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LRP10 variants in progressive supranuclear palsy

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Abstract

The aim of this study was to explore whether variants in *LRP10*, recently associated with Parkinson's disease and dementia with Lewy bodies, are observed in 2 large cohorts (discovery and validation cohort) of patients with progressive supranuclear palsy (PSP). A total of 950 patients with PSP were enrolled: 246 patients with PSP (n = 85 possible (35%), n = 128 probable (52%), n

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CRediT authorship contribution statement

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Disclosure statement

The authors declare that there are no conflicts of interest associated with this work.

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.2020.04.016.

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= 33 definite (13%)) in the discovery cohort and 704 patients with definite PSP in the validation cohort. Sanger sequencing of all *LRP10* exons and exon-intron boundaries was performed in the discovery cohort, and whole-exome sequencing was performed in the validation cohort. Two patients from the discovery cohort and 8 patients from the validation cohort carried a rare, heterozygous, and possibly pathogenic *LRP10* variant (p.Gly326Asp, p.Asp389Asn, and p.Arg158His, p.Cys220Tyr, p.Thr278Ala, p.Gly306Asp, p.Glu486Asp, p.Arg554*, p.Arg661Cys). In conclusion, possibly pathogenic *LRP10* variants occur in a small fraction of patients with PSP and may be overrepresented in these patients compared with controls. This suggests that possibly pathogenic *LRP10* variants may play a role in the development of PSP.

Keywords

Genetics; *LRP10*; Rare variants; Progressive supranuclear palsy

1. Introduction

Progressive supranuclear palsy (PSP) is an adult-onset, progressive neurodegenerative disorder clinically characterized by parkinsonism, vertical supranuclear gaze palsy, and postural instability with falls. Other PSP features include frontal lobe and bulbar dysfunction, and cognitive decline (Litvan et al., 1996b; Respondek et al., 2013). The clinical presentation of PSP is heterogeneous, and 10 different clinical phenotypes have been described in patients with PSP neuropathology (Höglinger et al., 2017). PSP brain pathology includes neurofibrillary tangles, neutrophil threads, tufted astrocytes, neuronal loss, and gliosis in multiple subcortical areas and other regions (Hauw et al., 1994).

PSP is usually considered a sporadic tauopathy of unknown etiology (Im et al., 2015). However, rare familial forms have been reported (Donker Kaat et al., 2009; Fujioka et al., 2014). Mutations in the *microtubule-associated protein tau (MAPT)* gene have been reported as the likely disease cause in a few pathologically confirmed patients with PSP (Fujioka et al., 2015; Poorkaj et al., 2002). Furthermore, genome-wide association studies have shown associations between PSP and the *MAPT, syntaxin-6 (STX6), myelin-associated oligodendrocyte basic protein (MOBP), and eukaryotic translation initiation factor 2-alpha kinase (EIF2AK)* genes, modulating the risk of developing PSP (Chen et al., 2018; Sanchez-Contreras et al., 2018). Mutations in the *leucine-rich repeat kinase 2 (LRRK2)* gene have also been implicated in a small number of PSP cases (Ross et al., 2006; Sanchez-Contreras et al., 2017) and are the most common genetic cause of Parkinson's disease (PD) (Healy et al., 2008). Interestingly, pleomorphic neuropathology has been observed in PD patients with *LRRK2* mutations, ranging from typical alpha-synuclein–positive pathology (seen in most cases) to PSP-like pathology (Zimprich et al., 2004). Indeed in the original Japanese family, which nominated the linkage region for *LRRK2*, the affected members presented with tauopathy (Ujiie et al., 2012). Because of these genetic and pathological overlaps between PD and PSP, we hypothesized that variants in the *low-density lipoprotein receptor related protein 10 (LRP10)* gene, recently associated with PD and dementia with Lewy bodies (Quadri et al., 2018; Vergouw et al., 2019), might also be implicated in PSP. LRP10 is a surface protein, whose function is largely elusive. However, some studies have suggested a

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role of LRP10 in ligand trafficking between the trans-Golgi network, endosomes, and the plasma membrane. Furthermore, LRP10 has been linked to the metabolism of amyloid-β and α-synuclein (Brodeur et al., 2012; von Einem et al., 2015, 2017).

The aim of this study is to explore whether possibly pathogenic variants in *LRP10* are observed in a large Dutch cohort of patients with PSP (discovery cohort) using Sanger sequencing. In addition, we try to validate our findings in a large cohort of patients with PSP (validation cohort) from the United States and Europe using whole-exome sequencing (WES).

2. Methods

2.1. Subjects

Patients with PSP from 2 large cohorts were enrolled in this study. PSP was diagnosed according to the criteria of the National Institute for Neurological Disorders and Stroke/ Society for PSP (NINDS-SPSP) (Litvan et al., 1996a). The discovery cohort consisted of 246 patients with PSP enrolled from a large Dutch cohort (Donker Kaat et al., 2007), consecutively collected between 2003 and 2012 (Table 1). Patients were ascertained at the outpatient clinic of the Erasmus Medical Center Rotterdam, at home or at nursing homes. At inclusion, information about patient's medical and family history and current medical status was collected. Furthermore, neurological examinationwas performed, and a blood sample was collected. The validation cohort consisted of 704 neuropathologically confirmed patients with PSP enrolled form a large cohort of patients from the United States and Europe (Höglinger et al., 2011) (Table 1). These patients were identified from brain banks, research hospitals, and neuropathologists. The study was approved by the relevant Institutional Ethical Authorities, and all participants or legal representatives signed informed consent.

2.2. Genetic analyses

2.2.1 . Genetic analyses in the 2 cohorts—Genomic DNA was isolated from blood in the discovery cohort and from brain tissue in the validation cohort using standard methods. Sanger sequencing was performed for the entire open reading frame and exon-intron boundaries of *LRP10* in the discovery cohort (protocol reported by Vergouw et al., 2019). WES was performed in the validation cohort (Supplementary Information). Possibly pathogenic *LRP10* variants identified by WES in the validation cohort were validated by Sanger sequencing (Supplementary Information). We considered variants as possibly pathogenic according to the following criteria: (1) heterozygous state; (2) rarity, defined as a frequency <0.1% in the Genome Aggregation Database (GnomAD v2.1); (3) exonic location and non-synonymous, or predicted to affect splicing; and (4) predicted as pathogenic by at least 5 of 11 in silico programs (Supplementary Information).

2.2.2. Additional genetic analyses in possibly pathogenic LRP10 variant carriers in the discovery cohort

WES, multiple ligation-dependent probe amplification (P051-Parkinson mix 1), and *C9orf72* repeat expansion analysis were performed in patients who carried possibly pathogenic *LRP10* variants to exclude possibly pathogenic variants in other known genes causing

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parkinsonism or dementia (Supplementary Table 1). The presence of possibly pathogenic variants in known genes causing parkinsonism or dementia in possibly pathogenic *LRP10* variant carriers decreases the chance of the *LRP10* variant to be truly pathogenic. WES and multiple ligation-dependent probe amplification were performed as reported previously by Vergouw et al. (2019). Details of the methods of the *C9orf72* repeat expansion analysis can be found in the Supplementary Information.

3. Results

3.1. Demographic and clinical characteristics of the 2 cohorts

The discovery cohort consisted of 85 (35%) patients with possible PSP, 128 (52%) with probable PSP (52%), and 33 (13%) with definite PSP. The mean disease onset age in this cohort was 65.8 ± 7.5 years and 52% of patients were male; 29% of patients had at least one first-degree relative and 9% had at least one second-degree relative with a neurodegenerative disease. The validation cohort consisted of 704 patients with definite PSP. The mean disease-onset age in this cohort was 68.1 ± 8.4 years (data only available in n = 476), and 54% of patients were male (Table 1).

3.2. Genetic findings

Two possibly pathogenic *LRP10* variants were detected in the discovery cohort, each in single patients (p.Gly326Asp and p.Asp389Asn). In the validation cohort, 7 possibly pathogenic LRP10 variants were detected in 8 patients (p.Arg158His, p.Cys220Tyr, p.Thr278Ala, p.Gly306Asp, p.Glu486Asp, p.Arg554*, and p.Arg661Cys; see Table 2 and Supplementary Table S2 for specifications). Supplementary Figure S1A shows the *LRP10* gene structure with the location of the identified variants, and Supplementary Figure S1B shows the LRP10 protein structure with the location of the amino acid changes. Other variants in *LRP10* which did not fulfill the criteria for possible pathogenicity, as described in Section 2.2.1., are depicted in Supplementary Table S3. Additional WES analysis (average depth of >170× with 99% of the target region covered >20×) in the possibly pathogenic *LRP10* variant carriers from the discovery cohort revealed a heterozygous *VPS13C* variant (p.Gln2546*, absent in GnomAD v2.1) in 1 patient (Supplementary Table S4). No other mutations in genes causing parkinsonism or dementia were found.

3.3. Clinical information of possibly pathogenic LRP10 variant carriers

An overview of the clinical information of the possibly pathogenic *LRP10* variant carriers is shown in Table 2. Patient 1 from the discovery cohort (*LRP10* p.Asp389Asn variant) experienced falls from the age of 61 years, followed by swallowing problems. At the age of 63 years, a mild downward vertical supranuclear gaze palsy, dysarthric speech, reduced arm swing, palatal tremor, and impaired balance, but no clear ataxia, were observed. He had a favorable response to levodopa. At neuropsychological examination, deficits were observed in attention, concentration, and executive functioning. Furthermore, mild memory and naming problems were seen. Brain MRI showed mild parieto-occipital and cerebellar atrophy and hypertrophy of the olivary nuclei. The patient died at the age of 66 years. Family history was negative for parkinsonism, dementia, or motor neuron disease. Brain autopsy was not performed. This patient was diagnosed with probable PSP during life

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according to the NINDS-SPSP criteria (Litvan et al., 1996a) and can retrospectively be classified as probable PSP with Richardson's syndrome according to the MDS criteria (Höglinger et al., 2017). Patient 2 from the discovery cohort (*LRP10* p.Gly326Asp variant) experienced tremor of the right leg from the age of 55 years, followed by falls, rigidity, swallowing, speech, and memory problems from the age of 60 years. At the age of 64 years, vertical supranuclear gaze palsy, bradykinesia, intermittent rest tremor of arms and legs, and balance problems were observed. She had a favorable response to levodopa. Neuropsychological examination showed severe deficits, especially with frontal subcortical and language problems. Brain MRI was unremarkable. The patient died at the age of 65 years. Family history was negative for parkinsonism, dementia, or motor neuron disease. Brain autopsy was not performed. This patient was diagnosed with possible PSP during life according to the NINDS-SPSP criteria (Litvan et al., 1996a) and can retrospectively be classified as probable PSP with predominant parkinsonism according to the MDS criteria (Höglinger et al., 2017).

4. Discussion

In this study, we explored the presence of *LRP10* variants in 2 cohorts with a total of 950 PSP patients (discovery cohort n = 246, validation cohort n = 704). The PSP diagnosis was pathologically confirmed in 78% of these patients. Two possibly pathogenic LRP10 variants (p.Gly326Asp and p.Asp389Asn) were identified in 2 patients from the discovery cohort, and 7 possibly pathogenic *LRP10* variants (p.Arg158His, p.Cys220Tyr, p.Thr278Ala, p.Gly306Asp, p.Glu486Asp, p.Arg554*, and p.Arg661Cys) were identified in 8 patients from the validation cohort. These variants are very rare, are predicted to be pathogenic by ≥5 in silico programs, and are mostly located in *LRP10* exon 5, where other probably pathogenic variants were previously found (Quadri et al., 2018). Interestingly, the frequency of possibly pathogenic *LRP10* variants is significantly higher in the validation cohort (8/1408 alleles = 0.6%) compared with a previous published control cohort of patients with abdominal aneurysms (Quadri et al., 2018) (1/1248 alleles = 0.08%; Fisher's exact test p-value 0.04). In addition, the p.Gly306Asp variant has been identified previously in 2 of 2835 patients with PD and 1 of 5343 controls (Kia et al., 2018), the p.Gly326Asp variant in 1 of 264 patients with multiple system atrophy and in no controls (Pihlström et al., 2018), and the p.Glu486Asp variant in 3 of 2835 patients with PD and 1 of 111 patients with dementia with Lewy bodies compared with none in 5343 and 233 controls, respectively (Kia et al., 2018). The p.Arg158His, p.Arg554*, and p.Arg661Cys variants have previously been identified in single controls (Kia et al., 2018; Guerreiro et al., 2018; Pihlström et al., 2018; Supplementary Table S5).

Both patients from the discovery cohort displayed uncommon PSP clinical features. Patient 1 had a palatal tremor, inferior olivary hypertrophy, and cerebellar atrophy. Inferior olivary hypertrophy is observed in 1.5% of pathologically confirmed patients with PSP (Katsuse and Dickson, 2004), but associated palatal tremor is very rare in PSP (Katsuse and Dickson, 2004; Suyama et al., 1997). The syndrome of progressive ataxia and palatal tremor (Mongin et al., 2016) may retrospectively also be considered in patient 1, yet the clinical phenotype is most consistent with PSP. An uncommon feature in patient 2 was the presence of an isolated tremor of the right leg in the first 5 years of the disease. Unfortunately, autopsy studies were

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not performed in these patients, and therefore, the diagnosis could not be verified at the pathological level. The absence of a family history of PSP or other neurodegenerative disorders in these 2 patients would be compatible with an incomplete penetrance or a de novo occurrence of the *LRP10* variants.

Of note, a *VPS13C* variant (p.Gln2546*) was observed in one *LRP10* variant carrier. Mutations in *VPS13C* are associated with autosomal recessive forms of early-onset parkinsonism (Lesage et al., 2016). In our patient, the variant was found in the heterozygous state and is therefore most likely an incidental finding.

Strengths of this study are the large sample size of the 2 PSP cohorts, the validation of our findings in an independent cohort, and the high percentage of neuropathologically confirmed patients with PSP. Limitations are the lack of screening for *LRP10* genomic deletions of multiplications (not detectable by Sanger methods).

In conclusion, this is the first study of *LRP10* in 2 large PSP cohorts. We showed that rare, possibly pathogenic *LRP10* variants occur in a small but substantial fraction of patients with PSP. Furthermore, possibly pathogenic *LRP10* variants may be overrepresented in patients with PSP compared with controls and may therefore play a role in disease pathogenesis. Further studies are warranted to replicate our findings and to study which molecular mechanisms underlie the possible association between *LRP10* and PSP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic and clinical characteristics

	n = 246	**n = 704**
Sex, male	127 (52%)	377 (54%)
Diagnosis (NINDS-SPSP)		
Possible PSP	85 (35%)	0 (0%)
Probable PSP	128 (52%)	0 (0%)
Definite PSP	33 (13%)	704 (100%)
Age at disease onset, y (n = 246;476)	65.8 (7.5)	68.1 (8.4)
Family history of neurodegenerative diseases (n = 244;0)		
1st degree	71 (29%)	NA
2nd degree	21 (9%)	NA
No	152 (62%)	NA
Deceased (n = 244;704)	242 (98%)	704 (100%)
Age at death, y (n = 241;698)	73.7 (7.3)	75.3 (8.2)

Values are presented as n (%) or mean (SD).

Key: NINDS-SPSP, National Institute for Neurological Disorders and Stroke/Society for PSP; PSP, progressive supranuclear palsy; NA, not available.

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Table 2

Possibly pathogenic *LRP10* variants

	Genetic information									Clinical information			
	Genomic position	**Nucleotide change**	**Amino acid change**	**Exon**	**Coding effect**	**dbSNP 142 accession number**	**Allele frequency GnomAD (alleles)**	**Functional predictions: Pathogenic (total)**	**Splicing predictions: Deleterious (total)**	**Patient**	**NINDS-SPSP criteria**	**Age at onset (y)**	**Age at death (y)**
Discovery cohort													
	14:23345322	c.1165 G>A	p.Asp389Asn	5	Missense	rs754181235	0.01% (37)	6/11	n.a.	1	Probable PSP	61	66
	14:23345134	c.977 G>A	p.Gly326Asp	5	Missense	rs547591765	0.006% (14)	6/11	n.a.	2	Possible PSP	55	65
Validation cohort													
	14:23344630	c.473 G>A	p.Arg158His	5	Missense	rs764424911	0.005% (13)	6/11	n.a.	1	Definite PSP	68	75
	14:23344816	c.659 G>A	p.Cys220Tyr	5	Missense	rs867533372	.	10/11	n.a.	2	Definite PSP	70	74
	14:23344989	c.832 A>G	p.Thr278Ala	5	Missense	.	.	5/11	n.a.	3	Definite PSP	74	87
	14:23345074	c.917 G>A	p.Gly306Asp	5	Missense	rs375748692	0.007% (21)	9/11	n.a.	4	Definite PSP	NA	66
										5	Definite PSP	74	80
	14:23345931[a]	c.1458 G>C	p.Glu486Asp	6	Missense	rs142130715	0.01% (32)	11/11	0/4	6	Definite PSP	78	83
	14:23346254	c.1660 C>T	p.Arg554*	7	Stop gain	rs201213246	0.01% (28)	n.a.	n.a.	7	Definite PSP	74	84
	14:23346575	c.1981C>T	p.Arg661Cys	7	Missense	rs771796662	0.004% (10)	8/11	n.a.	8	Definite PSP	NA	84

The Genome Reference Consortium Human Build 37 (hg19) and NM_014045–4 LRP10 transcript were used.

Splicing prediction programs: SSF, MaxEnt, NNSPLICE, GeneSplicer.

Key: GnomAD, Genome Aggregation Database; NINDS-SPSP, National Institute for Neurological Disorders and Stroke/Society for progressive supranuclear palsy; n.a., not applicable; NA, not available.

[a]This variant was not validated by Sanger sequencing because no additional DNA was available.