to a first-degree cousin couple. The oldest sibling started with bilateral growing of soft tissues in the malar region at three years old, which evolved with significant maxillary hypertrophy and compression of the brainstem. At 17 years old, he presented mental deterioration, limb tremors, ataxia, gingival overgrowth, and fibrous dysplasia. At his last evaluation, at 38 years old, he was bedridden and dependent on assisted ventilation. His younger brother presented with a similar clinical evolution, starting also at three years old. His condition evolved with the same characteristics and, at 27 years old, he was also bedridden and with tracheostomy. Chromosomal Microarray Analysis for both siblings did not show pathogenic CNVs, however, it showed multiple regions of homozygosity (ROH) in the autosomal genome of both. Whole Exome Sequencing was performed using the Agilent SureSelect Human All Exon V5 capture kit (Agilent Technologies) and the Illumina HiSeq™ 2000 platform (Illumina©, Inc.). Data analyses, including annotation and variant classification, were carried at the Genomic Diagnostics Division from the Department of Human Genetics at the Radboud University Medical Center in Nijmegen, Netherlands. A novel biallelic frameshift variant in the TBC1D2B gene (NM_144572.1) was found in both siblings - Chr15(GRCh37): g.78337330del c.595del p.(Val199Trpfs*22) - which creates a new stop codon at position 22. This gene is encompassed in one of the ROHs shared by the two brothers. The homozygous variant was confirmed by Sanger sequencing in both siblings and was found in heterozygous form in each of their parents. There are strong similarities of clinical characteristics, and its evolution, among the patients described here and the reported cases, including a cherubism-like phenotype with progressive gingival overgrowth. This is the fourth family in the world in which a bi-allelic loss-of-function variant in the TBC1D2B gene has been found, in two patients with similar phenotypes. These results support that loss of TBC1D2B is the cause for this rare condition.