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Short communication

LRP10 variants in Parkinson's disease and dementia with Lewy bodies in the South-West of the Netherlands

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ABSTRACT

Objective: To analyse *LRP10* variants, recently associated with the development of Parkinson's disease (PD), Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB), in a series of patients and controls from the South-West of the Netherlands (Walcheren).

Methods: A series of 130 patients with PD, PDD or DLB were clinically examined, and a structured questionnaire used to collect information about family history of PD and dementia. The entire *LRP10* coding region was sequenced by Sanger methods in all patients, and haplotype analysis was performed for one recurrent *LRP10* variant. The fragments containing possibly pathogenic *LRP10* variants were sequenced in 62 unaffected control subjects from the same region. Other known PD-associated genes were analyzed by exome sequencing and gene dosage in the carriers of *LRP10* variants.

Results: Four patients were carriers of a rare heterozygous, possibly pathogenic *LRP10* variant: p.Arg151Cys, p.Arg263His, and p.Tyr307Asn. None of these variants was detected among the controls, nor were additional mutations identified in known PD-associated genes in the four *LRP10* variant carriers. The previously reported p.Tyr307Asn variant was identified in two patients (with PD and PDD), who are connected genealogically within six generations, and in one of their relatives with cognitive decline. Haplotype analysis suggests a common founder for the p.Tyr307Asn variant carriers analyzed.

Discussion: We report three possibly pathogenic *LRP10* variants in patients with PD and PDD from a local Dutch population. The identification of additional patients carrying the p.Tyr307Asn variant provides some further evidence that this variant is pathogenic for PD and PDD.

1. Introduction

Parkinson's disease (PD), Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) are common neurodegenerative diseases, which share clinical, pathological and genetic features [1,2]. These disorders occur in approximately 1–2% of the population above 60 years old [3,4], and their common hallmark is Lewy body pathology, observed primarily in the brainstem in PD, and more diffusely throughout the brain in PDD and DLB [2,5].

Although PD, PDD and DLB manifest mostly as sporadic diseases, during the last decades mounting evidence showed that genetic factors play an important role in the disease etiopathogenesis [6–8]. Recently, genetic defects in the low-density lipoprotein receptor related protein 10 gene (*LRP10*) have been reported in familial PD, PDD and DLB [9].

The aim of this study was to screen *LRP10* in a series of patients and unaffected subjects from an isolated region in the South-West of the Netherlands.

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Table 1
Details of the possibly pathogenic *LRP10* variants identified in this study and previous studies.

Genomic position	Nucleotide change	Amino acid change	Exon	Coding effect	dbSNP accession number	MAF GnomAD (alleles)	Functional predictions: pathogenic (total)	Study	Patients	Diagnosis	AAO (years)	AAD (years)	First symptom
14:23345076	c.919T > A	p.Tyr307Asn	5	missense	rs139650807	0.005% (15)	11/11	Current	Patient II-2 (Family 1)	PD	63	–	Rest tremor
								Current	Patient II-2 (Family 2)	PDD	69	79	Motor difficulties
								Current	Patient II-3 (Family 2)	Cognitive decline*	78	–	n.a.
								Quadri et al., 2018 [9]	Patient II-1 (Family 5)	PDD	71	–	Rest tremor
								Tesson et al., 2018 [12]	Patient I-9 (FPD-083)	PD	73	n.a.	Rest tremor
								Tesson et al., 2018 [12]	Patient II-1 (FPD-083)	PD	45	n.a.	Rest tremor
14: 23344945	c.788G > A	p.Arg263His	5	missense	rs372858291	0.0007% (2)	6/11	Current	Patient III-1 (Family 3)	PD	68	–	Rest tremor and bradykinesia
14:23344608	c.451C > T	p.Arg151Cys	5	missense	rs774043484	0.006% (16)	9/11	Current	Patient II-2 (Family 4)	PDD	66	74	Rest tremor and hypokinesia

GRCh37: genome reference consortium human 37; *LRP10* variant nomenclature is assigned based on reference sequence NM_014045.4; MAF: minor allele frequency; GnomAD: Genome Aggregation Database; AAO: age at onset; AAD: age at death; *: progressive cognitive decline of neurodegenerative nature; n.a. not available; PD: Parkinson's disease; PDD: Parkinson's disease dementia.

2. Methods

2.1. Participants

Between 2007 and 2010 we ascertained a series of 130 patients with PD (n = 71), PDD (n = 55), or DLB (n = 4), as well as 62 unrelated and unaffected subjects originating from a region in the South-West of the Netherlands (Walcheren). This area had maintained the features of an island until 1870, and for centuries its population remained geographically isolated from the surrounding areas. All patients were neurologically examined by a neurologist (A.R.). Structured questionnaires were used to collect information about family history of PD and dementia and The Mini Mental State Examination (MMSE) was administered as screening tool for the cognitive status. Clinical follow-up was available until July 2018. The diagnosis of PD required the exclusion of secondary causes of parkinsonism, and the presence of at least two of the following signs: bradykinesia, rigidity, or rest tremor; or, presence of one of these signs together with improvement with dopaminergic medications. Diagnosis of DLB or PDD was made according to the criteria described by McKeith and co-workers [10] and by Emre and co-workers [11], respectively. Unaffected spouses of patients or of relatives were recruited as controls. Blood samples were collected from patients, available relatives and controls for DNA isolation. The study protocol was approved by the Medical Ethics Committee of the Erasmus Medical Centre Rotterdam, the Netherlands (MEC-2005-206) and written informed consent was obtained by all participating subjects.

2.2. Genetic studies

The entire open reading frame and the intron-exon boundaries of *LRP10* were sequenced in all patients using a reported Sanger protocol [9] with minor modifications (Supplementary Information). Variants were considered as possibly pathogenic if they were: (1) present in heterozygous state (as expected for variants acting in a dominant fashion); (2) rare, defined as with a minor allele frequency (MAF) < 0·001 by the Genome Aggregation Database (gnomAD v2.1.1; https://gnomad.broadinstitute.org/); (3) exonic and non-synonymous, or predicted to affect splicing; and (4) predicted as pathogenic by at least five of 11 *in-silico* programs (Supplementary Information). The *LRP10* fragments containing possibly pathogenic variants identified in the patients were sequenced in the controls.

Whole exome sequencing (WES) and multiple ligation probe amplification (MLPA, P051-Parkinson mix 1, MRC Holland) were also performed in the patients who carried possibly pathogenic *LRP10* variants to rule out mutations in other known genes associated with PD or parkinsonism (Supplementary Table S1).

Haplotype analysis of a 6-Mb genomic region flanking *LRP10* was performed in the carriers of one recurrent *LRP10* variant (c.919T > A, p.Tyr307Asn), by typing short tandem repeat (STR) markers. DNA of the Italian PDD patient previously reported by us with the same variant [9], was also included in this analysis (Supplementary Fig. S1).

LRP10 protein conservation analysis was performed using the T-Coffee multiple sequence alignment program (https://www.ebi.ac.uk/Tools/msa/tcoffee/) (Supplementary Fig. S2). Details on the methodologies are reported in the Supplementary Information.

3. Results

The demographic and clinical characteristics of the 130 index patients are reported in Supplementary Table S2. The index patients had a mean age at disease onset of 62.4 ± 9.6 years and the 62 unrelated and unaffected participants had a mean age of 63.5 ± 12.3 years at recruitment.

Four index patients carried *LRP10* variants that fulfil our criteria for being considered as possibly pathogenic: c.451C > T/p.Arg151Cys

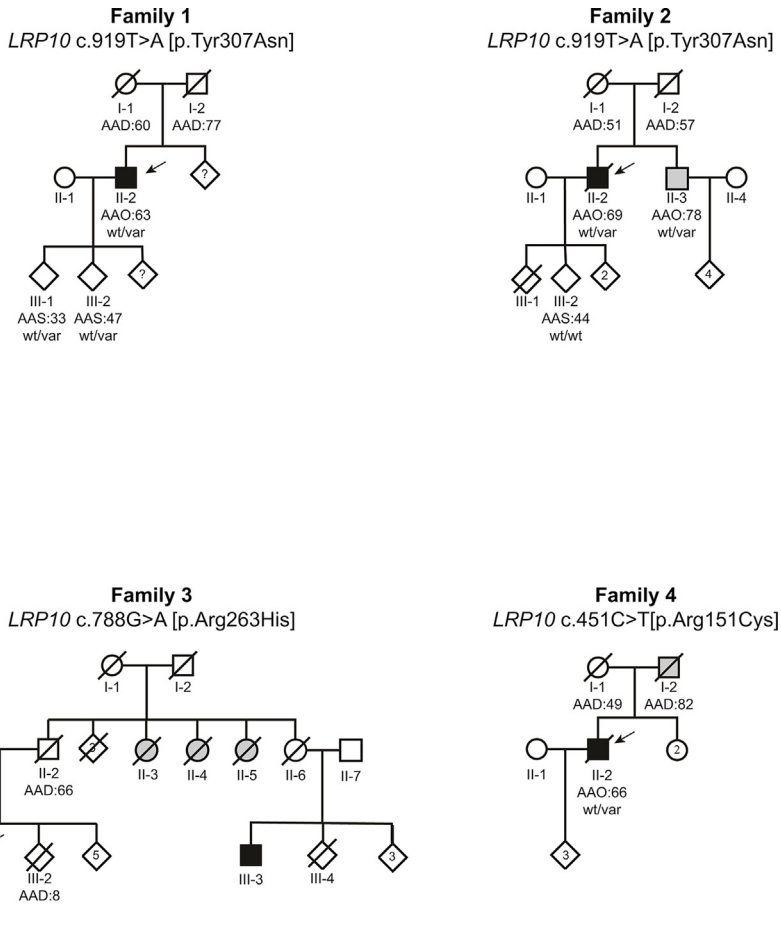

Fig. 1. Pedigrees of patients carrying *LRP10* variants.
Circles indicate females, squares indicate males, diamonds indicate sex-disguised individuals; black symbols indicate patients affected by Parkinson's disease or Parkinson's disease dementia; grey symbols indicate patients with Alzheimer's disease, cognitive decline or unspecified type of dementia; diagonal lines indicate deceased individuals; arrows indicate index patients; numbers within a circle, square or diamond indicate the number of individuals; question marks indicate that there is no information about individuals' disease status. AAD: age at death; AAO: age at onset; AAS: age at sampling; wt: wild-type; var: variant.

(gnomAD MAF 0.000056, 16 alleles) in one patient; c.788G > A/p.Arg263His (gnomAD MAF 0.000007, 2 alleles) in another patient; and c.919T > A/p.Tyr307Asn (gnomAD MAF 0.000059, 15 alleles) in two other patients (Table 1). None of these variants were detected among the 62 unaffected subjects. Additional variants detected in patients but not fulfilling our criteria to be considered as possibly pathogenic are reported in Supplementary Table S3. Our WES and MLPA analyses in the four patients carrying *LRP10* possibly pathogenic variants detected no pathogenic variants in any of the other known genes associated with PD or parkinsonism (WES reached an average depth > 190×, with 99.1% of the target region covered > 20×).

Two patients, whose genealogy can be traced back to a common ancestor within six generations, carry the *LRP10* p.Tyr307Asn heterozygous variant. The diagnosis of PD in the first patient (Family 1, II-2) was established based on rigidity, bradykinesia, reduced arm swing and reduced facial expression, after he presented with rest tremor of the left hand at 63 years of age. The patient had multiple depressive episodes. He did not report PD or dementia among his first degree relatives (Fig. 1). DNA was available from two of his offspring, asymptomatic at the age of 33 and 47 years, respectively; both also carried the *LRP10* p.Tyr307Asn variant in heterozygous state (Fig. 1 and Supplementary Fig. S1). The second patient carrying the *LRP10* p.Tyr307Asn variant (Family 2, II-2) developed motor difficulties in the right leg at the age of 69. PD was diagnosed one year later based on bradykinesia, reduced facial expression, hypersalivation and orthostasis, in absence of rest tremor. He developed a paresis of the left arm after a small intracerebral hemorrhage in the right basal ganglia at the age of 75, followed by cognitive deterioration and periods of confusion. A dementia was diagnosed one year later and he died at 79 years old. He did not report PD among his first degree relatives. However, his brother was recently diagnosed with a progressive cognitive decline of neurodegenerative nature, and DNA testing revealed that he also carries the *LRP10* p.Tyr307Asn variant (Fig. 1 and Supplementary Fig. S1).

A third patient (Family 3, III-1), carrying a *LRP10* p.Arg263His variant, developed a rest tremor of both hands and bradykinesia at 68 years of age. The PD diagnosis was established two years later, when rigidity and reduced facial expression were also present. He has mild memory impairments, concentration and orientation problems at the current age of 78. One of his cousins was also diagnosed with PD (paternal side), the patient's father had memory complaints and his three sisters were affected by dementia (Fig. 1). Unfortunately, co-segregation studies could not be performed in the affected relatives due to unavailability of DNA.

A fourth patient (Family 4, II-2), carrying a *LRP10* p.Arg151Cys variant, was diagnosed with PD based on hypokinesia and rest tremor of the left hand at 66 years of age. He developed rigidity, hallucinations and depression several years later, and memory complaints at the age of 70. A diagnosis of dementia was established at 73 years of age, one year before he died. His father suffered from Alzheimer's disease, walking problems and frequent falls which started at the end of his seventies.

As expected from the genealogical links, our haplotype studies showed that the patients in the two Dutch families with the *LRP10* p.Tyr307Asn variant share an extended haplotype of several megabases flanking the *LRP10* gene. The Italian PDD patient previously reported by us with the same variant [9] shares a smaller haplotype of ~1 Mb, therefore compatible with a common but more distant ancestor.

4. Discussion

Here we report three rare, possibly pathogenic *LRP10* variants in a relatively small series of 130 patients from the South-West of the Netherlands. The identified variants were absent in 62 unaffected

subjects from the same region, and extremely rare in public databases (Table 1). Moreover, WES and MLPA performed in our four index patients with *LRP10* variants detected no pathogenic variants in any of the other genes previously associated with PD or parkinsonism.

Of interest, the p.Tyr307Asn variant identified here in two Dutch patients with PD and PDD and in one relative cognitive decline, was initially observed by us in one patient with PDD from Italy [9]. The same variant was subsequently reported in a parent-offspring pair with PD, in a screening of 25 PD/DLB French families [12]; another two relatives affected by PD in that family did not share the p.Tyr307Asn variant, and might represent phenocopies.

Thus, the *LRP10* p.Tyr307Asn variant has been identified at least three times so far, in independent studies targeting patients of European ancestry with familial forms of PD, PDD or DLB, and including a total of 701 unrelated probands: 608 patients of European ancestry in our initial study [9]; 25 French patients studied by Tesson and colleagues [12]; and 68 Dutch patients in the current study (here we consider Family 1 and 2 as part of one extended kindred). The frequency of this variant among patients with familial forms of PD, PDD or DLB (3/701) is significantly higher compared to that present in GnomAD v2.1.1 (13/74109, only considering non-Finnish Europeans and Latino individuals, two-sided Fisher's Exact test, $p = 0.0048$). Furthermore, functional studies showed that this variant leads to decreased stability of the LRP10 protein compared to the wild-type [9]. Taken together, these genetic and functional data support the contention that this variant plays a role in the development of PD and PDD. The penetrance of the p.Tyr307Asn variant as well as of the p.Arg151Cys and p.Arg263His variants might be incomplete. However, an accurate estimation is currently impossible because, although PD occurred sporadically in some carriers, in many of them the parents had died before the age at disease development observed in their offspring, and the patients' offspring are still younger than that age.

Considering together all patients with p.Tyr307Asn reported so far (n = 6), the initial diagnosis was PD in five patients and progressive cognitive decline of neurodegenerative nature in one, rest tremor was the presenting sign in four out of the five patients diagnosed with PD, and mean age at onset was 66.5 years (SD: 11.6; range: 45–78; Table 1). During the course of PD, two patients developed dementia (one Italian patient and the Dutch patient II-2 - Family 2), two had no cognitive impairments (French patients), and one had multiple depressive periods (Dutch patient II-2 – Family 1).

Limited data are available for the p.Arg263His and p.Arg151Cys variants reported here in two patients with PD and PDD, respectively. Besides being very rare, predicted to be pathogenic by the majority of *in-silico* programs used here, and to replace highly conserved amino acids located within conserved protein stretches (Supplementary Fig. S2), no additional affected carriers have been reported so far, and functional data are not available. Therefore pathogenicity cannot be confidently established. Of note, the p.Arg151Cys substitution was previously found by us [9] in one of 645 Dutch patients with abdominal aortic aneurysms. However, the neurological status of this subject is unknown.

In conclusion, we report *LRP10* possibly pathogenic variants in patients with PD, PDD and dementia from a local Dutch population. Although our data cannot conclusively prove pathogenicity, the identification of additional patients with PD, PDD and dementia carrying the *LRP10* p.Tyr307Asn variant provides further evidence that this variant might be pathogenic.

Author contributions

LJMV assisted in the clinical data collection, supervised genetic experiments, analyzed and interpreted data and wrote the initial draft of the manuscript. AR undertook clinical and genealogical studies, analyzed and interpreted data and wrote part of the initial manuscript. THW assisted in the clinical data collection, supervised genetic experiments, analyzed and interpreted data. SM and GJB undertook genetic experiments. CC and GDM undertook clinical studies. FJdJ provided overall study direction, supervision, and revised the manuscript. JCvS and VB designed the study, provided overall study direction, supervision, and revised the manuscript. MQ undertook and supervised genetic experiments, designed the study, provided overall study direction, supervision, and revised the manuscript. All authors critically reviewed the manuscript and approved the final submitted version.

Potential conflicts of interest

MQ received honoraria from the Centre for human Drug Research (the Netherlands); VB received research grants from the Stichting Parkinson Fonds (the Netherlands); the ZonMw (the Netherlands), under the aegis of the EU Joint Programme - Neurodegenerative Disease Research (JPND), the Centre for Human Drug Research (Leiden, the Netherlands); and the Erasmus MC, Rotterdam; he receives compensation for serving as Section Editor of Current Neurology and Neuroscience Reports, and Editor-in-Chief of Parkinsonism & Related Disorders; he received honoraria from the International Parkinson and Movement Disorder Society, the Centre for Human Drug Research (the Netherlands), and the Sun Pharmaceutical Laboratories Limited (India). The remaining Authors have nothing to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.05.037.

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