**NOVEL GBE1 MUTATION IN A JAPANESE FAMILY WITH ADULT POLYGLUCOSAN BODY DISEASE**

Adult polyglucosan body disease (APBD) is an autosomal recessive leukoencephalopathy caused by a deficiency of glycogen branching enzyme (GBE), leading to deposition of PBs in the central and peripheral nervous systems. The main clinical features are adult-onset progressive neurogenic bladder dysfunction, gait disturbance, and peripheral neuropathy. The majority of patients with APBD are of Ashkenazi Jewish ancestry and have a common p.Tyr329Ser mutation in the GBE1 gene encoding GBE. We identified a novel GBE1 mutation in a Japanese family with APBD using exome sequencing.

**Case reports.** Two brothers (patients 1 and 2, 72 and 66 years old, respectively) were admitted to our hospital because of gait disturbance. Ages at onset were 70 and 62 years, respectively. Their family history revealed consanguinity with their parents being first cousins. Both patients showed muscle weakness with atrophy in the legs and generalized hyporeflexia. Extensor plantar reflexes and myoclonus of the legs were observed in patient 1, while ophthalmoplegia, bulbar palsy, and sensory disturbance of the distal lower extremities and urinary incontinence were present in patient 2. Their Mini-Mental State Examination scores were 28/30 and 19/30, respectively, indicating slight executive dysfunction in patient 2.

Glycated hemoglobin revealed diabetes mellitus in patient 1. Both patients showed normal findings in the CSF. T2-weighted sagittal MRIs of both patients showed atrophy of the medulla and the spinal cord. MRI with fluid-attenuated inversion recovery axial sequences demonstrated hyperintense white matter abnormalities, predominantly in the periventricular regions and posterior limb of the internal capsule, as well as pyramidal tracts and medial lemniscus of the pons and the medulla (figure, A). Nerve conduction studies indicated the findings of axonal sensory-motor neuropathy, predominantly in the lower limbs.

To explore the genetic cause of the disease, after obtaining informed consent, we performed exome sequencing for the brothers as well as their younger sister, who was asymptomatic and neurologically intact.

Discussion. In the present patients, we identified a novel homozygous c.929A>G missense mutation in the GBE1 gene (p.Tyr310Cys). We consider that this is a disease-causing mutation, as their asymptomatic sister was found to carry it with a heterozygous state and did not show any neurologic abnormalities. This mutation was not found in 800 healthy individuals and known to affect an amino acid residue conserved among mammals. This is the report of Japanese patients with genetically confirmed APBD.

To date, 19 different mutations in the GBE1 gene have been found to cause APBD, all of which are missense mutations except for 1 frameshift, 1 splice site, and 1 intronic indels mutations. These GBE1 missense mutations localized in the catalytic core of GBE result in disrupting protein structure or affecting catalysis. The most common mutation is p. Tyr329Ser (c.986A>C), which was reported in Ashkenazi Jewish patients. More recently, novel missense mutations were detected in non-Jewish patients including Italians and Germans. They demonstrated atypical symptoms, such as episodic vomiting, hearing loss, or unilateral plexopathy, respectively. Ophthalmoplegia and bulbar palsy observed in patient 2 were very rare or atypical symptoms of APBD. These clinical features of patient 2 were quite different from those of patient 1, although both patients showed muscle weakness and hyporeflexia, indicating intrafamilial variability. These findings suggest clinical heterogeneity of APBD especially in non-Jewish patients including Japanese.

By contrast, medullary and spinal atrophy, periventricular white matter abnormalities with lesions in the posterior limb of the internal capsule,
pyramidal tracts, and medial lemniscus of the pons and medulla, which were observed in our patients, are characteristic MRI features of patients with APBD. These neuroradiologic findings are useful for diagnosing APBD in patients with an unknown etiology of leukoencephalopathy.

As exome sequencing is becoming a less expensive and more reliable method for detecting inherited
disorders, it is more efficient than whole-genome sequencing. Our study reconfirmed the diagnostic utility of exome sequencing in a family with a rare and atypical neurologic disorder.

From the Department of Neurology (Y.H., K.M.), Maebashi Red Cross Hospital; Department of Neurology (T.M., H.L., J.M., S.T.), Graduate School of Medicine, Tokyo University; Department of Neurology (Y.F., Y.I.), Gunma University Graduate School of Medicine, Maebashi; Department of Computational Biology and Medical Sciences (S.M.), Graduate School of Frontier Sciences, Tokyo University, Chiba; and Department of Neurology (M.S.), Hirnuki University Graduate School of Medicine, Japan.

Author contributions: Dr. Harigaya, Dr. Matsukawa, and Dr. Fujita contributed to this study by design and conceptualization, analysis of data, and drafting the manuscript. Dr. Mizushima contributed to this study by revising the manuscript. Dr. Ishiura, Dr. Mitsui, and Dr. Morishita contributed to this study by analysis of data and revising the manuscript. Dr. Shoji and Dr. Ikeda contributed to this study by revising the manuscript. Dr. Tsuji contributed to this study by design and conceptualization and revising the manuscript. All the authors approved the final version of this article to be published.

Study funding: This work was supported in part by KAKENHI (Grants-in-Aid for Scientific Research on Innovative Areas [22129001 and 22129002]), a Grant-in-Aid (H26-Itaku[Nan]-Ippan-006) from the Ministry of Health, Labour and Welfare.

Disclosure: Dr. Harigaya reports no disclosures. Dr. Matsukawa received funds from JSPS KAKENHI grant number 15H06160 and GlaxoSmithKline. Dr. Fujita and Dr. Mizushima report no disclosures. Dr. Ishiura has received speaker honoraria from Sanofi and GlaxoSmithKline. Dr. Fujita and Dr. Mizushima report no disclosures. Dr. Mitsui has served on the editorial boards of the Journal of Bioinformatics and Computational Biology and the Journal of BMC Genomics and the Journal of Bioinformatics and Computational Biology. Dr. Shoji was funded by KAKENHI (Grants-in-Aid for Scientific Research [C, 15K09306]) from the Ministry of Education, Culture, Sports, Science and Technology of Japan; and has served on the editorial boards of the Journal of BMC Genomics and the Journal of Bioinformatics and Computational Biology. Dr. Tsuji was funded by KAKENHI (Grants-in-Aid for Scientific Research [C, 16K09665]) from the Ministry of Education, Culture, Sports, Science and Technology of Japan. Dr. Ikeda was funded by KAKENHI (Grants-in-Aid for Scientific Research [C, 15K09334]) from the Ministry of Education, Culture, Sports, Science and Technology of Japan. Dr. Tsuji was funded by KAKENHI (Grants-in-Aid for Scientific Research on Innovative Areas [22129001 and 22129002]) from the Ministry of Education, Culture, Sports, Science and Technology of Japan; and a grant-in-aid (H26-Itaku[Nan]-Ippan-006) from the Ministry of Health, Labour and Welfare (MHLW). Go to Neurology.org/ng for full disclosure forms. The Article Processing Charge was paid by the authors.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Received November 17, 2016. Accepted in final form January 24, 2017.

Correspondence to Dr. Harigaya: y-harigaya@maebashi.jrc.or.jp

Novel GBE1 mutation in a Japanese family with adult polyglucosan body disease
Yasuo Harigaya, Takashi Matsukawa, Yukio Fujita, et al.
Neurol Genet 2017;3;
DOI 10.1212/NXG.0000000000000138

This information is current as of February 24, 2017

Updated Information & Services
including high resolution figures, can be found at:
http://ng.neurology.org/content/3/2/e138.full.html

References
This article cites 7 articles, 0 of which you can access for free at:
http://ng.neurology.org/content/3/2/e138.full.html##ref-list-1

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
All Genetics
http://ng.neurology.org/cgi/collection/all_genetics
Glycogenoses
http://ng.neurology.org/cgi/collection/glycogenoses
Metabolic disease (inherited)
http://ng.neurology.org/cgi/collection/metabolic_disease_inherited
MRI
http://ng.neurology.org/cgi/collection/mri

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://ng.neurology.org/misc/about.xhtml#permissions

Reprints
Information about ordering reprints can be found online:
http://ng.neurology.org/misc/addir.xhtml#reprintsus