Format: Abstract

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TRAPPC11 and GOSR2 mutations associate with hypoglycosylation of α-dystroglycan and muscular dystrophy.

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Abstract

BACKGROUND: Transport protein particle (TRAPP) is a supramolecular protein complex that functions in localizing proteins to the Golgi compartment. The TRAPPC11 subunit has been implicated in muscle disease by virtue of homozygous and compound heterozygous deleterious mutations being identified in individuals with limb girdle muscular dystrophy and congenital muscular dystrophy. It remains unclear how this protein leads to muscle disease. Furthermore, a role for this protein, or any other membrane trafficking protein, in the etiology of the dystroglycanopathy group of muscular dystrophies has yet to be found. Here, using a multidisciplinary approach including genetics, immunofluorescence, western blotting, and live cell analysis, we implicate both TRAPPC11 and another membrane trafficking protein, GOSR2, in α-dystroglycan hypoglycosylation.

CASE PRESENTATION: Subject 1 presented with severe epileptic episodes and subsequent developmental deterioration. Upon clinical evaluation she was found to have brain, eye, and liver abnormalities. Her serum aminotransferases and creatine kinase were abnormally high. Subjects 2 and 3 are siblings from a family unrelated to subject 1. Both siblings displayed hypotonia, muscle weakness, low muscle bulk, and elevated creatine kinase levels. Subject 3 also developed a seizure disorder. Muscle biopsies from subjects 1 and 3 were severely dystrophic with abnormal immunofluorescence and western blotting indicative of α-dystroglycan hypoglycosylation. Compound heterozygous mutations in TRAPPC11 were identified in subject 1: c.851A>C and c.965+5G>T. Cellular biological analyses on fibroblasts confirmed abnormal membrane trafficking. Subject 3 was found to have compound heterozygous mutations in GOSR2: c.430G>T and c.2T>G. Cellular biological analyses on fibroblasts from subject 3 using two different model cargo proteins did not reveal defects in protein transport. No mutations were found in any of the genes currently known to cause dystroglycanopathy in either individual.

CONCLUSION: Recessive mutations in TRAPPC11 and GOSR2 are associated with congenital muscular dystrophy and hypoglycosylation of α-dystroglycan. This is the first report linking membrane trafficking proteins to dystroglycanopathy and suggests that these genes should be considered in the diagnostic evaluation of patients with congenital muscular dystrophy and dystroglycanopathy.

KEYWORDS: Dystroglycan; Dystroglycanopathy; GOSR2; Glycosylation; Golgi; Membrane traffic; Muscular dystrophy; TRAPPC11

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