Compound heterozygosity of low-frequency promoter deletions and rare loss-of-function mutations in TXNL4A causes Burn-McKeown syndrome.

Mutations in components of the major spliceosome have been described in disorders with craniofacial anomalies, e.g., Nager syndrome and mandibulofacial dysostosis type Guion-Almeida. The U5 spliceosomal complex of eight highly conserved proteins is critical for pre-mRNA splicing. We identified biallelic mutations in TXNL4A, a member of this complex, in individuals with Burn-McKeown syndrome (BMKS). This rare condition is characterized by bilateral choanal atresia, hearing loss, cleft lip and/or palate, and other craniofacial dysmorphisms. Mutations were found in 9 of 11 affected families.
In 8 families, affected individuals carried a rare loss-of-function mutation (nonsense, frameshift, or microdeletion) on one allele and a low-frequency 34 bp deletion (allele frequency 0.76%) in the core promoter region on the other allele. In a single highly consanguineous family, formerly diagnosed as oculo-oto-facial dysplasia, the four affected individuals were homozygous for a 34 bp promoter deletion, which differed from the promoter deletion in the other families. Reporter gene and in vivo assays showed that the promoter deletions led to reduced expression of TXNL4A. Depletion of TXNL4A (Dib1) in yeast demonstrated reduced assembly of the tri-snRNP complex. Our results indicate that BMKS is an autosomal-recessive condition, which is frequently caused by compound heterozygosity of low-frequency promoter deletions in combination with very rare loss-of-function mutations.