B4GALNT1

Hereditary spastic paraplegia is caused by biallelic mutations in the B4GALNT1 (beta-1,4-N-acetylgalactosaminyltransferase 1) gene. The B4GALNT1 gene encodes ganglioside GM2/GD2 synthase (GM2S), which catalyzes the transfer of N-acetylgalactosamine to lactosylceramide, GM3, and GD3 to generate GA2, GM2, and GD2, respectively. The present study attempted to characterize a novel B4GALNT1 variant (NM_001478.5:c.937G>A p.Asp313Asn) detected in a patient with progressive multi-system neurodegeneration as well as deleterious variants found in the general population in Japan. Peripheral blood T cells from our patient lacked the ability for activation-induced ganglioside expression assessed by cell surface cholera toxin binding. Structural predictions suggested that the amino acid substitution, p.Asp313Asn, impaired binding to the donor substrate UDP-GalNAc. An in vitro enzyme assay demonstrated that the variant protein did not exhibit GM2S activity, leading to the diagnosis of HSP26. This is the first case diagnosed with SPG26 in Japan. We then extracted 10 novel missense variants of B4GALNT1 from the whole-genome reference panel jMorp (8.3KJPN) of the Tohoku medical megabank organization, which were predicted to be deleterious by Polyphen-2 and SIFT programs. We performed a functional evaluation of these variants and demonstrated that many showed perturbed subcellular localization. Five of these variants exhibited no or significantly decreased GM2S activity with less than 10% activity of the wild-type protein, indicating that they are carrier variants for HSP26. These results provide the basis for molecular analyses of B4GALNT1 variants present in the Japanese population and will help improve the molecular diagnosis of patients suspected of having HSP [1)]

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Inamori KI, Nakamura K, Shishido F, Hsu JC, Nagafuku M, Nitta T, Ikeda J, Yoshimura H, Kodaira M, Tsuchida N, Matsumoto N, Uemura S, Ohno S, Manabe N, Yamaguchi Y, Togayachi A, Aoki-Kinoshita KF, Nishihara S, Furukawa JI, Kaname T, Nakamura M, Shimohata T, Tadaka S, Shirota M, Kinoshita K, Nakamura Y, Ohno I, Sekijima Y, Inokuchi JI. Functional evaluation of novel variants of B4GALNT1 in a patient with hereditary spastic paraplegia and the general population. Front Neurosci. 2024 Jul 31;18:1437668. doi: 10.3389/fnins.2024.1437668. PMID: 39145292; PMCID: PMC11322347.