Hereditary spastic paraplegia

Hereditary spastic paraplegias (HSPs) are clinically and genetically heterogeneous disorders characterized by lower extremity spasticity and weakness (occurring in variable proportions). When symptoms begin after childhood, they usually progress slowly and steadily. When symptoms begin in very early childhood, they may be non-progressive and resemble spastic diplegic cerebral palsy.

HSP is classified as “uncomplicated” if neurologic impairment is limited to lower extremity spastic weakness, hypertonic urinary bladder disturbance, and mild diminution of lower extremity vibration sensation. HSP is classified as “complicated” if the impairment present in uncomplicated HSP is accompanied by other systemic or neurologic abnormalities such as ataxia, seizures, cognitive impairment, dementia, amyotrophy, extrapyramidal disturbance, or peripheral neuropathy (in the absence of other causes for these additional features).

Neurologic examination of individuals with uncomplicated HSP demonstrates variable degrees of increased muscle tone (spasticity) particularly in the hamstrings, quadriceps, gastrocnemius-soleus, and adductor muscles; weakness in the iliopsoas, hamstring, and tibialis anterior muscles; hyperreflexia at the patella and ankles; often (though not always) mildly reduced vibration sensation in the toes; extensor plantar responses; and spastic gait.

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)]

Among the 10 patients, one SPG7 patient, one SPG11 patient, and one pure SPG31 patient were detected. Two variants (deletion of exon 3-9 of SPG7 gene and the heterozygous mutation c.1861C > T/p.Q621* of SPG11 gene) were novel and three (c.1150_1150 + 1insCTAC/p.G384Afs*13 in SPG7 gene, c.3075dupA/p.E1026Rfs*4 in SPG11 gene, and c.478delA/p.R160Gfs*63 of REEP1 gene/SPG31) were previously reported. The SPG11 patient presented mild intellectual with peripheral neuropathy

and thin corpus callosum (TCC) with no white matter abnormalities (WMA). The SPG7 patient detected in this study is the third SPG7 family reported in China; he manifested peripheral neuropathy, scoliosis, and polydactyly which expand the phenotype spectrum of SPG7.

Conclusions: The AAO overlapped among each HSP subtype, which limited the ability to predict the subtype of HSP from AAO. Compared with non-Asian patients, the mutation frequency of SPG7 is relatively low in Asian populations. Considering the varieties of mutation types of HSP, we suggested targeted sequencing gene panels should be combined with MLPA for diagnosis of HSP [2)]

[1)]
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[2)]
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