BIALLELIC VARIANTS IN CSTB CAUSE A DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY WITH DYSKINESIA

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Background: Biallelic CSTB (cystatin B) variants primarily cause Unverricht-Lundborg disease, a progressive myoclonic epilepsy. 90-99% of cases have two dodecamer repeat expansions in the promoter region. More recently, four patients in two families with homozygous CSTB variants causing premature stop codons were described with severe developmental delay, microcephaly, movement disorders, seizures, hypomyelination and cerebral atrophy.

Materials/Methods: Patients with biallelic SNVs or indels in CSTB were identified either at Texas Children's Hospital or by searching for additional cases in the Center for Mendelian Genomics, Baylor Genetics Laboratory and GeneDx databases. All probands were diagnosed via index or trio exome sequencing with confirmation by Sanger sequencing.

Results: We identified an additional seven patients with severe infantile-onset neurodevelopmental disease and biallelic CSTB SNVs and/or indels. All presented in the first year of life with developmental concerns. All patients were found to have microcephaly and severe developmental delay. Only one patient achieved independent sitting and feeding. Importantly, five out of seven patients exhibited developmental regression between five months and three years of age, often losing all previously acquired skills. All patients had a hyperkinetic movement disorder, including dystonia, chorea and myoclonus. Five out of seven had seizures, typically tonic or myoclonic, and two had medically refractory epilepsy. All exhibited hypotonia, and most developed appendicular hypertonia/spasticity with time. Brain MRI features included immature sulcation, hypomyelination, and reduced brain volume. In cases where serial imaging was available, progressive cerebral atrophy was apparent. Molecular analysis revealed c.[202C>T];[67-1G>C] (1 patient), c.[67-1G>C];[c.10G>A] (1 patient), c.[202C>T];[66+2T>C] (3 siblings), homozygous c.67-1G>C (1 patient), and c.[1_2insAT];[c.67-1G>C] (1 patient). [c.10G>A] and [66+2T>C] represent novel variants.

Conclusions: Biallelic deleterious variants (frameshift, splice-site or missense variants affecting the critical domains) in CSTB cause a progressive, severe developmental and epileptic encephalopathy with dyskinesia distinct from Unverricht-Lundborg disease. This condition is characterized by severe developmental delay, microcephaly, a hyperkinetic movement disorder, epilepsy, hypotonia, spasticity, hypomyelination and progressive cerebral atrophy.