

Clinical and Pathological Phenotypes of *LRP10* Variant Carriers with Dementia

Leonie J. M. Vergouw^{a,1}, Hanneke Geut^{b,c,1}, Guido Breedveld^d, Demy J. S. Kuipers^d, Marialuisa Quadri^d, Netherlands Brain Bank^c, Annemieke J. M. Rozemuller^c, John C. van Swieten^a, Frank Jan de Jong^a, Wilma D. J. van de Berg^{b,2} and Vincenzo Bonifati^{d,2,*}


^aErasmus MC, University Medical Center Rotterdam, Department of Neurology and Alzheimer Center, Rotterdam, the Netherlands

^bNetherlands Institute for Neuroscience, Amsterdam, the Netherlands

^dErasmus MC, University Medical Center Rotterdam, Department of Clinical Genetics, Rotterdam, the Netherlands

^eAmsterdam UMC, Vrije Universiteit Amsterdam, Department of Pathology, Amsterdam Neuroscience, Amsterdam, the Netherlands

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Abstract.

Background: Rare variants in the *low-density lipoprotein receptor related protein 10* gene (*LRP10*) have recently been implicated in the etiology of Parkinson's disease (PD) and dementia with Lewy bodies (DLB).

Objective: We searched for *LRP10* variants in a new series of brain donors with dementia and Lewy pathology (LP) at autopsy, or dementia and parkinsonism without LP but with various other neurodegenerative pathologies.

Methods: Sanger sequencing of *LRP10* was performed in 233 donors collected by the Netherlands Brain Bank.

Results: Rare, possibly pathogenic heterozygous *LRP10* variants were present in three patients: p.Gly453Ser in a patient with mixed Alzheimer's disease (AD)/Lewy body disease (LBD), p.Arg151Cys in a DLB patient, and p.Gly326Asp in an AD patient without LP. All three patients had a positive family history for dementia or PD.

Conclusion: Rare *LRP10* variants are present in some patients with dementia and different brain pathologies including DLB, mixed AD/LBD, and AD. These findings suggest a role for *LRP10* across a broad neurodegenerative spectrum.

Keywords: Genetic predisposition to disease, genotype, *LRP10*, neuropathology, phenotype

INTRODUCTION

Genetic factors play an important role in the etiology of both Parkinson's disease (PD) as well as dementia with Lewy bodies (DLB) [1–3]. Among

PD patients, 5–10% are estimated to carry disease-causing rare mutations [3], including variants in the *SNCA* gene, which are causal for PD as well as DLB. Moreover, common variants in *SNCA* and *GBA* are risk factors for both PD and DLB, which further highlights the genetic overlap between these disorders. Although mutations in more than 20 genes are known to cause monogenic forms of PD, additional rare disease-associated genetic variants in familial PD and DLB likely remain to be identified [1, 4].

¹These authors contributed equally to this work.

²Joint senior authorship.

*Correspondence to: Prof. Dr. Vincenzo Bonifati, Department of Clinical Genetics, Erasmus MC, University Medical Center Rotterdam, P.O. Box 2040, 3000 CA Rotterdam, the Netherlands. Tel.: +31107043355; E-mail: v.bonifati@erasmusmc.nl.

We recently reported rare variants in the *low-density lipoprotein receptor related protein 10* gene (*LRP10*) in familial forms of PD and DLB, including one large Italian family with genome-wide significant linkage evidence for late-onset, autosomal-dominant inherited PD and DLB. All ten affected relatives and three unaffected relatives (age 45–58 years) carried the same rare *LRP10* variant, suggesting an age-related or incomplete penetrance. Several smaller families showed additional, albeit more limited, evidence of segregation of *LRP10* variants with disease [5]. In three probands with *LRP10* variants, autopsy studies showed diffuse-neocortical Lewy pathology (LP) and concomitant AD-type pathology.

Since our initial report, additional rare *LRP10* variants have been reported in patients with PD, DLB, or other neurodegenerative diseases by some but not all studies [6–13]. Three case-control studies searched whole-exome sequencing data from sporadic PD, DLB, and multiple system atrophy (MSA) cases, and detected no evidence of association between rare *LRP10* variants and disease [6–8]. However, these studies included mostly sporadic cases and controls with a younger average age, and they might have been underpowered to detect association due to the rarity of pathogenic *LRP10* variants, their likely incomplete penetrance, and the etiological heterogeneity of these diseases. A French exome mining study found a p.Tyr307Asn variant that co-segregated with PD in two out of four members of the same family [9]. Although the pathogenicity of this variant may therefore be questioned, phenocopies are known to occur in around 5% of familial PD patients from families with monogenic forms of PD. Lastly, two Chinese and one Dutch cohort studies of sporadic and familial PD and DLB patients provided independent, albeit limited, additional evidence for an association of *LRP10* variants with disease [11–13]. In addition, we recently found evidence for enrichment of rare, possibly pathogenic *LRP10* variants in a large cohort of patients with progressive supranuclear palsy (PSP), mostly with a pathologically confirmed diagnosis [14]. In conclusion, despite some negative reports, additional evidence has been collected on a role for rare *LRP10* variants in independent PD cohorts, and potentially other neurodegenerative diseases such as PSP. However, confirmation in independent large families as well as more extensive functional evidence is needed. Moreover, the findings of possibly pathogenic *LRP10* variants in other neurodegenerative diseases need confirmation in pathologically-confirmed series.

Only few studies in the literature deal with the normal function of *LRP10* in the human brain. *LRP10* encodes transmembrane protein LRP10, which shuttles between the plasma membrane and the Golgi system and co-localizes with VPS35, a retromer component and the product of another known PD-causing gene [15–17]. LRP10 also interacts with GGA proteins, which are reported to affect α -synuclein trafficking and aggregation [18, 19]. Furthermore, LRP10 has been implicated in the metabolism of APOE lipoproteins and direct as well as GGA-mediated regulation of APP trafficking and processing, and may therefore also influence amyloid- β homeostasis [16, 20, 21]. Taken together, this suggests a broad role for *LRP10* in neurodegeneration.

The aim of this study was to search for *LRP10* variants in a series of 233 brain donors from the Netherlands Brain Bank (NBB), who were clinically diagnosed with dementia, and had LP at autopsy or, if LP-negative, had developed parkinsonism in addition to dementia during their lifetime.

MATERIALS AND METHODS

Donor selection

The entire series of brains available from the NBB ($n=3,853$) from 1989 to 2017 was considered for inclusion in the study according to the selection criteria. For all donors, a written informed consent for brain autopsy and the use of the material and clinical information for research purposes had been obtained from the donor or the next of kin.

For Group 1, inclusion criteria were: 1) Braak Lewy body stage ≥ 4 according to the BrainNet Europe (BNE) criteria [22]; 2) presence of dementia; 3) at least low levels of AD type pathology according to National Institute on Aging–Alzheimer’s Association (NIA-AA) guidelines [23]. Out of all brain donors from the NBB, 432 donors showed Braak Lewy body stage ≥ 4 , out of whom 324 showed dementia. Of these donors, 252 showed at least low levels AD type pathology. Some of these donors had already been screened for *LRP10* variants in a previous study [5], or did not have frozen tissue available for DNA extraction, and were excluded. Therefore, 126 donors could be included in the current study.

For Group 2, inclusion criteria were: 1) presence of dementia and parkinsonism; 2) presence of any type of neurodegenerative disease upon autopsy; 3) Braak Lewy body stage 0 or 1 according to the BNE

criteria [22]. Parkinsonism was defined as bradykinesia in combination with rigidity and/or tremor. Donors with possible drug-induced parkinsonism were excluded. Out of all brain donors from the NBB, 591 donors showed parkinsonism, of whom 543 had sufficient information on cognitive status. Dementia was present in 394 of these donors, of whom 182 did not show LP, and 148 did not take drugs that could be a sufficient explanation for the presence of parkinsonism. Seven cases had a known causal genetic mutation. Out of the other 141 cases, tissue was available for DNA extraction in 107 cases that had not been screened before for the presence of *LRP10* variants.

Donors with known disease-causing mutations in genes other than *LRP10* were excluded. Fresh-frozen brain tissue from cerebellum, cortical, or subcortical grey matter was available from 126 donors from Group 1 and 107 donors from Group 2.

Clinical information

Clinical information was abstracted from the database from the NBB and included information on sex, age at onset, age at death, disease duration from time at onset of first symptoms, presence and timing of parkinsonism and dementia, a history of parkinsonism or dementia in first-degree or second-degree relatives, the clinical diagnosis by the treating physician, and cause of death.

Neuropathological assessment

For all donors in the study selection, standardized neuropathological examinations had been performed by an experienced neuropathologist (AJMR) (open access: www.brainbank.nl). Neuropathological assessment was done according to NIA-AA and BNE guidelines [22, 23], and standardized evaluation strategies for cerebral amyloid angiopathy (CAA) [24], granulovacuolar degeneration [25], limbic-predominant age-related TDP-43 encephalopathy (LATE) [26], and aging-related tau astroglialopathy (ARTAG) [27].

For the possibly pathogenic *LRP10* variant carriers, 17 different brain regions were formalin-fixed and paraffin-embedded, cut into 8 μm sections, and stained with hematoxylin and eosin. For selected cortical regions, histological stainings were performed using Congo red and Gallyas silver stains. Immunohistochemical analysis was performed on selected brainstem, limbic, and neocortical regions using pri-

mary antibodies against α -synuclein (clone KM51; 1:500; Monosan, The Netherlands), hyperphosphorylated tau (clone AT8; 1:1000; Innogenetics, Belgium), amyloid- β (clone 6F/3D; 1:100; Dako, USA) and phospho-TDP43 (rabbit polyclonal; 1:1000 Cosmo Bio, USA). Stages of amyloid- β plaques, neurofibrillary pathology, and neuritic plaques were scored according to the NIA-AA guidelines [23], and stages of LP were scored according to BNE criteria [22]. Standardized staging systems for CAA [24], granulovacuolar degeneration [25], and LATE [26] were applied. Presence of ARTAG was evaluated based on tau immunostaining (clone AT8) of sections of the hippocampus at the level of the lateral geniculate nucleus, amygdala, and temporal pole [27].

Sanger sequencing

Genomic DNA was isolated from brain tissue using standard methods. We performed Sanger sequencing using the reported protocol of Quadri et al. (2018) [5] with minor modifications, for the entire open reading frame and the exon-intron boundaries of *LRP10*. A total volume of 20 μl , containing 2.0 μl of 10X Fast Start Taq DNA Polymerase buffer, 1.6 μl of 2.5 mM dNTPs, 1.0 μl of 10 μM forward primer, 1.0 μl of 10 μM reverse primer, 0.10 or 0.15 μl of FastStart Taq. DNA Polymerase (Roche, Basel, Switzerland), and 25 ng of genomic DNA, was used to amplify the fragments. We added 4 μl of 1X GC-RICH solution (Roche) for exon 1, 5, and 7. An overview of used primers can be found in Supplementary Table 1. We performed the initial denaturation for 5 min at 94°C followed by 30 cycles of 30 s at 94°C, 30 s at 60°C, 90 s at 72°C, with a final extension step for 5 min at 72°C. We used 5 units of ExoI and 0.5 unit of Fast AP (Thermo Fisher Scientific, Waltham, MA, USA) for 45 min at 37°C and 15 min at 80°C to remove unconsumed dNTPs and primers from the PCR product (3 μl). The Big Dye Terminator (version 3.1; Thermo Fisher Scientific) was used according to the manufacturer's protocol to sequence both DNA strands directly and sephadexG50 (GE Healthcare, Little Chalfont, UK) was used to remove dye terminators. We used an ABI 3730XL Genetic Analyzer (Thermo Fisher Scientific) and Seqscape v3.0 (Thermo Fisher Scientific) for the analysis. The *LRP10* NM_0140445.4 transcript was used for sequence variants annotation and the Human Genome Variome Society recommendations [28] was used for variants nomenclature.

We considered variants as possibly pathogenic according to the previously used criteria: 1) heterozygous state; 2) minor allele 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 five of 11 *in-silico* programs [5, 13].

Whole exome sequencing, copy number analysis, and APOE genotyping

To exclude (possibly) pathogenic variants in other known genes causing parkinsonism or dementia (Supplementary Table 2) we performed whole exome sequencing (WES) and multiple ligation-dependent probe amplification (MLPA, P051-Parkinson mix 1) in the possibly pathogenic *LRP10* variant carriers. WES was performed with the same protocol as previously reported in Jamra et al. (2017) [29]. An average depth of >84× was reached, with 99% of the target region covered >20×.

For copy number analysis, The P051-D1 Parkinson kit (MRC Holland) was used according to the manufacturer's protocol. An ABI 3730XL Genetic Analyzer (Thermo Fisher Scientific) and Seqscape v3.0 (Thermo Fisher Scientific) were used for analysis. *APOE* genotyping was performed using TaqMan® SNP Genotyping Assay (Thermo Fisher Scientific).

RESULTS

Clinicopathological characteristics of the study groups

Demographic, clinical, and neuropathological information from the 233 selected donors are summarized in Supplementary Tables 3 and 4. In Group 1, pathological diagnoses included PD with dementia, DLB, AD with LP, mixed AD and Lewy body disease (AD/LBD), frontotemporal dementia (FTD) with LP, and PSP with LP. Distribution of LP was amygdala-predominant (24%), limbic-transitional (38%), or diffuse-neocortical (38%). In Group 2, pathological diagnoses included AD, FTD, vascular dementia, PSP, auto-immune encephalitis, corticobasal degeneration, CRASH syndrome, multiple sclerosis, MSA, neurodegeneration with brain iron accumulation, neuronal intranuclear inclusion disease, and spinocerebellar ataxia. Among donors with a specified clinical diagnosis, 77.5% was con-

firmed upon autopsy in Group 1 and 61.3% in Group 2.

Genetic findings

Two donors (Patients 1 and 2) from Group 1 carried each a different, possibly pathogenic *LRP10* variant: c.1357G>A (p.Gly453Ser) and c.451C>T (p.Arg151Cys) (mean allele frequency (MAF) GnomAD 0.004% and 0.006%, respectively, predicted as pathogenic in 5/11 and 9/11 *in-silico* programs respectively, Table 1 and Supplementary Table 5). One donor (Patient 3) from Group 2 carried a possibly pathogenic *LRP10* variant: c.977G>A (p.Gly326Asp) (MAF GnomAD 0.006%, predicted as pathogenic in 6/11 *in-silico* programs, Table 1 and Supplementary Table 5). Additional *LRP10* variants, which did not fulfill our criteria for possible pathogenicity, are listed in Supplementary Tables 5 and 6. Additional WES and MLPA in possibly pathogenic *LRP10* variant carriers showed only one possibly pathogenic variant, namely the *ABCA7* p.Gly1741Arg variant in Patient 1 (Supplementary Table 7). *APOE* genotypes of Patients 1, 2, and 3 were $\epsilon 3/\epsilon 4$, $\epsilon 3/\epsilon 3$, and $\epsilon 2/\epsilon 4$ respectively.

Clinical phenotype of the LRP10 variant carriers

Patient 1, carrier of the p.Gly453Ser variant, was clinically diagnosed with DLB. Throughout her life, the patient suffered from recurrent depressions, anxiety, and panic attacks. At the age of 64, she developed severe constipation and a tremor of both hands, left more than right, progressing into a hypokinetic-rigid syndrome a year later. Her cognition rapidly deteriorated and neuropsychological examination showed deficits in short term memory, difficulties with calculations, visuoconstruction, and orientation. Brain MRI showed mild general atrophy. Visual hallucinations, personality changes, and apraxia developed during the course of the disease. The patient died at the age of 72 due to pneumonia in an end-stage of dementia. The father of the patient had been diagnosed with PD.

Patient 2, carrier of the p.Arg151Cys variant, was clinically diagnosed with AD. She died at the age of 90 due to cachexia and decubitus wounds, after a disease duration of 10 years. The dementia was characterized by memory loss, anxiety, visual hallucinations, and delusions. Any other neurological symptoms, in particular parkinsonism, were not mentioned in the clinical records. Her mother was also

Table 1
Possible pathogenic LRP10 variants

Genomic position	Nucleotide change	Amino acid change	Exon	Coding effect	dbSNP 142 accession number	MAF GnomAD (alleles)	Functional predictions: pathogenic (total)	Study	Patient number	Clinical diagnosis	Age at onset (y)	Age at death (y)	Pathological diagnosis
14:23345514	c.1357G>A	p.Gly453Ser	5	missense	rs146378015	0.004% (10)	5/11	Current Kia et al., 2019 [6]	1 n.a.	DLB	64 n.a.	72 n.a.	Mixed AD/LBD n.a.
14:23344608	c.451C>T	p.Arg151Cys	5	missense	rs774043484	0.006% (16)	9/11	Current Vergouw et al., 2019 [13]	2 Patient II-2 (family 4)	AD PD with dementia	80 66	90 74	DLB n.a.
14:23345134	c.977G>A	p.Gly326Asp	5	missense	rs547591765	0.006% (14)	6/11	Current Vergouw et al., 2020 [14]	3 n.a.	AD PSP	77 55	88 65	AD n.a.
								Philström et al., 2018 [8]	n.a.	MSA	n.a.	n.a.	MSA

The Genome Reference Consortium Human Build.37 (hg19) and transcript NM.014045-4 were used. MAF, minor allele frequency; GnomAD, Genome Aggregation Database; n.a., not available; AD, Alzheimer's disease; PSP, progressive supranuclear palsy; MSA, multiple system atrophy; DLB, dementia with Lewy bodies; PD, Parkinson's disease; LBD, Lewy body disease.

Table 2
Clinical and pathological characteristics of possibly pathogenic *LRP10* variant carriers

	Patient 1	Patient 2	Patient 3
<i>LRP10</i> variant	p.Gly453Ser	p.Arg151Cys	p.Gly326Asp
Sex	F	F	M
Age at death y	72	90	88
Clinical diagnosis	DLB	AD	AD
Age at onset y	64	80	77
Disease duration y	8	10	11
Dementia duration y	6	6	7
Parkinsonism	yes	not mentioned in clinical records	yes
Family history	father with PD	mother with dementia	brother and two aunts with dementia
Cause of death	pneumonia at end-stage dementia	cachexia and pressure ulcers at end-stage dementia	pneumonia at end-stage dementia
Neuropathological diagnosis	mixed AD/LBD	DLB	AD
PMD <i>h</i>	5.5	5.5	5.0
<i>APOE</i> genotype	3/4	3/3	2/4
Brain weight g	1043	1053	1133
Atrophy	moderate frontotemporal and hippocampal atrophy, severe dilation of temporal horn of lateral ventricle	none	mild frontotemporal atrophy, severe diffuse dilation of ventricles
Pigmentation substantia nigra	pale	pale	normal
Pigmentation locus coeruleus	pale	pale	normal
Thal amyloid- β phase [23]	5	3	5
Braak neurofibrillary stage [23]	6	4	4
CERAD score [23]	C	B	B
AD-level [23]	high	intermediate	intermediate
Braak Lewy body stage [22]	6	6	0
McKeith Lewy body stage [22]	neocortical	neocortical	none
Microvascular lesions	yes	no	yes
Hippocampal sclerosis	no	no	no
Argyrophilic grain disease	no	no	no
ARTAG [27]	yes	yes	yes
CAA type	2	1	1
Thal CAA stage [24]	1	1	1
Granulovacuolar degeneration [25]	yes, stage ≥ 4	yes, stage ≥ 4	yes, stage ≥ 4
Spongiform changes	severe	no	mild
LATE [26]	yes, stage 1	no	no

DLB, dementia with Lewy bodies; AD, Alzheimer's disease; PD, Parkinson's disease; LBD, Lewy body disease; PMD, postmortem delay; ARTAG, aging-related tau astrogliopathy; CAA, cerebral amyloid angiopathy; LATE, limbic-predominant age-related TDP43 encephalopathy.

demented, but the clinical diagnosis of the mother is not known.

Patient 3, carrier of the p.Gly326Asp variant, was clinically diagnosed with AD. The patient had a disease duration of 11 years, starting with mild memory disturbances. Seven years before death, neuropsychological examination only showed mild short-term memory problems, and walking became insecure. In the following years, the patient developed parkinsonism, aphasia, frontal disinhibited behavior, and anxiety. He died at the age of 88 due to pneumonia. The brother and two aunts of the patient also suffered from dementia (Table 2).

Pathological characteristics of the LRP10 variant carriers

Macroscopic examination of the brains of the three possibly pathogenic *LRP10* variant carriers showed mild to moderate frontotemporal atrophy in Patients 1 and 3 (Table 2). Microscopy showed LP in brainstem, limbic, and neocortical brain areas in Patients 1 and 2 (Fig. 1. I–IIA, B), but no LP in Patient 3 (Fig. 1. IIIA, B). Nigral degeneration was present in Patients 1 and 2. An intermediate or high level of AD-type pathology was present in Patients 2 and 3, and Patient 1, respectively (Fig. 1. I–IIIC–E). All three patients

showed ARTAG, as well as CAA, including capillary CAA in Patients 2 and 3, and granulovacuolar degeneration in hippocampus and amygdala (Fig. 1. I–IIIF, II–IIIG). Patient 1 showed LATE stage 1 (Fig. 1G). The neuropathological diagnoses in the three patients can be summarized as mixed AD/LBD, DLB, and AD, respectively.

DISCUSSION

We found two possibly pathogenic *LRP10* variants among 126 donors with dementia and LP, and one among 107 donors with dementia and parkinsonism without LP. The first variant, p.Gly453Ser,

was carried by a patient with clinically diagnosed DLB and mixed AD/LBD upon autopsy. The second variant, p.Arg151Cys, was carried by a patient clinically diagnosed with AD, and a neuropathological diagnosis of DLB. The third variant, p.Gly326Asp, was carried by a patient with clinically diagnosed AD plus parkinsonism, and pure AD pathology upon autopsy. In the patient with the *LRP10* p.Gly453Ser variant, an additional rare variant (p.Gly1741Arg) in *ABCA7* was found. Rare disease-associated variants in *ABCA7* are considered risk factors for AD and PD [30, 31], and therefore, the *ABCA7* p.Gly1741Arg variant may have contributed to the mixed AD/LBD pathology in this patient, together with the *LRP10* p.Gly453Ser variant.

While the three *LRP10* variants are extremely rare in control databases, they have all been reported in independent studies in other patients with neurodegenerative diseases. The p.Gly453Ser variant has previously been found in a patient with clinically diagnosed PD [6]. The p.Arg151Cys variant has previously been identified in a patient with PD with dementia, who had a father with AD and gait problems [13]. This variant was also observed by us in one out of 645 controls who were not neurologically examined [5]. Last, the p.Gly326Asp variant has been previously reported in a pathologically con-

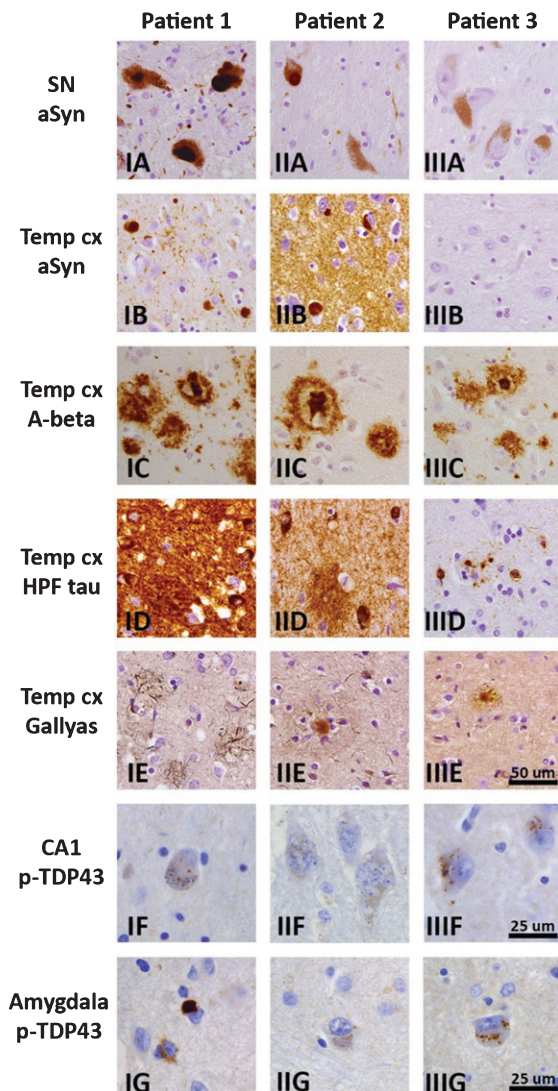


Fig. 1. (Continued).

Fig. 1. Brain pathology in three patients with possibly pathogenic *LRP10* variants, with representative photomicrographs of selected brain regions for Patient 1 (IA–G), Patient 2 (IIA–G), and Patient 3 (IIIA–G). Immunohistochemistry for α -synuclein (clone KM51) showed Lewy bodies and Lewy neurites in brainstem, limbic and neocortical brain areas in Patients 1 and 2 (I–IIA, B), but no α -synuclein immunoreactivity in Patient 3 (IIIA, B). Diffuse and cored amyloid- β plaques (clone 6F/3D) were present in neocortical regions, amygdala, and striatum in all three patients, and extended into the CA4 region, midbrain, and cerebellum in Patients 1 and 3. Amyloid- β positive plaques in the temporal pole are shown in panel I–IIIC. Immunostaining for hyperphosphorylated tau (clone AT8) showed neurofibrillary tangles, threads, and plaques in the hippocampus and temporal pole in all three patients, and extended into the peristriate and striate areas of the occipital cortex in Patient 1. A moderate or high load of neurofibrillary pathology was present in the temporal pole in Patient 3 (IIID), and Patients 1 and 2 (I–IID), respectively. Gallyas silver stain showed a moderate or high load of neuritic plaques in neocortical regions in Patients 2 and 3 (IIE, IIIE), and Patient 1 (IE), respectively. Immunostaining for phospho-TDP43 (polyclonal rabbit antibody) showed granulovacuolar degeneration in the hippocampus and amygdala of all three patients (I–IIIF, II–IIIG). Additionally, Patient 1 showed TDP-43-positive neuronal inclusions and threads in the amygdala fitting limbic-predominant age-related TDP-43 encephalopathy (LATE; IG). Scalebar in IIIE represents 50 μ m and applies to panels A–E. Scalebars in IIIF and IIIG represent 25 μ m and apply to panels I–IIIF–G. SN, substantia nigra, Temp cx, temporal pole.

firmed MSA patient [8], and found by us in a patient with clinically diagnosed PSP [14]. The lack of pathological examination in some of the previously reported patients complicates the overall interpretation of these findings.

We acknowledge that in some of these patients, the *LRP10* variant could have been a chance occurrence, with no roles in the disease development. Of note, the identified *LRP10* variants are all classified as ‘variants of uncertain significance’ by the American College of Medical Genetics guidelines [32]. However, these guidelines are intended to guide genetic testing in clinical practice, and therefore use strict criteria for pathogenicity. Because of the exploratory nature of the current study and the limited knowledge in the literature on *LRP10* mutations, we have used less strict criteria to define pathogenicity. Although more research is needed on the pathogenicity of the described *LRP10* variants, our results suggest a pathogenic role for these *LRP10* variants in a broad spectrum of neurodegenerative disorders.

LRK2 is a paradigmatic example of marked pathological pleomorphism associated with pathogenic variants in the same gene, even in different members of the same family [33]. Similarly, *LRP10* variants may be related to a variety of neuropathological lesions, including LP, AD pathology, and possibly tauopathies. Especially the association with AD pathology, next to LP, is interesting as all three *LRP10* variant carriers reported in this study, as well as the three patients we previously described [5], had an intermediate or high level of AD pathology. Our detection of a possibly pathogenic *LRP10* variant in an AD case without LP may suggest a role for LRP10 in the accumulation of amyloid- β or hyperphosphorylated tau. LRP10 is known to be involved in APP trafficking and amyloid- β homeostasis [16, 20], suggesting the relevance of these pathways for the pathogenesis of neurodegeneration in subjects with *LRP10* variants. This should be further investigated in future studies.

Of note, all three *LRP10* variant carriers in this study had one or more first- or second-degree relatives with parkinsonism or dementia, as expected in an autosomal-dominant inherited disease. Unfortunately, the family of these brain donors could not be contacted. As all patients died several years ago, their house physicians at the time of death have unsuccessfully tried to contact living family members upon our request. Therefore, a co-segregation analysis of the *LRP10* variants could not be performed, which is a limitation of our study.

In conclusion, we observed possibly pathogenic *LRP10* variants in two patients with Lewy body diseases, and in one with pure AD pathology. Further studies of *LRP10* in large, well-characterized cohorts of patients with different types of neuropathology are warranted.

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SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <https://dx.doi.org/10.3233/JAD-200318>.

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