TRAPPC11

The protein encoded by this gene is a subunit of the TRAPP (transport protein particle) tethering complex, which functions in intracellular vesicle trafficking. This subunit is involved in early-stage endoplasmic reticulum-to-Golgi vesicle transport. Alternative splicing of this gene results in multiple transcript variants. [provided by RefSeq, Jan 2013

Several individuals with TRAPPC11 mutations have been reported with muscle weakness and other features including brain, liver, skeletal and eye involvement. A detailed analysis of brain and muscle pathology will further our understanding of the presentation and aetiology of TRAPPC11 disease.

Methods: We describe five cases of early-onset TRAPPC11-related muscular dystrophy with a systematic review of muscle pathology in all five individuals, post-mortem brain pathology findings in one and membrane trafficking assays in another.

Results: All affected individuals presented in infancy with muscle weakness, motor delay and elevated serum creatine kinase (CK). Additional features included cataracts, liver disease, intellectual disability, cardiomyopathy, movement disorder and structural brain abnormalities. Muscle pathology in all five revealed dystrophic changes, universal hypoglycosylation of alpha-dystroglycan and variably reduced dystrophin-associated complex proteins. Membrane trafficking assays showed defective Golgi trafficking in one individual. Neuropathological examination of one individual revealed cerebellar atrophy, granule cell hypoplasia, Purkinje cell (PC) loss, degeneration and dendrite dystrophy, reduced alpha-dystroglycan (IIH6) expression in PC and dentate neurones and absence of neuronal migration defects.

Conclusions: This report suggests that recessive mutations in TRAPPC11 are linked to muscular dystrophies with hypoglycosylation of alpha-dystroglycan. The structural cerebellar involvement that we document for the first time resembles the neuropathology reported in N-linked congenital disorders of glycosylation (CDG) such as PMM2-CDG, suggesting defects in multiple glycosylation pathways in this condition [1)].

Propranolol was found to affect the expression of genes previously associated with ET and other movement disorders such as TRAPPC11. Pathway enrichment analysis of these convergent drug-targeted genes identified multiple terms related to calcium signaling, endosomal sorting, axon guidance, and neuronal morphology. Furthermore, genes targeted by ET drugs were enriched within cell types having high expression of ET-related genes in both cortical and cerebellar tissues. Altogether, the results highlight potential cellular and molecular mechanisms associated with tremor reduction and identify relevant genetic biomarkers for drug responsiveness in ET [2)].

1)
Munot P, McCrea N, Torelli S, Manzur A, Sewry C, Chambers D, Feng L, Ala P, Zaharieva I, Ragge N, Roper H, Marton T, Cox P, Milev MP, Liang WC, Maruyama S, Nishino I, Sacher M, Phadke R, Muntoni F. TRAPPC11-related muscular dystrophy with hypoglycosylation of alpha-dystroglycan in skeletal muscle and brain. Neuropathol Appl Neurobiol. 2022 Feb;48(2):e12771. doi: 10.1111/nan.12771. Epub 2021 Nov 11. PMID: 34648194.
2)

Castonguay CE, Liao C, Khayachi A, Liu Y, Medeiros M, Houle G, Ross JP, Dion PA, Rouleau GA. Transcriptomic effects of propranolol and primidone converge on molecular pathways relevant to essential tremor. NPJ Genom Med. 2022 Aug 4;7(1):46. doi: 10.1038/s41525-022-00318-9. PMID: 35927430.