CASK mutation identified by whole exome sequencing in a patient that expands the clinical spectrum for MICPCH syndrome

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A 23-year-old mixed-European female with no family history of intellectual disability presented with multiple malformations and developmental delays. She exhibits microcephaly, severe intellectual disability, dyspraxia, congenital quadriplegia, dystonia of the upper extremities, spasticity, and scoliosis. Brain imaging revealed pontine and cerebellar hypoplasia with intact corpus callosum. We noted down-slanting palpebral fissures, midface hypoplasia, high-arched palate, dental crowding, large tongue, and long narrow asymmetric face. Chromosome analysis, metabolic testing, and microarray all revealed no abnormalities. Whole exome sequencing revealed c.2065A>T, a single nucleotide change in the *CASK* gene, which is located on chromosome Xp11.4 and encodes for a calcium/calmodulin-dependent serine protein kinase. This protein is essential in synaptic function and brain development. The *de novo* nonsense mutation truncates the CASK protein, which is likely the etiology of the patient's adverse phenotype. The major features in our patient resemble those reported in MICPCH syndrome (microcephaly with pontine and cerebellar hypoplasia). Since MICPCH syndrome is a rare X-lined dominant disorder (OMIM #300749) associated with mutations in the *CASK* gene, we believe our patient expands the phenotypic profile of *CASK* mutations.

Presentations	London Dysmorphology Database	Moog et al. 2011	Patient
Microcephaly	+	+	+
Pontocerebellar hypoplasia	+	+	+
Intellectual disability	+	+	+
Seizures/abnormal EEG	+	+	+
Long philtrum	+	+	+
Epicanthic folds	+	+	+
Large Ear	+	+	+
Prominent nasal bridge	+	+	+
Hyoptonia	+	+	-
Spasticity	+	+	-
Scoliosis	+	-	+
Sensorineural deafness	-	+	+
Hypermetropia	-	-	+
Midface hypoplasia	-	-	+
Dental crowding	-	-	+
Hypersomnolence	-	-	+

Moog U, Kutsche K, Kortüm F, et al. Phenotypic spectrum associated with *CASK* loss-of-function mutations. *J Med Genet* 2011 48(11):741-751.