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Cardiac ^{123}I-Meta-Iodobenzylguanidine Scintigraphy and Lewy Body Pathology in a Patient with Amyotrophic Lateral Sclerosis and Parkinsonism–Dementia Complex of Kii, Japan

Amyotrophic lateral sclerosis and parkinsonism–dementia complex (ALS/PDC) is a rare endemic condition on the Kii peninsula of Japan and the island of Guam. It is characterized clinically by parkinsonism, dementia, and symptoms of motor neuron disease and pathologically by the presence of numerous tau protein deposits in the central nervous system (CNS).[1,2] Meta-iodobenzylguanidine (MIBG), which is an analogue of norepinephrine, is used in cardiac ^{123}I-MIBG scintigraphy to map the function of cardiac sympathetic nerve terminals.[3] We report a Kii ALS/PDC patient with low cardiac MIBG uptake and Lewy bodies in both the CNS and the cardiac sympathetic plexus.

A 74-year-old man who was a lifelong resident of the Kii peninsula, presented with a 7-year history of L-dopa-resistant parkinsonism and subcortical dementia without any ALS features. MRI revealed severe atrophy of the frontal and temporal lobes. SPECT and PET identified regions of markedly low cerebral blood flow and glucose metabolism in the frontal and temporal lobes. ^{123}I-MIBG scintigraphy demonstrated a total lack of cardiac uptake at age 71 (Fig. 1A). He was neither a diabetic nor on any medications known to influence cardiac MIBG uptake.

When he died of pneumonia, an autopsy was performed after obtaining informed consent from the patient's family. The formalin-fixed brain specimen weighed 1255 g. Gross inspection showed moderate atrophy of the frontal and temporal lobes, mild atrophy of the hippocampus and striatum, and severe depigmentation of the substantia nigra and locus coeruleus. Gallyas–Braak staining revealed numerous neurofibrillary tangles without senile plaques, mainly in the temporal cortex, frontal cortex, and brain stem (Fig. 1B). A moderate decrease in and degeneration of the anterior horn cells in the spinal cord were observed. Hematoxylin & eosin (H&E) staining and antiphosphorylated α-synuclein

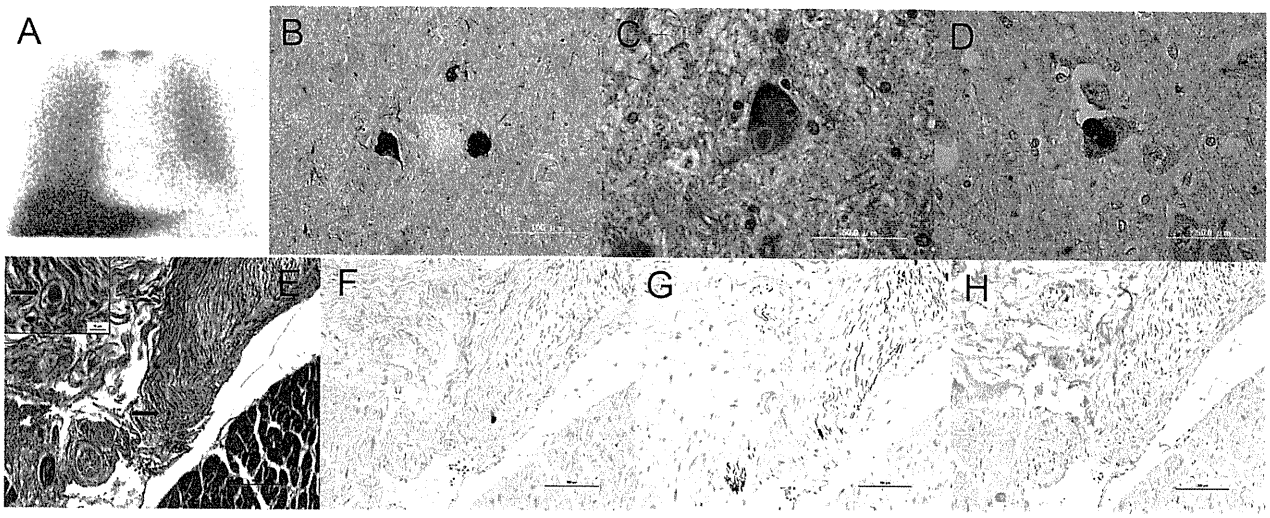

FIG. 1. Cardiac MIBG scintigraphy, and neuropathological and cardiac sympathetic nerve studies. **A**: Delayed-phase cardiac MIBG scintigram. The heart-to-mediastinum ratio was 1.40 at early phase and 1.20 at delayed phase, with a washout rate of 62.9%. **B**: Gallyas–Braak-stained section. Note neurofibrillary tangles (NFTs) in the substantia nigra. **C**: Hematoxylin and eosin (H&E)–stained section. Note the presence of Lewy body in the substantia nigra. **D**: Phosphorylated α-synuclein (psyn#64)-immunostained section. Note α-synuclein-immunopositive Lewy body in the substantia nigra. **E**: H&E-stained section. Note Lewy body in the unmyelinated nerve fascicles of the cardiac plexus (arrow) and its magnification (inset). **F**: Psyn#64-immunostained section. Note α-synuclein deposits in the unmyelinated nerve fascicles of the cardiac plexus. **G**: Phosphorylated neurofilament (pNF)–immunostained section. Note the presence of pNF immunostaining in the unmyelinated nerve fascicles of the cardiac plexus. **H**: Tyrosine hydroxylase (TH)–immunostained section. Note the lack of TH immunostaining in the unmyelinated nerve fascicles of the cardiac plexus.

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immunostaining revealed that α-synuclein-positive pathology, including Lewy bodies (LBs), was identified in the substantia nigra (Fig. 1C,D), locus coeruleus, dorsal vagal nucleus, raphe nucleus, amygdala, and intermediolateral column of the spinal cord. Examination of the cardiac plexus identified LBs (Fig. 1E) and antiphosphorylated α-synuclein-positive structures (Fig. 1F) with relatively preserved antiphosphorylated neurofilament immunostaining (Fig. 1G) and a lack of anti–tyrosine hydroxylase immunostaining (Fig. 1H). Antihuman phosphorylated tau protein immunostaining did not show any inclusions, and the heart itself did not show any pathological changes. This study was approved by the Ethics Committee of Mie University Graduate School of Medicine.

This report describes, for the first time, the relationship between low cardiac uptake on ^{123}I-MIBG scintigraphy and LB pathology in cardiac sympathetic nerves in a patient with Kii ALS/PDC. Colocalization of tau and α-synuclein is a rare finding in the CNS of patients with Kii ALS/PDC (unpublished data). Therefore, the relationship between tau and α-synuclein is not clear. The involvement of the cardiac sympathetic nerves in this patient suggests α-synucleinopathy rather than tauopathy. We cannot exclude the possibility that the present patient may have coincident Parkinson's disease. Further studies should be carried out in a larger sample of Kii ALS/PDC patients in order to clarify whether low cardiac MIBG uptake is a common finding in Kii ALS/PDC.

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SHORT COMMUNICATION

PLA2G6 variant in Parkinson's disease

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***PLA2G6* was reported recently as the causative gene for *PARK14*-linked autosomal recessive early-onset dystonia-parkinsonism. In a recent study in Singapore, heterozygous *PLA2G6* p.P806R (c.2417C>G) mutation in exon 17 was reported to be a possible Parkinson's disease (PD)-related mutation. To determine the significance of the *PLA2G6* mutation, we conducted an association study by performing direct sequencing of *PLA2G6* exon 17 in 379 Japanese sporadic PD patients and 310 controls in the Japanese general population. In this group, we found 12 patients (12/379=3.16%) and 10 controls (10/310=3.23%) with a heterozygous p.P806R mutation (P=0.96, χ^2=0.0019). Therefore, our large case–controlled study suggests that *PLA2G6* p.P806R is not a disease-associated polymorphism in PD. Moreover, we performed direct sequencing of all exons and exon-intron boundaries of *PLA2G6* in 116 Japanese patients with sporadic PD. Two single heterozygous variants (p.R301C or p.D331N) were found (both frequencies: 1/379 patients vs 0/310 controls) and the roles of their variants were unclear. Finally, combined with the previous report, our findings emphasize that *PLA2G6* mutations are unlikely to be the major causes or risk factors of PD at least in Asian populations. However, further large studies in various populations are needed because patients with *PLA2G6* mutations can show heterogeneous clinical features.**
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Keywords: genetics; Parkinson's disease; parkinsonism-dystonia; *PLA2G6*; *PARK14*

Parkinson's disease (PD, OMIM no. 168600) is the second most common neurodegenerative disorder next to Alzheimer's disease. Although the cause remains unclear, PD is thought to be a heterogeneous disease caused by the interaction of multiple genetic factors and environmental factors associated with aging. Indeed, case–control studies identified some genetic risk factors for PD, such as *SNCA*,[1–4] *LRRK2*[3–8] and *GBA* variants.[9–11] To elucidate the exact etiology of PD, identifying the effect of each of the multiple factors and their combined effects is important.

Recently, *PLA2G6* was reported to be the causative gene for *PARK14* in patients with autosomal recessive early-onset dystonia-parkinsonism.[12] *PLA2G6* is also the causative gene for infantile neuroaxonal dystrophy, neurodegeneration associated with brain iron accumulation and Karak syndrome.[13–15] Some patients with neurodegeneration associated with brain iron accumulation show very early-onset and rapid psychomotor regression, early cerebellar signs, pyramidal signs and visual disturbances. Patients with *PLA2G6* mutations frequently exhibit brain iron accumulation, which is a feature of neurodegeneration associated with brain iron accumulation. In our recent study, we revealed two novel compound heterozygous *PLA2G6* mutations in Japanese patients who had levodopa-responsive parkinsonism with or without brain iron accumulation.[16] Although there are few *PLA2G6* mutation analyses in parkinsonism so far, its role in parkinsonism or PD and the mechanism of neurodegeneration and iron accumulation have not been clarified.

Very recently, Tan *et al.*[17] in Singapore reported the results of *PLA2G6* analysis in 96 PD patients with young-age onset/dystonia. One of the 96 patients, who had a novel heterozygous p.P806R (c.2417C>G) mutation in exon 17, had typical features of late-onset PD with levodopa responsiveness and dystonic spasms. Although they could not conduct a segregation analysis, this mutation was not found in 100 healthy controls. Their result emphasized the potential role of this mutation and the *PLA2G6* mutation as pathogenic mutations or risk factors for PD in Chinese or other races. To confirm this intriguing finding of *PLA2G6*, we conducted an extended mutation analysis and association study in Japanese patients with sporadic PD and normal controls.

The study was approved by the Institutional Review Board of Juntendo University, and all subjects provided an informed consent. We collected blood samples from each participant and extracted genomic DNA by using standard methods. Sequences of the primers/probes and conditions of PCR/sequencing are available upon request to the corresponding author or the first author. We directly sequenced the exon 17 of *PLA2G6* from 379 Japanese patients with sporadic PD and 310 normal Japanese subjects as controls (Table 1).

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Table 1 Profile of analyzed subjects and allele frequency of *PLA2G6* p.P806R (c.2417C>G) in Japanese patients with sporadic Parkinson's disease (SPD) and control subjects from the general population

	Japanese SPD			*Japanese control from the general population*		
	All analyzed subjects	*Heterozygous (C/G)*	*Wild type (C/C)*	*All analyzed subjects*	*Heterozygous (C/G)*	*Wild type (C/C)*
Number of patients (F:M)	379 (198:181)	12 (3:9)	367 (195:172)	310 (188:122)	10 (6:4)	300 (182:118)
Age at sampling[a] (range, *n*=number)	60.2 ± 14.0 (12–92, *n*=378)	58.6 ± 22.4 (12–87, *n*=12)	60.3 ± 13.7 (12–92, *n*=366)	58.5 ± 13.2 (23–98, *n*=294)	60.7 ± 12.8 (35–81, *n*=10)	58.5 ± 13.2 (23–98, *n*=284)
Age at onset[a] (range, *n*=number)	52.7 ± 14.3 (7–88, *n*=375)	52.7 ± 22.3 (11–83, *n*=12)	52.7 ± 14.0 (7–88, *n*=365)			
Disease duration[a] (range, *n*=number)	7.4 ± 5.6 (0–40, *n*=375)	5.9 ± 5.3 (1–18, *n*=12)	7.5 ± 5.6 (0–40, *n*=363)			
Allele frequency (%)		1.58			1.61	

No homozygous *PLA2G6* p.P806R mutation was found in this study. Genotypes of the patients and controls were concordant with Hardy–Weinberg equilibrium.
[a]Data are mean ± s.d.

We identified a heterozygous p.P806R mutation in 12 patients with PD and in 10 controls (χ^2=0.0019, P=0.96; odds ratio (genotype)=1.02, 95% confidence interval: 0.44–2.37, Table 1). We found no homozygous p.P806R mutations. The allele frequency was 1.58% in sporadic PD and 1.61% in controls. We also found heterozygous synonymous p.T787T (c.2355C>T) variant in two patients and one control. No other variants were found in exon 17. Moreover, we performed direct sequencing of all exons and exon–intron boundaries of *PLA2G6* in 116 Japanese patients with sporadic PD (males 60, females 56; age range, 12–92 years; mean age, 60.7 ± 18.1 years; mean disease duration, 6.3 ± 5.8 years). Among them, we found two novel single heterozygous non-synonymous variants (p.R301C, p.D331N). Both frequencies of the two variants were 1/379=0.26% in patients and 0/310=0% in Japanese normal controls. The roles of their rare variants found in Japanese patients with sporadic PD remained unclear (Table 2).

The reported clinical features of neurodegeneration associated with mutations in the *PLA2G6* gene (PLAN) are axonal dystrophy, dystonia, dementia, visual disturbances, cerebellar signs and brain atrophy with or without iron accumulation.[12–15,18,19] Showing clinical heterogeneity, patients with *PARK14*-linked parkinsonism have levodopa responsiveness, levodopa-induced dyskinesia and dementia with an older-age onset and a longer disease duration than those with infantile neuroaxonal dystrophy.[12,16] These studies have suggested that patients with *PLA2G6* mutation can show heterogeneous phenotype.

Although the precise function of *PLA2G6* in neurodegeneration and iron accumulation remains obscure, defective phospholipid metabolism is implicated in neurodegenerative diseases featuring brain iron dyshomeostasis.[14] *PLA2G6* is thought to be responsible for the development of autosomal recessive disorders through its loss of function; hence, the role of a single heterozygous *PLA2G6* mutation is intriguing. Indeed, two of the 10 infantile neuroaxonal dystrophy patients were previously reported to have one-allele mutations, suggesting that single heterozygous mutation in *PLA2G6* could be pathogenic.[19]

The aim of this study was to clarify the role of the *PLA2G6* mutation in PD. Although patients with *PLA2G6* mutations have been reported to show atypical parkinsonism, the heterozygous *PLA2G6* p.P806R mutation was found in late-onset PD patients with typical parkinsonism.[17] In our extended case–controlled study of a large sample size, no association of *PLA2G6* p.P806R was identified in Japanese PD patients and controls. Thus, our data suggest that *PLA2G6* p.P806R is a non-PD-associated polymorphism at least in Japanese PD patients. This result should help clinicians in genetic counseling for PD patients.

Furthermore, in the previous report, there were no other possible PD-associated variants in any of the 17 exons in the 96 PD patients.[17] Therefore, combined with the data from Singapore,[17] our findings emphasize that *PLA2G6* mutations are unlikely to be the major causes or risk factors of PD at least in Asian populations.

However, because there have been no adequate *PLA2G6* mutation analyses in parkinsonism, disease-associated variants in *PLA2G6* could exist in patients with atypical/typical parkinsonism, or PD in specific races. In parkinsonism-dystonia patients, *PLA2G6* mutations have thus far been reported in only certain populations, such as Indians, Pakistanis and Iranians.[12,15,19] In heterogeneous clinical setting of patients with *PLA2G6* mutations, the roles of *PLA2G6* should be clarified including the effect of heterozygous mutation. As brain iron accumulation is frequently observed in common diseases, such as PD and Alzheimer's disease, the role of *PLA2G6* in iron accumulation is elusive in neurodegenerative disorders.

Table 2 *PLA2G6* variants (excluding p.P806R) found in patients with sporadic PD and the allele frequency

				Frequency in this study		
Exon	*Position*	*Amino acid*	*Accession number*	*Patients (%)*	*Allele frequency in patients (%)*	*Controls (%)*
2	c.87G>A	p.V29V	rs2267369	18/116 (15.52)	8.19	
7	c.901C>T	p.R301C	(novel)	1/379 (0.26)	0.13	0/310 (0)
7	c.991G>A	p.D331N	(novel)	1/379 (0.26)	0.13	0/310 (0)

Abbreviation: PD, Parkinson's disease.

Thus, further large studies in various populations and functional studies for *PLA2G6* are needed in neurodegenerative disorders with or without brain iron accumulation.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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