Supplementary Material

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

Supplementary Table 1. PCR primers for *LRP10* genomic region

***LRP10* genomic DNA NM_014045.4**		
Primer name	**Primer sequence 5'>3'**	**Amplicon size (bp)**
LRP10-ex1-fwd	CAAAGTTTGGCCCGAAGAGG	522
LRP10-ex1-rev	gggcaggcaggatagagtgc	
LRP10-ex2-fwd	cggatggctcccttgagttg	287
LRP10-ex2-rev	cacaccgagcctcagcttcc	
LRP10-ex3-fwd	cctccttgcagagcccagac	325
LRP10-ex3-rev	gaagtgatccctgaagacttccaatg	
LRP10-ex4-fwd	gcaccaggggaggagaaagc	367
LRP10-ex4-rev	gcagaggcaccatggagagg	
LRP10-ex5A-fwd	GCCAAGgtaggctggacagg	860
LRP10-ex5B-rev	TGGTAGTTGCAGCGGTCAGC	
LRP10-ex5B-fwd	GTCCCCTCCCTGCCTTGC	1020
LRP10-ex5C-rev	tcaggatctggacctgtcccttac	
LRP10-ex6-fwd	gggaaagccatggcacagc	342
LRP10-ex6-rev	ggccaaaggctgaatgaagg	
LRP10-ex7A-fwd	cctcctggtcccagttctgc	813
LRP10-ex7B-rev	CCCACCAAGTCCCTGAAATCC	

Supplementary Table 2. Genes previously established or nominated as causative in parkinsonism or dementia

Chr	Start	End	Gene	Mode of Inheritance
			PD genes	
1	8021714	8045342	*PARK7*	AR
1	17312453	17338467	*ATP13A2*	AR
1	20959948	20978004	*PINK1*	AR
1	65720133	65881552	*DNAJC6*	AR
2	25013136	25016251	*PTRHD1*	AR
6	161768590	163148834	*PARK2*	AR
15	62144588	62352664	*VPS13C*	AR
21	33997269	34100351	*SYNJ1*	AR
22	32870707	32894818	*FBXO7*	AR
22	38507502	38577857	*PLA2G6*	AR
1	11072462	11085549	*TARDBP*	AD
1	155204239	155214653	*GBA**	AD
3	132136361	132257876	*DNAJC13*	AD
4	90645250	90759447	*SNCA*	AD
7	56169266	56174187	*CHCHD2*	AD
12	40618813	40763087	*LRRK2*	AD
14	23340822	23350789	*LRP10*	AD
16	46693589	46723144	*VPS35*	AD
17	42422491	42430474	*GRN*	AD
17	43971702	44105700	*MAPT*	AD
20	5049129	5093736	*TMEM230*	AD
X	154487526	154493852	*RAB39B*	X-linked R
			FTD genes	
1	11072462	11085549	*TARDBP*	AD
3	87276413	87304698	*CHMP2B*	AD
7	144149034	144533488	*TBK1*	AD
9	35056065	35072739	*VCP*	AD
16	31191431	31206192	*FUS*	AD
17	43971702	44105700	*MAPT*	AD
17	42422491	42430474	*GRN*	AD
X	56590025	56593443	*UBQLN2*	X-linked D
			AD genes	
1	227057885	227083804	*PSEN2*	AD

11	121322912	121504471	*SORL1*	AD
14	73603143	73690399	*PSEN1*	AD
19	1040102	1065571	*ABCA7**	AD
21	27252861	27543446	*APP*	AD
			Perry syndrome gene	
2	74588281	74619214	*DCTN1*	AD
			Niemann-Pick C genes	
14	74942900	74960084	*NPC2*	AR
18	21086148	21166581	*NPC1*	AR

* also risk gene. The Genome Reference Consortium Human Build 37 (hg19) was used. AR, autosomal recessive; AD, autosomal dominant or Alzheimer's disease; PD, Parkinson's disease; FTD, frontotemporal dementia

Supplementary Table 3. Demographic and clinical characteristics of the two study groups

Study group	**Group 1 Dementia with Lewy pathology**	**Group 2 Dementia and parkinsonism without Lewy pathology**
N	126	107
Sex *M*, n (%)	56 (44%)	56 (52%)
Age at death *y*, mean ± SD	78.1 ± 9.2	74.4 ± 11.2
Age at onset *y*, mean ± SD	67.2 ± 13.5	66.2 ± 11.8
Disease duration *y*, mean ± SD	9.6 ± 5.9	8.1 ± 5.9
Dementia duration *y*, mean ± SD	6.3 ± 4.3	5.1 ± 3.6
Parkinsonism, n (%)	72 (56%)	107 (100%)
Familial parkinsonism, n/N (%)	8/21 (38%)	4/22 (18%)
Familial dementia, n/N (%)	46/68 (68%)	36/66 (55%)
Clinical diagnoses, n (%)		
AD	48 (38%)	20 (19%)
Corticobasal syndrome	2 (2%)	2 (2%)
DLB	24 (19%)	5 (5%)
Frontotemporal dementia	4 (3%)	26 (24%)
Multiple system atrophy	1 (1%)	2 (2%)
PD with dementia	22 (17%)	7 (7%)
Progressive supranuclear palsy	1 (1%)	13 (12%)
Vascular dementia	9 (7%)	18 (17%)
No definite clinical diagnosis	15 (12%)	14 (13%)

AD, Alzheimer's disease; DLB, dementia with Lewy bodies; PD, Parkinson's disease

Supplementary Table 4. Pathological characteristics of the two study groups

	Group 1 Dementia with Lewy pathology	Group 2 Dementia and parkinsonism without Lewy pathology
N	126	107
PMD *h*, mean ± SD	5.5 ± 1.4	5.6 ± 1.5
***APOE* ε4,**		
N	75	87
0	24 (32%)	50 (58%)
1	39 (52%)	25 (29%)
2	12 (16%)	11 (13%)
Thal amyloid-β phase, median (IQR)	4 (3-4)	2 (0-4)
Braak neurofibrillary stage, median (IQR)	5 (3-6)	3 (1-4)
CERAD score, median (IQR)	B (B-C)	A (O-B)
AD-level,		
N	123	98
not	0 (0%)	25 (26%)
low	24 (20%)	34 (35%)
intermediate	49 (40%)	21 (21%)
high	50 (41%)	18 (18%)
Braak Lewy body stage		
typical, n (%); median stage (IQR)	109 (87%); 6 (5-6)	107 (100%); 0 (0-0)
atypical, n (%)	17 (13%)	0 (0%)
McKeith Lewy body stage,		
N	110	107
none	0 (0%)	104 (97%)
brainstem predominant	0 (0%)	3 (3%)
limbic-transitional	42 (38%)	0 (0%)
neocortical-diffuse	42 (38%)	0 (0%)
amygdala predominant	26 (24%)	0 (0%)
Microvascular lesions, n (%)	45 (36%)	44 (41%)
Hippocampal sclerosis, n (%)	27 (21%)	17 (16%)
Argyrophilic grain disease, n (%)	5 (4%)	7 (7%)
CAA, n (%)		
type 1	51 (40%)	12 (11%)
type 2	57 (45%)	40 (37%)
Pathological diagnoses, n (%)		
AD without Lewy pathology		37 (34%)
AD with Lewy pathology	38 (30%)	
Auto-immune encephalitis		1 (1%)
Corticobasal degeneration		1 (1%)
CRASH syndrome		1 (1%)
DLB	38 (30%)	
Frontotemporal dementia	1 (1%)	29 (27%)
Mixed AD/LBD	28 (22%)	
Multiple sclerosis		1 (1%)

Multiple system atrophy		1 (1%)
Neurodegeneration with brain iron accumulation		1 (1%)
Neuronal intranuclear inclusion disease	20 (16%)	1 (1%)
PD with dementia	1 (1%)	15 (14%)
Progressive supranuclear palsy		1 (1%)
Spinocerebellar ataxia		18 (17%)
Vascular dementia		

PMD, postmortem delay; AD, Alzheimer's disease; CAA, cerebral amyloid angiopathy; DLB, dementia with Lewy bodies; PD, Parkinson's disease

Supplementary Table 5. *In-silico* pathogenicity predictions

				Variant-effect predictions software (scores)										
Genomic position	**Nucleotide change**	**Amino acid change**	**GERP**	**SIFT**	**Polyphen2 HDIV**	**Polyphen2 HVAR**	**LRT**	**Mutation Taster**	**Mutation Assessor**	**FATHMM**	**MetaSVM**	**MetaLR**	**CADD phred**	**M-CAP**
14:23344608	c.451C>T	p.Arg151Cys	5.01	D (0.0)	P (0.472)	B (0.037)	D (0.000)	D (1.000)	M (2.285)	D (-3.92)	D (0.545)	D (0.777)	32	D (0.172)
14:23345134	c.977G>A	p.Gly326Asp	4.14	T (0.368)	B (0.297)	B (0.172)	N (0.009)	D (0.887)	L (1.245)	D (-3.23)	D (0.067)	D (0.644)	15.59	D (0.034)
14:23345514	c.1357G>A	p.Gly453Ser	5.08	D (0.024)	P (0.944)	B (0.113)	N (0.000)	D (1.000)	L (1.175)	D (-3.34)	T (-0.475)	T (0.330)	21.0	D (0.031)
14:23341951	c.39C>T	p.Gly13=	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
14:23344264	c.216G>C	p.Arg72Ser	5.13	T (1.0)	B (0.064)	B (0.047)	D (0.000)	D (0.997)	L (1.385)	T (1.64)	T (-1.076)	T (0.046)	3.153	T (0.014)
14:23344572	c.415A>G	p.Met139Val	2.05	T (0.302)	B (0.002)	B (0.003)	N (0.665)	N (1.000)	N (-0.625)	D (-2.19)	T (-1.010)	T (0.026)	3.321	NA
14:23346279	c.1685G>A	p.Arg562His	5.23	T (0.68)	D (0.999)	D (0.972)	D (0.000)	D (1.000)	M (2.2)	D (-3.37)	D (0.451)	D (0.772)	26.6	NA
14:23346529	c.1935C>T	p.Pro645=	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

The Genome Reference Consortium Human Build 37 (hg19), transcript NM_014045-4 and ANNOVAR_V5.0.sh were used. GERP, Genomic Evolutionary Rate Profiling; SIFT, Sorting Intolerant From Tolerant; PolyPhen2 HDIV, Polymorphism Phenotyping version 2 human diversity; PolyPhen2 HVAR, Polymorphism Phenotyping version 2 human variation; LRT, Likelihood Ratio Test; FATHMM, Functional Analysis Through Hidden Markov Models; SVM, Support Vector Machine; LR, Logistic Regression; CADD, Combined Annotation Dependent Depletion; M-CAP, Mendelian Clinically Applicable Pathogenicity; T, tolerated; D, damaging/disease causing; B, benign; N, polymorphism/neutral; P, polymorphism automatic; L, low; M, medium; NA, not available.

Supplementary Table 6. Other *LRP10* variants which did not fulfill our criteria for possible pathogenicity

Patient (s)	Genomic position	Nucleotide change	Amino acid change	Exon	Coding effect	dbSNP 142 accession number	Allele frequency GnomAD (alleles)	Functional predictions: pathogenic (total)
4-6	14:23341951	c.39C>T	p.Gly13=	2	synonymous	rs34294471	2.73% (7725)	n.a.
7	14:23344264	c.216G>C	p.Arg72Ser	4	missense	rs201675483	0.011% (28)	2/11
8	14:23344572	c.415A>G	p.Met139Val	5	missense	rs28534929	0.70% (1974)	1/10
9-11	14:23346279	c.1685G>A	p.Arg562His	7	missense	rs142153001	0.70% (1974)	9/10
12	14:23346529	c.1935C>T	p.Pro645=	7	synonymous	-	0.002% (6)	n.a.

The Genome Reference Consortium Human Build 37 (hg19) and transcript NM_014045-4 were used. Only variants in exons or at the exon-intron boundary (-10/+10) are displayed. MAF, minor allele frequency; GnomAD, Genome Aggregation Database; n.a., not applicable

Supplementary Table 7. Possible pathogenic variant in other known genes causing parkinsonism or dementia in possibly pathogenic *LRP10* carriers

Patient	Gene	Genomic position	Nucleotide change	Amino acid change	Exon	Coding effect	dbSNP 142 accession number	MAF GnomAD (alleles)	GERP
1	*ABCA7*	19:1058688	c.5221G>A	p.Gly1741Arg	38	missense	rs1311222336	0.0004 (1)	4.23

		Variant-effect predictions software (scores)										
		SIFT	**Polyphen2 HDIV**	**Polyphen2 HVAR**	**LRT**	**Mutation Taster**	**Mutation Assessor**	**FATHMM**	**MetaSVM**	**MetaLR**	**CADD phred**	**M-CAP**
1	*ABCA7*	D (0)	P (1)	P (0.999)	na	D (1)	M (3.3)	D (-2.42)	D (0.965)	D (0.86)	D (31)	D (0.214)

The Genome Reference Consortium Human Build 37 (hg19), transcript NM_019112 and ANNOVAR_V5.0.sh were used. GERP, Genomic Evolutionary Rate Profiling; SIFT, Sorting Intolerant From Tolerant; PolyPhen2 HDIV, Polymorphism Phenotyping version 2 human diversity; PolyPhen2 HVAR, Polymorphism Phenotyping version 2 human variation; LRT, Likelihood Ratio Test; FATHMM, Functional Analysis Through Hidden Markov Models; SVM, Support Vector Machine; LR, Logistic Regression; CADD, Combined Annotation Dependent Depletion; M-CAP, Mendelian Clinically Applicable Pathogenicity; T, tolerated; D, damaging/disease causing; B, benign; N, polymorphism/neutral; P, polymorphism automatic; L, low; M, medium; NA, not available