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

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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.[1] The majority of patients with APBD are of Ashkenazi Jewish ancestry and have a common p.Tyr329Ser mutation in the *GBE1* gene encoding GBE.[1,2] 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 sensorymotor neuropathy, predominantly in the lower limbs.

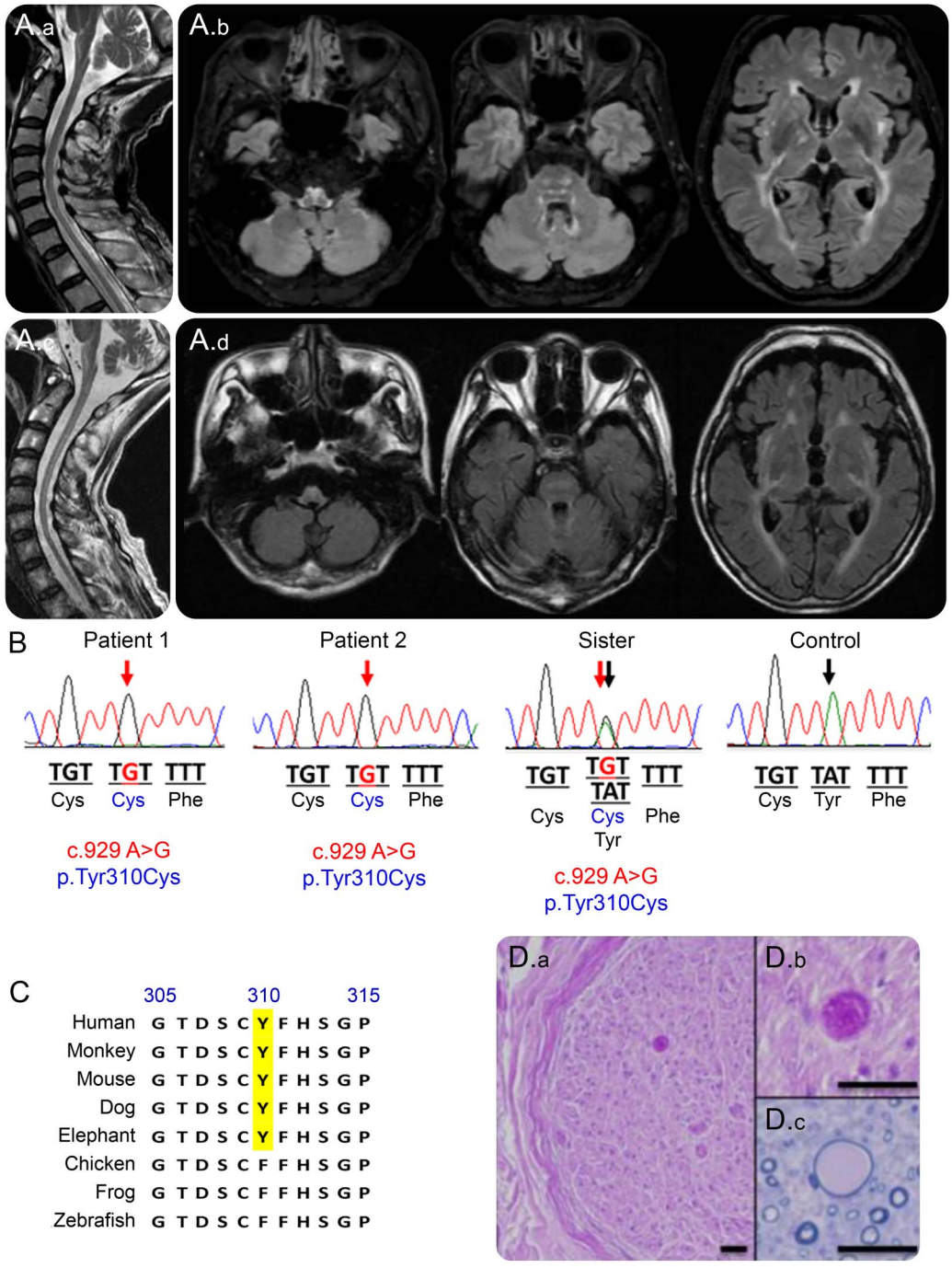
To explore the genetic cause of the disease, after obtaining informed consent, we performed exome sequencing for the brothers as well as their younger sister, who was asymptomatic and neurologically intact. A novel homozygous c.929A>G missense mutation (p.Tyr310Cys) in the *GBE1* gene was identified in patients 1 and 2. This variant was also present in the sister with a heterozygous state. Sanger sequencing of the PCR product containing the exon 7 region of the *GBE1* gene validated the presence of this homozygous mutation in the brothers and the heterozygous mutation in their sister (figure, B). This variant affects a highly conserved amino acid found within the GBE protein (figure, C). The diagnosis of APBD was made by confirming the intra-axonal deposition of PB in the sural nerve biopsy specimen from patient 1 (figure, D).

Discussion. In the present patients, we identified a novel homozygous c.929A>G 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.[1–7] 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.[1,2] More recently, novel missense mutations were detected in non-Jewish patients including Italians and Germans.[4–6] They demonstrated atypical symptoms, such as episodic vomiting, hearing loss, or unilateral plexopathy, respectively.[4–6] 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,

Figure Brain MRI, novel *GBE1* gene mutation, and polyglucosan bodies in sural nerve



(A) Brain MRIs of patient 1 (A.a, A.b) and patient 2 (A.c, A.d) showed atrophy of the medulla and the spinal cord (A.a and A.c, sagittal T2-weighted images), and hyperintense white matter lesions in the periventricular regions, posterior portions of the internal capsule, pyramidal tracts, and medial lemniscus of the pons and medulla (A.b and A.d, respectively, axial fluid-attenuated inversion recovery images). (B) Sanger sequencing confirmed that the A to G transition at position 929 (c.929A>G), with replacement of tyrosine with cysteine at codon 310 (p.Tyr310Cys), was in a homozygous state in patients 1 and 2, and a heterozygous state in their sister. (C) The affected amino acid is highlighted by the yellow rectangle. This tyrosine at position 310 is highly conserved among mammals but not in other species. (D) Axial sections of the sural nerve biopsy specimen of patient 1 showed several round periodic acid–Schiff (PAS)-positive PBs (D.a and D.b, scale bar = 25 μm). Axial epoxy section showed a large intra-axonal PB and loss of myelinated fibers (D.c, toluidine blue, scale bar = 25 μm). PB, polyglucosan body.

pyramidal tracts, and medial lemniscus of the pons and medulla, which were observed in our patients, are characteristic MRI features of patients with APBD.[1] 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.

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