De novo mutations in beta-catenin (CTNNB1) appear to be a frequent cause of intellectual disability: expanding the mutational and clinical spectrum.

Recently, de novo heterozygous loss-of-function mutations in beta-catenin (CTNNB1) were described for the first time in four individuals with intellectual disability (ID), microcephaly, limited speech and (progressive) spasticity, and functional consequences of CTNNB1 deficiency were characterized in a mouse model. Beta-catenin is a key downstream component of the canonical Wnt signaling pathway. Somatic gain-of-function mutations have already been found in various tumor types, whereas germline loss-of-function mutations in animal models have been shown to influence neuronal development and maturation. We report on 16 additional individuals from 15 families in whom we newly
identified de novo loss-of-function CTNNB1 mutations (six nonsense, five frameshift, one missense, two splice mutation, and one whole gene deletion). All patients have ID, motor delay and speech impairment (both mostly severe) and abnormal muscle tone (truncal hypotonia and distal hypertonia/spasticity). The craniofacial phenotype comprised microcephaly (typically -2 to -4 SD) in 12 of 16 and some overlapping facial features in all individuals (broad nasal tip, small alae nasi, long and/or flat philtrum, thin upper lip vermilion). With this detailed phenotypic characterization of 16 additional individuals, we expand and further establish the clinical and mutational spectrum of inactivating CTNNB1 mutations and thereby clinically delineate this new CTNNB1 haploinsufficiency syndrome.