DYRK1A and 21q22.13 deletion syndrome

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Dual-specificity tyrosine-(Y)-phosphorylation-regulated kinase 1 A (DYRK1A) is a highly conserved gene located in the Down syndrome critical region. It has an important role in early development and regulation of neuronal proliferation. Microdeletions of chromosome 21q22.12q22.3 that include DYRK1A (21q22.13) are rare and only a few pathogenic single-nucleotide variants (SNVs) in the DYRK1A gene have been described, so as of yet, the landscape of DYRK1A disruptions and their associated phenotype has not been fully explored. We have identified 14 individuals with de novo heterozygous variants of DYRK1A; five with microdeletions, three with small insertions or deletions (INDELs) and six with deleterious SNVs. The analysis of our cohort and comparison with published cases reveals that phenotypes are consistent among individuals with the 21q22.12q22.3 microdeletion and those with translocation, SNVs, or INDELs within DYRK1A. All individuals shared congenital microcephaly at birth, intellectual disability, developmental delay, severe speech impairment, short stature, and distinct facial features. The severity of the microcephaly varied from -2 SD to -5 SD. Seizures, structural brain abnormalities, eye defects, ataxia/broad-based gait, intrauterine growth restriction, minor skeletal abnormalities, and feeding difficulties were present in two-thirds of all affected individuals. Our study demonstrates that haploinsufficiency of DYRK1A results in a new recognizable syndrome, which should be considered in individuals with Angelman syndrome-like features and distinct facial features. Our report represents the largest cohort of individuals with DYRK1A disruptions to date, and is the first attempt to define consistent genotype-phenotype correlations among subjects with 21q22.13 microdeletions and DYRK1A SNVs or small INDELs.