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Mutation analysis of *LRP10* in Japanese patients with familial Parkinson's disease, progressive supranuclear palsy, and frontotemporal dementia

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ABSTRACT

Mutations of the gene encoding low-density lipoprotein receptor–related protein 10 (*LRP10*) were recently detected in patients (heterogeneous races) with autosomal dominant inheritance of familial Parkinson's disease. The patients with Parkinson's disease, Parkinson's disease with dementia, and dementia with Lewy bodies whose brain pathology indicated deposit of alpha-synuclein along with the co-occurrence of tau pathology and amyloid-beta plaques presented *LRP10* mutations. LRP10 is localized in the vesicular structures and trans-Golgi network; its alteration leads to alpha-synuclein aggregation. Thus, we conducted the genetic screening of *LRP10* among 187 patients with familial Parkinson's disease and 19 patients with atypical parkinsonian disorders, including frontotemporal dementia, progressive supranuclear palsy, and corticobasal syndrome. There were no putative pathogenic variants among patients with Parkinson's disease. We detected one rare variant, p.D198N, in a patient with frontotemporal dementia, without a cosegregation study. Overall, our findings showed that *LRP10* variants are not causative for disease in our cohort.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder next to Alzheimer's disease (Goedert et al., 2013) and is a major cause of dopaminergic neuronal loss in the substantia nigra. Lewy bodies and neurites are pathological hallmarks of the disease. Alpha-synuclein is a major component of Lewy bodies. High expression levels of alpha-synuclein are thought to be related to the onset of PD. Approximately 5%–10% of the patients with PD have a positive family history. Molecular analyses have revealed several pathogenic mutations in genes, such as alpha-synuclein (*SNCA*), leucine-rich repeat kinase 2 (*LRRK2*), parkin RBR E3 ubiquitin protein ligase (*PRKN*), and PTEN-induced kinase 1 (*PINK1*) in the last 20 years (Deng et al., 2017). In addition, mutations in the coiled-coil-helix-coiled-coil-helix domain containing 2 (*CHCHD2*) and vacuolar protein sorting 13 homolog C (*VPS13C*) genes have recently been identified (Funayama et al., 2015; Lesage et al., 2016).

Recently, a novel pathogenic mutation in low-density lipoprotein receptor–related protein 10 (LRP10) was reported based on the genetic analysis of a large Italian family showing the autosomal dominant inheritance mode; in this family, the patients presented middle-aged onset, good response to levodopa, and typical parkinsonism or dementia with Lewy bodies (DLB) (Quadri et al., 2018). The autopsy of three patients with *LRP10* mutations demonstrated the presence of widespread Lewy bodies and neurites in the brain, hyperphosphorylated tau protein in neurofibrillary tangles and threads, and amyloid-beta cored plaques in the neocortex. In the previous study, patients belonging to different geographical regions, Europe, South America, and Asia, were enrolled. Nine variants of *LRP10* were identified: c.1424+5delG, c.1424+5G>A, c.632dupT (p.A212Sfs*17), c.919T>A (p.T307A), c.1807G>A (p.G603A), c.703C>T (p.A235C), c.1549_1551delAAT (p.A517del), c.1598G>T (p.A533L), and c.2095C>T (p.P699S). A subsequent study reported c.1438C>T (p.L480P), c.1696C>T (p.L566P), and c.1838C>T (p.A613V) as possible pathogenic variants among patients with sporadic PD in China (Shi et al., 2018). However, the other three studies supported the rarity of *LRP10* variants among patients with sporadic PD, familial PD, and multiple system atrophy (MSA) mainly in European-ancestry cohorts (Kia et al., 2018; Pihlstrom et al., 2018;

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Tesson et al., 2018); significance of p.T307A is still controversial. Most of the patients in these previous studies were derived from sporadic cases (not familial cases); thus, the prevalence and effects of *LRP10* variants in patients with familial PD still remain unclear.

In this study, we surveyed the variants of *LRP10* among the mostly late-onset patients with synucleinopathies such as familial PD, PD with dementia (PDD), and DLB and those with tauopathies such as progressive supranuclear palsy (PSP), frontotemporal dementia (FTD), and corticobasal syndrome (CBS) in a Japanese cohort. Our findings will expand the understanding of *LRP10* variants and neurodegenerative disorders.

2. Material and methods

2.1. Participants

The study was approved by the Ethics Committee of Juntendo University, and all subjects gave written informed consent for participation in the study. All patients were of Japanese origin and were clinically, but not pathologically, diagnosed. Samples and clinical data were obtained from the gene bank of Juntendo University. Autosomal dominant inheritance was defined by the presence of affected individuals in at least two consecutive generations. Autosomal recessive inheritance was defined by the presence of two or more affected siblings.

Patients harboring variants in *PRKN*, *SNCA*, and *PINK1* and exons 21, 31, and 41 of *LRRK2* were excluded from the study. Enrolled patients were divided into two groups, PD/PDD/DLB and PSP/FTD/CBS. Patients in the PD/PDD/DLB group included 81 males and 106 females (n = 187). Mean age (±standard deviation) at onset was 62.0 years (±7.76), mean age at examination was 67.0 years (±8.12), 171 patients had PD, and 16 patients were clinically diagnosed with PDD/DLB (Table 1). All patients showed autosomal dominant inheritance and met standard clinical diagnostic criteria (Emre et al., 2007; Gibb and Lees, 1988; McKeith et al., 2005).

Patients in the PSP/FTD/CBS group included 13 males and six females (n = 19). Mean age at onset was 65.1 years (±8.9), and mean age at examination was 68.6 years (±9.88). Fifteen patients had PSP, three had FTD, and one had CBS, according to standard criteria (Hoglinger et al., 2017; Mathew et al., 2012; Rascovsky et al., 2011). All patients had a family history of neurodegenerative disorders, showing 16 autosomal dominant and three autosomal recessive inheritance patterns (Supplementary Table 1).

Exons and exon-intron boundaries of *LRP10* were analyzed in the two groups. For the PSP/FTD/CBS group, we screened for variants in the microtubule associated protein tau (*MAPT*) and granulin precursor (*GRN*) genes using methods previously described (Nakayama et al., 2019).

2.2. Procedures and genetic analyses

Genomic DNA was extracted from peripheral blood using a standard protocol. All exons and intron-exon boundaries of *LRP10* were amplified from genomic DNA using polymerase chain reaction (PCR) primers, which were prepared according to an original report (Quadri et al., 2018) or were originally designed by ExonPrimer (https://ihg.helmholtz-muenchen.de/ihg/ExonPrimer.html) using an NCBI reference sequence (ID: NM_014045). We used the standard protocols of ABI BigDye Terminator chemistry (Applied Biosystems, Foster City, CA, USA) for direct sequencing. The DNA sequences were analyzed using ABI3130 Genetic Analyzer (Applied Biosystems).

Table 1
Demographic data of the enrolled patients

Clinical features	PD/PDD/DLB group	PSP/FTD/CBD group
Total number of patients	187	19
Gender	81: 106	13: 6
Average age at onset	62.0 ± 7.76	65.1 ± 8.91
Average ate at examination	67.0 ± 8.12	68.6 ± 9.88
Clinical diagnosis	PD (171), PDD/DLB (16)	PSP (15), FTD (3), CBS (1)

Key: CBS, corticobasal syndrome; CBD, corticobasal degeneration; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; PD, Parkinson's disease; PDD, Parkinson's disease with dementia; PSP, progressive supranuclear palsy.

2.3. Reverse-transcriptase–PCR and quantitative PCR

2.3.1. Reverse-transcriptase–PCR analysis

Total RNA was isolated from peripheral blood of the patient harboring 1424+8G>A and a patient as control who did not have *LRP10* mutation, using a PAXgene Blood RNA Kit (QIAGEN, Valencia, CA, USA). Total RNA was used to synthesize cDNA. ReverTra Ace qPCR RT Master Mix (TOYOBO, Osaka, Japan) was used for the reverse transcription reaction. The cDNA was amplified by PCR using AmpliTaq Gold 360 Master Mix (Life Technologies) and the primers described in Supplementary Table 1, inside of exons 4, 5, and 6. If exon skipping exists, a primer in 4 and 6 works and 298-bp fragment would be seen. If not, a primer in 4 and 5 works, 424-bp fragment would be found. Reverse transcriptase PCR products were visualized by MultiNA (SHIMADZU, Kyoto, Japan). Both products' lengths were 424 bp.

2.3.2. Quantitative PCR

A real-time quantitative PCR (qPCR) experiment was set up including *LRP10* and β-actin for the normalization to determine the expression levels of a case of carrying *LRP10* 1424+8G>A and a case of PD without *LRP10* variants. Total RNA was isolated from peripheral blood of the patient harboring 1424+8G>A and a patient as control, using a PAXgene Blood RNA Kit (QIAGEN, Valencia, CA, USA). Cybergreen (Thermo Fisher Scientific) assays spanning genomic intron-exon junctions were designed. The primers were purchased from Thermo Fisher Scientific (MA, USA), and suitable probes were selected from the Primer Express 3.0. Cybergreen assay conditions were as follows: *LRP10*, 95 °C for 20 seconds initial denaturation, followed by 40 cycles of 95 °C for one second, decrease of 2.42° per second and 60 °C for 30; *β-actin*, 20 seconds initial denaturation, followed by 40 cycles of 95 °C for one second, decrease of 2.42° per second and 60 °C for 30. All PCR reactions were prepared with KAPA SYBR Fast qPCR Kit (Kapa Biosystems) and performed using QuantStudio 7 flex (Thermo Fisher Scientific). Standard curves were generated for each assay run. The reaction volume per well was 20 μL (cDNA was 40 ng). All samples were run in triplicate.

2.4. Bioinformatics analysis

Sequence analysis was conducted using ABI PRISM DNA Sequencing Analysis software Version 5.1. Heterozygous bases were identified by overlapping peaks at the same position. We monitored the quality values of sequence data and performed manual inspection when quality scores were lower than 20. The BLAST-like alignment tool was used to detect sequence variants, by comparison with reference sequences (Kent, 2002).

Pathogenicity of the identified variants was predicted using the following bioinformatics tools: PolyPhen-2 (Adzhubei et al., 2010), MutationTaster (Schwarz et al., 2010), Sorting Intolerant from Tolerant (Vaser et al., 2016), Protein Variation Effect Analyzer (Choi and Chan, 2015), Rare Exome Variant Ensemble Learner, Combined Annotation-Dependent Depletion (Kircher et al., 2014), and Human Splicing Finder (Desmet et al., 2009). The frequencies of each variant were investigated using the genome aggregation database (gnomAD), exome aggregation consortium (ExAC) database (Lek et al., 2016), and integrative Japanese genome variation database,

which is the largest public gene data bank in Japan (Nagasaki et al., 2015). Evolutionary conservation of the mutated amino acids was evaluated using the National Center for Biotechnology Information (NCBI) HomoloGene (http://www.ncbi.nlm.nih.gov/homologene/).

3. Results

3.1. The results of the genetic analysis in LRP10

Among the 187 patients with PD, PDD, and DLB, we found 6 variants in *LRP10*, which include one synonymous variant (c.39C>T), four nonsynonymous variants (c.32_33insCCT, p.R48W, p.R151H, and p.D518N), and one variant in the splicing region (c.1424 + 8G>A) (Table 2). The prediction tools indicated that the three non-synonymous variants (p.R48W, p.R151H, and p.D518N) are "benign" based on the existence of known rs numbers and relatively high prevalence among the populations; the frequencies of p.R48W, p.R151H, and p.D518N were 0.015, 0.002, and 0.03, respectively. Regarding p.D518N, a previous report supports our findings with regard to the absence of differences in frequencies between the PD group and control group (Shi et al., 2018). c.32_33insCCT (p.L11_G12insL) is thought not to be a pathogenic variant due to our bioinformatics analysis (Table 2). And the referred sequences show six tandem repeats of leucine in the region and deletion variant of the tandem repeats (p.L11del) is reported more than 0.1% in ExAC (Allele frequency in East Asia: 0.002672). It is suggested that the variation of tandem repeats may be no significance. Furthermore, we detected four variants, which include one synonymous variant (c.39C>T, p.G13G) and three non-synonymous variants (p.R48W, p.R151H, and p.D198N), among the 19 patients in the PSP/FTD/corticobasal degeneration group (Fig. 1A and B). We did not find any rare or pathogenic variants in *MAPT* or *GRN*, in the PDP/FTD/corticobasal degeneration group.

Based on our bioinformatics analyses, we consider p.D198N a rare and potential disease associated variant, according to the guidelines for investigating causality of sequence variants in human disease (MacArthur et al., 2014). Our analysis indicated the following as evidences for considering that p.D198N is involved: (1) nonexistence of rs numbers, (2) high disease-causing propensity according to the results of Combined Annotation-Dependent Depletion, (3) absence of records in gnomAD, ExAC, and integrative Japanese genome variation database, (4) none of pathogenic variants in the genes: *MAPT* and *GRN* commonly seen in the familial FTD. However, the other prediction tools such as PolyPhen-2, MutationTaster, and Sorting Intolerant from Tolerant did not show the potential protein functional changes caused by the variant. c.1424+8G>A is located close to c.1424+5G>A, which was reported as a pathogenic variant associated with DLB (Quadri et al., 2018). Thus, we conducted reverse transcription PCR and real-time PCR. There were no differences in expression levels between controls and a patient harboring c.1424+8G>A, which indicate that 1424+8G>A does not affect splicing (Fig. 2A and B).

3.2. Reverse transcriptase PCR and qPCR analyses of c.1425+8G>A

Reverse transcription PCR analysis showed that c.1425+8G>A did not lead to exon skipping, and in qPCR analysis, there was no variation in expression levels, when compared with controls. Thus, c.1425+8G>A is not considered to be a pathogenic variant.

3.3. Clinical presentation of the patient harboring p.D198N

The proband with p.D198N (II-1) was a female patient (Fig. 1C). At the age of 65 years, she experienced gait disturbance and needed a cane when she walked. Two years later, the attending doctor noticed her akinesia and rigidity. At the age of 68 years, she was admitted to our hospital. Our first neurological examinations indicated wide-based gait, small steps, rigidity in the right hand, positive retropulsion, forced grasp reflex, gegenhalten in both hands, tonic planter response, snout reflex, and palmomental reflex. Frontal signs were positive. Furthermore, she did not present apparent cognitive dysfunction and dysautonomia. Anecdotally, her mother was diagnosed with PD and her father was diagnosed with parkinsonism in his last years. However, their clinical details are unknown. Magnetic resonance imaging of the brain showed symmetric atrophies in the temporal and parietal lobes (Fig. 1D and E). [^{123}I]N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) tropane (^{123}I-FP-CIT) single-photon emission computed tomography revealed the left-dominant decrease that is specific to nondisplaceable binding ratios (Fig. 1F). Brain single-photon emission computed tomography N-isopropyl-p-[^{123}I]-iodoamphetamine imaging, programmed by the freeware iSSP (Nihon Medi-Physics, Nishinomiya, Hyogo, Japan) (Nishioka et al., 2016), showed marked bilateral hypoperfusion in the frontal anterior temporal and parietal lobes (Fig. 1G). She did not

Table 2
Bioinformatics data of the detected variants in the studied cohort

Variant	c.32_33insCCT	c.142C>T	c.452G>A	c.592G>A	c.1425+8G>A	c.1552G>A
Amino acid change	p.L11_G12insL	p.R48W	p.R151H	p.D198N		p.D518N
rs number	-	rs2273837	rs201144028	-	rs146010729	rs74357167
Position in hg19	chr14:23341544-23341545	chr14:23342582	chr14:23344609	chr14:23344749	chr14:23345589	chr14:23346025
PolyPhen-2/prediction and confidence						
HumDiv	NA	Benign/0.004	Benign/0.083	Benign/0.018	NA	Probably damaging/0.993
HumVar	NA	Benign/0.002	Benign/0.022	Benign/0.014	NA	Possibly damaging/0.702
Mutation Taster	Polymorphism	Disease causing	Disease causing	Polymorphism	Polymorphism	Disease causing
SIFT	Damaging	Damaging/0.015	0.002/Damaging	Tolerated/1.00	NA	Damaging/0.011
PROVEAN	Neutral/0.39	Neutral/1.18	Deleterious/−2.97	Neutral/1.62	NA	Neutral/−0.82
REVEL (over 0.55 indicates double high proportion as disease variants)	NA	0.123	0.416	0.073	NA	0.394
CADD/Phred (cutoff between 10 and 20)	16.72	23.4	23.2	20.5	8.315	33
ExAC (allele frequency in East Asian population)	NA	0.01503	0.002435	NA	0.002429	0.03004
IJGVD	NA	0.0339 (231/6591)	0.0113 (79/6895)	NA	NA	NA
Human splicing finder	NA	NA	NA	NA	Probably no impact on splicing.	NA

Key: CADD, Combined Annotation−Dependent Depletion; ExAC, Exome Aggregation Consortium; iJGVD, Integrative Japanese Genome Variation Database; NA, not assessed; PROVEAN, Protein Variation Effect Analyzer; REVEL, Rare Exome Variant Ensemble Learner; SIFT, Sorting Intolerant From Tolerant.

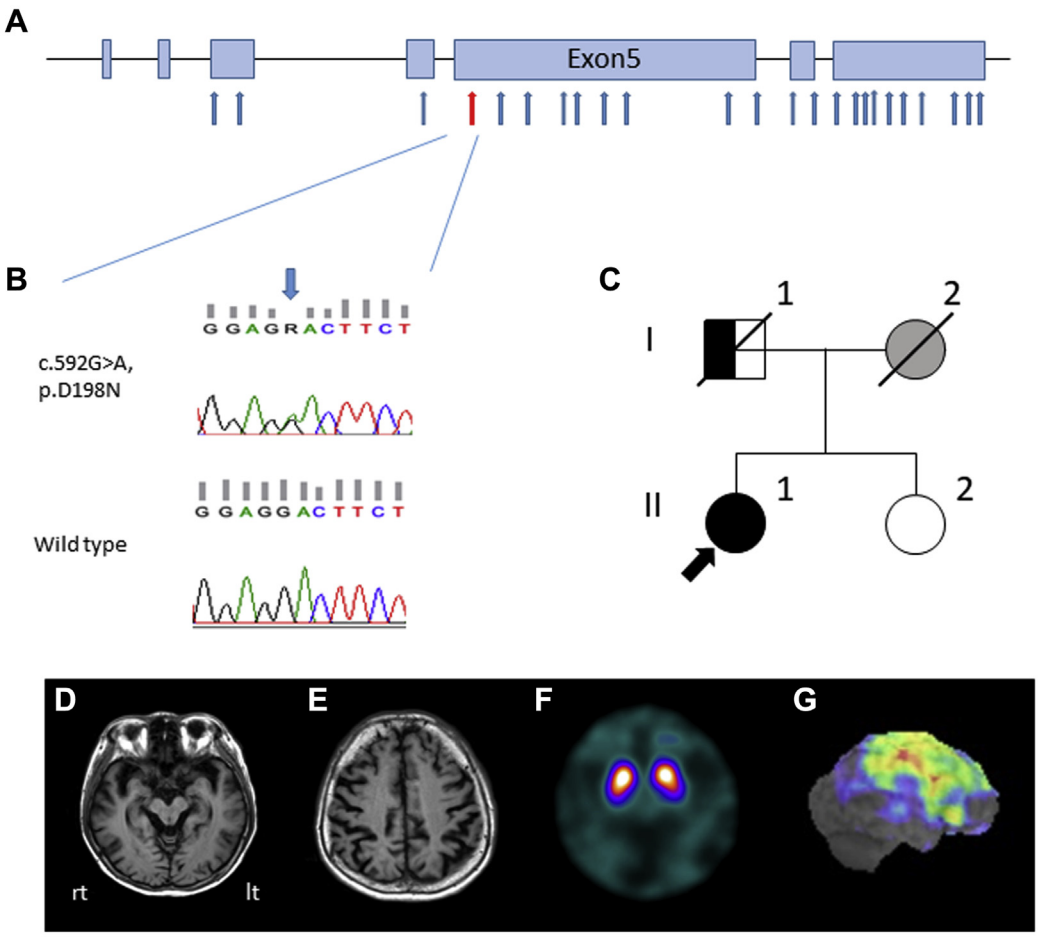

Fig. 1. The schema of *LRP10* gene structure and the results of sequencing, family pedigree, and neuroimaging of a patient harboring p.D198N. (A) Schema of *LRP10* gene structure. Red arrow indicates p.D198N, and blue arrows indicate variants or mutations related to familial Parkinson's disease (PD), reported previously. (B) Direct sequencing by Sanger's method presented a heterozygous variant of *LRP10*, p.D198N. (C) Family pedigree of the patient with p.D198N. Half black circle indicates parkinsonism. Gray circle indicates PD. Black circle indicates clinically diagnosed frontotemporal dementia. The black arrow indicates proband. Only patient II-1 was assessed by genetic testing and p.D198N was confirmed. (D and E) Brain MRI T1 wedged image of patient II-1 presenting atrophic changes in the frontotemporoparietal lobes. (F) [^{123} I]N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) tropane (^{123}I-FP-CIT) single-photon emission computed tomography (SPECT) image revealing the left-dominant decrease that is specific to nondisplaceable binding ratios (SBR). (G) Brain SPECT N-isopropyl-p-[^{123}I]-iodoamphetamine image showing marked bilateral hypoperfusion in the frontal, anterior temporal, and parietal lobes. Abbreviations: rt, right; lt, left. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

show a good response to levodopa. Cognitive decline and apathy gradually became prominent. Eventually, she was unable to live in her home by herself and was admitted in the inpatient faculty two years after the onset of motor symptoms. We clinically diagnosed her with probable behavior variant FTD based on standard criteria of behavior variant FTD (Rascovsky et al., 2011).

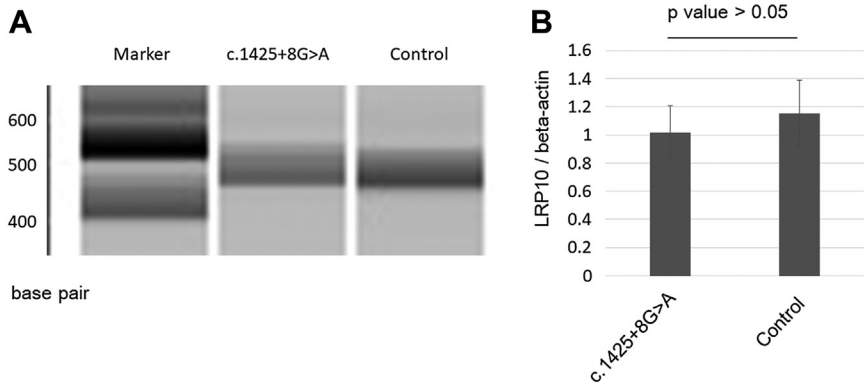

Fig. 2. Results of reverse transcription polymerase chain reaction (PCR) and real-time PCR in the patient with c.1424+8G>A. (A) reverse transcription PCR shows no differences between c.1424+8G>A and control. Control is a patient with Parkinson's disease (PD) without any *LRP10* mutation. (B) Real-time PCR showed no difference in expression levels between 1424+8G>A and controls. The vertical axis shows the value of *LRP10* quantity divided by *β-actin* quantity. These results suggest that c.1424+8G>A does not cause exon skipping of exon 5 of *LRP10*.

4. Discussion

One patient, clinically diagnosed with FTD, harbored a p.D198N variant in *LRP10*. This variant is rare and potentially associated with the disease. No pathogenic variants in *LRP10* were found in the PD/PDD/DLB group, which included patients with autosomal dominant inheritance. However, a previous study reported pathogenic mutations in patients with familial PD (Quadri et al., 2018). The absence of pathogenic variants in the present Japanese cohort may be due to differences in race or regional distribution of *LRP10* variants. This phenomenon is seen for other pathogenic variants in genes related to familial PD, such as *CHCHD2* and F-box protein 7 (*FBXO7*) (Conedera et al., 2016; Funayama et al., 2015). Alternatively, *LRP10* variants are generally not causative for familial PD.

Guerreiro et al. identified two variants of *LRP10*, p.A212Sfs*17 and p.A517del; however, these variants matched with those reported by Quadri et al. because both studies shared the same patient cohort. Of the 1040 patients with Lewy body dementia examined, they identified one protein-truncating variant, p.Q67* from one patient. However, groupwise association study showed no association of the variant with Lewy body dementia (Guerreiro et al., 2018). Shi et al. assessed *LRP10*, using exome sequencing, in patients with sporadic PD (n = 2835) and controls (n = 5343) in an Asian cohort. They detected four nonsynonymous variants, p.S134N, p.L480F, p.L566F, and p.A613V, in patients with sporadic PD, and no rare variants in 750 controls, among the Han population. They concluded that *LRP10* variants had incomplete penetrance in the cohort of sporadic PD (Shi et al., 2018). In addition, Tesson et al. reported the prevalence of *LRP10* variants, in patients of French origin showing autosomal dominant inheritance of PD (Tesson et al., 2018). They identified five missense variants in three families, including p.Y307N that did not cosegregate with the disease. In contrast, p.Y307N was reported to be a pathogenic variant by Quadri (Quadri et al., 2018). Kia et al. assessed 72 nonsynonymous variants in 2835 patients clinically diagnosed with PD (including familial and sporadic PD), and 111 patients pathologically confirmed with DLB, of European descent. The frequencies of all variants were not significantly different compared with controls. Their gene-based collapsing analysis did not identify any association between rare variants and PD (Kia et al., 2018). In addition, Pihlstrom et al. assessed potentially pathogenic variants in exome data, in 264 patients with MSA and 462 controls (Pihlstrom et al., 2018). The study did not provide evidence of pathogenicity of *LRP10* variants in patients with MSA. Therefore, there is controversy over whether rare variants in *LRP10* are associated with alpha-synucleinopathies such as PD, DLB/PDD, or MSA. Further studies are needed to establish the causality of *LRP10* variants.

Postmortem studies on 3 patients with *LRP10* mutations, whose clinical symptoms match those of PD, PDD, and DLB, initially indicated DLB pathology, along with the co-occurrence of tau pathology and amyloid-beta plaques (Quadri et al., 2018). Thus, *LRP10* variants might associate with the mixed pathologies such as overexpression of alpha-synuclein, tau protein, and amyloid-beta, resulting in parkinsonism and progressive cognitive decline. We detected one potential associated variant, p.D198N, in a patient clinically diagnosed with FTD. Commonly, the pathological findings of FTD indicate heterogeneity with tau-positive, ubiquitin-positive, and TDP-43–positive inclusions (Seelaar et al., 2011). These findings suggest that multiple LRP10 functions could result in aggregation of abnormal proteins in the brain, and severe neuronal loss. Based on pedigree analysis, the proband with p.D198N was clinically diagnosed as FTD, but her father presented parkinsonism and her mother was diagnosed with PD. Three members in the family presented different symptoms. We could not carry out the genetic testing and confirm the segregation because of the death of the parents. Thus, we did not define p.D198N as a pathogenic variant.

LRP10 plays another role in neuronal cell degeneration as an amyloid precursor protein sorting receptor (Brodeur et al., 2012). The low-density lipoprotein receptor family interacts with amyloid precursor protein, and the resultant proteolysis produces amyloid-beta (Wagner and Pietrzik, 2012). *LRLR-related protein 1* (*LRP1*) variants are linked to Alzheimer's disease (Kang et al., 2000). LRP pathway involves amyloid deposition and a clearance pathway for amyloid-beta. *LRP10* is a homologous gene of LRP and a member of the subfamily of low-density lipoprotein receptor. LRP10 is localized in vesicular structures and the trans-Golgi network, which regulates exocytosis. In a previous report on *LRP10* mutations and familial PD, brain pathology of patients harboring *LRP10* mutation presented hyperphosphorylated tau protein in neurofibrillary tangles and threads (Quadri et al., 2018). Evidence seems to support the correlation between *LRP10* variants and overexpression and abnormal aggregation of a multitude of proteins, including alpha-synuclein, tau protein, and amyloid-beta. The genetic screening of *LRP10* for a multitude of neurodegenerative disorders, especially in Alzheimer's disease, is needed in further studies.

To conclude, we did not detect pathogenic variants in *LRP10* among patients with familial PD, PDD, and DLB in Japan. We found a rare variant, p.D198N, in a patient with FTD. It is unclear whether p.D198N is pathogenic because of the lack of functional analysis, small sample size, and absence of available segregation data. Further studies are warranted to confirm disease association and causality of variants in *LRP10*. These should include functional analysis and more patients, not only with PD but also other neurodegenerative disorders.

Disclosure

The authors report no conflicts of interest relevant to the manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2019.08.030.

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