Supplementary Information

Diagnostic exome sequencing in early-onset Parkinson's disease confirms VPS13C as a rare cause of autosomal-recessive Parkinson's disease

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Content:

Supplementary Table 1: Catalog of OMIM entries and genes related to PD and Parkinson syndromes, as generated by our WES bioinformatics pipeline through a keyword-based online search (keywords: Parkinson and parkinsonism; several selected genes associate with multiple disease entities, some of which do not relate to PD but were automatically listed by our bioinformatics system for reasons of data completeness)

OMIM gene	Gene-symbol	Omim disease	Disease
103950	A2M	104300	{Alzheimer disease, susceptibility to}
103730	ADH1C	103780	{Alcohol dependence, protection against}
103730	ADH1C	168600	{Parkinson disease, susceptibility to}
604581	AFG3L2	614487	Spastic ataxia 5, autosomal recessive
604581	AFG3L2	610246	Spinocerebellar ataxia 28
107741	APOE	603075	{?Macular degeneration, age-related}
107741	APOE	0	{Myocardial infarction susceptibility}
107741	APOE	104310	Alzheimer disease-2
107741	APOE	0	Hyperlipoproteinemia, type III
107741	APOE	611771	Lipoprotein glomerulopathy
107741	APOE	269600	Sea-blue histiocyte disease
104760	APP	104300	Alzheimer disease 1, familial
104760	APP	605714	Cerebral amyloid angiopathy, Dutch, Italian, Iowa, Flemish, Arctic variants
610513	ATP13A2	606693	Kufor-Rakeb syndrome
610513	ATP13A2	617225	Spastic paraplegia 78, autosomal recessive
182350	ATP1A3	614820	Alternating hemiplegia of childhood 2
182350	ATP1A3	601338	CAPOS syndrome
182350	ATP1A3	128235	Dystonia-12
300556	ATP6AP2	300423	?Mental retardation, X-linked, syndromic, Hedera type
300556	ATP6AP2	300911	?Parkinsonism with spasticity, X-linked
601517	ATXN2	183090	{Amyotrophic lateral sclerosis, susceptibility to, 13}
601517	ATXN2	168600	{Parkinson disease, late-onset, susceptibility to}
601517	ATXN2	183090	Spinocerebellar ataxia 2
607047	ATXN3	109150	Machado-Joseph disease
606075	C10orf2	271245	Mitochondrial DNA depletion syndrome 7 (hepatocerebral type)
606075	C10orf2	616138	Perrault syndrome 5
606075	C10orf2	609286	Progressive external ophthalmoplegia with mitochondrial DNA deletions, autosomal dominant 3
614297	C19orf12	615043	?Spastic paraplegia 43, autosomal recessive
614297	C19orf12	614298	Neurodegeneration with brain iron accumulation 4
614260	C9orf72	105550	Frontotemporal dementia and/or amyotrophic lateral sclerosis 1
615903	CHCHD10	616209	?Myopathy, isolated mitochondrial, autosomal dominant
615903	CHCHD10	615911	Frontotemporal dementia and/or amyotrophic lateral sclerosis 2
615903	CHCHD10	615048	Spinal muscular atrophy, Jokela type
607042	CLN3	204200	Ceroid lipofuscinosis, neuronal, 3

609825	COQ2	146500	{Multiple system atrophy, susceptibility to}
609825	COQ2	607426	Coenzyme Q10 deficiency, primary, 1
124030	CYP2D6	608902	{Codeine sensitivity}
124030	CYP2D6	608902	{Debrisoquine sensitivity}
601143	DCTN1	105400	{Amyotrophic lateral sclerosis, susceptibility to}
601143	DCTN1	607641	Neuropathy, distal hereditary motor, type VIIB
601143	DCTN1	168605	Perry syndrome
611203	DNAJC5	162350	Ceroid lipofuscinosis, neuronal, 4, Parry type
608375	DNAJC6	615528	Parkinson disease 19a, juvenile-onset
608375	DNAJC6	615528	Parkinson disease 19b, early-onset
600495	EIF4G1	614251	{Parkinson disease 18}
605648	FBXO7	260300	Parkinson disease 15, autosomal recessive
309550	FMR1	300624	Fragile X syndrome
309550	FMR1	300623	Fragile X tremor/ataxia syndrome
309550	FMR1	311360	Premature ovarian failure 1
134790	FTL	600886	Hyperferritinemia-cataract syndrome
134790	FTL	615604	L-ferritin deficiency, dominant and recessive
134790	FTL	606159	Neurodegeneration with brain iron accumulation 3
606463	GBA	127750	{Lewy body dementia, susceptibility to}
606463	GBA	168600	{Parkinson disease, late-onset, susceptibility to}
606463	GBA	608013	Gaucher disease, perinatal lethal
606463	GBA	230800	Gaucher disease, type I
606463	GBA	230900	Gaucher disease, type II
606463	GBA	231000	Gaucher disease, type III
606463	GBA	231005	Gaucher disease, type IIIC
600225	GCH1	128230	Dystonia, DOPA-responsive, with or without hyperphenylalaninemia
600225	GCH1	233910	Hyperphenylalaninemia, BH4-deficient, B
300144	GLUD2	168600	{Parkinson disease, age of onset, modifier}
138945	GRN	607485	Aphasia, primary progressive
138945	GRN	614706	Ceroid lipofuscinosis, neuronal, 11
138945	GRN	607485	Frontotemporal lobar degeneration with ubiquitin-positive inclusions
613609	HFE	614193	[Transferrin serum level QTL2]
613609	HFE	104300	{Alzheimer disease, susceptibility to}
613609	HFE	612635	{Microvascular complications of diabetes 7}
613609	HFE	176100	{Porphyria cutanea tarda, susceptibility to}
613609	HFE	176200	{Porphyria variegata, susceptibility to}
613609	HFE	235200	Hemochromatosis
613609	HLA-H	614193	[Transferrin serum level QTL2]
613609	HLA-H	104300	{Alzheimer disease, susceptibility to}
613609	HLA-H	612635	{Microvascular complications of diabetes 7}
613609	HLA-H	176100	{Porphyria cutanea tarda, susceptibility to}
613609	HLA-H	176200	{Porphyria variegata, susceptibility to}
613609	HLA-H	235200	Hemochromatosis
602821	KIF5A	617235	Myoclonus, intractable, neonatal

602821	KIF5A	604187	Spastic paraplegia 10, autosomal dominant
609007	LRRK2	607060	{Parkinson disease 8}
157140	MAPT	168600	{Parkinson disease, susceptibility to}
157140	MAPT	600274	Dementia, frontotemporal, with or without parkinsonism
157140	MAPT	172700	Pick disease
157140	MAPT	601104	Supranuclear palsy, progressive
157140	MAPT	260540	Supranuclear palsy, progressive atypical
300005	MECP2	300496	{Autism susceptibility, X-linked 3}
300005	MECP2	300673	Encephalopathy, neonatal severe
300005	MECP2	300260	Mental retardation, X-linked syndromic, Lubs type
300005	MECP2	300055	Mental retardation, X-linked, syndromic 13
300005	MECP2	312750	Rett syndrome
300005	MECP2	312750	Rett syndrome, atypical
300005	MECP2	312750	Rett syndrome, preserved speech variant
606989	MPO	104300	{Alzheimer disease, susceptibility to}
606989	MPO	0	{Lung cancer, protection against, in smokers}
606989	MPO	254600	Myeloperoxidase deficiency
163729	NOS3	104300	{Alzheimer disease, late-onset, susceptibility to}
163729	NOS3	0	{Coronary artery spasm 1, susceptibility to}
163729	NOS3	189800	{Hypertension, pregnancy-induced}
163729	NOS3	145500	{Hypertension, susceptibility to}
163729	NOS3	601367	{Ischemic stroke, susceptibility to}
163729	NOS3	0	{Placental abruption}
606157	PANK2	607236	HARP syndrome
606157	PANK2	234200	Neurodegeneration with brain iron accumulation 1
602544	PARK2	607572	{Leprosy, susceptibility to}
602544	PARK2	211980	Adenocarcinoma of lung, somatic
602544	PARK2	167000	Adenocarcinoma, ovarian, somatic
602544	PARK2	600116	Parkinson disease, juvenile, type 2
603390	PDE8B	614190	Pigmented nodular adrenocortical disease, primary, 3
603390	PDE8B	609161	Striatal degeneration, autosomal dominant
190040	PDGFB	615483	Basal ganglia calcification, idiopathic, 5
190040	PDGFB	607907	Dermatofibrosarcoma protuberans
190040	PDGFB	607174	Meningioma, SIS-related
173410	PDGFRB	615007	Basal ganglia calcification, idiopathic, 4
173410	PDGFRB	616592	Kosaki overgrowth syndrome
173410	PDGFRB	228550	Myofibromatosis, infantile, 1
173410	PDGFRB	601812	Premature aging syndrome, Penttinen type
608309	PINK1	605909	Parkinson disease 6, early onset
603604	PLA2G6	256600	Infantile neuroaxonal dystrophy 1
603604	PLA2G6	610217	Neurodegeneration with brain iron accumulation 2B
603604	PLA2G6	612953	Parkinson disease 14, autosomal recessive
191840	PLAU	104300	{Alzheimer disease, late-onset, susceptibility to}
191840	PLAU	601709	Quebec platelet disorder

174763	POLG	203700	Mitochondrial DNA depletion syndrome 4A (Alpers type)
174763	POLG	613662	Mitochondrial DNA depletion syndrome 4B (MNGIE type)
174763	POLG	607459	Mitochondrial recessive ataxia syndrome (includes SANDO and SCAE)
174763	POLG	157640	Progressive external ophthalmoplegia, autosomal dominant 1
174763	POLG	258450	Progressive external ophthalmoplegia, autosomal recessive 1
604325	PPP2R2B	604326	Spinocerebellar ataxia 12
603424	PRKRA	612067	Dystonia 16
176640	PRNP	245300	{Kuru, susceptibility to}
176640	PRNP	137440	Cerebral amyloid angiopathy, PRNP-related
176640	PRNP	123400	Creutzfeldt-Jakob disease
176640	PRNP	137440	Gerstmann-Straussler disease
176640	PRNP	603218	Huntington disease-like 1
176640	PRNP	600072	Insomnia, fatal familial
176640	PRNP	606688	Prion disease with protracted course
104311	PSEN1	613737	Acne inversa, familial, 3
104311	PSEN1	607822	Alzheimer disease, type 3
104311	PSEN1	607822	Alzheimer disease, type 3, with spastic paraparesis and apraxia
104311	PSEN1	607822	Alzheimer disease, type 3, with spastic paraparesis and unusual plaques
104311	PSEN1	613694	Cardiomyopathy, dilated, 1U
104311	PSEN1	600274	Dementia, frontotemporal
104311	PSEN1	172700	Pick disease
612719	PTS	261640	Hyperphenylalaninemia, BH4-deficient, A
300774	RAB39B	311510	?Waisman syndrome
300774	RAB39B	300271	Mental retardation, X-linked 72
158378	SLC20A2	213600	Basal ganglia calcification, idiopathic, 1
611146	SLC30A10	613280	Hypermanganesemia with dystonia 1
608736	SLC39A14	617013	Hypermanganesemia with dystonia 2
126455	SLC6A3	188890	{Nicotine dependence, protection against}
126455	SLC6A3	613135	Parkinsonism-dystonia, infantile
163890	SNCA	127750	Dementia, Lewy body
163890	SNCA	168601	Parkinson disease 1
163890	SNCA	605543	Parkinson disease 4
602569	SNCB	127750	Dementia, Lewy body
604297	SYNJ1	615530	Parkinson disease 20, early-onset
313650	TAF1	314250	Dystonia-Parkinsonism, X-linked
313650	TAF1	300966	Mental retardation, X-linked, syndromic 33
600075	TBP	168600	{Parkinson disease, susceptibility to}
600075	TBP	607136	Spinocerebellar ataxia 17
191290	TH	605407	Segawa syndrome, recessive
616101	TMEM240	607454	Spinocerebellar ataxia 21
605692	TRPM7	105500	{Amyotrophic lateral sclerosis-parkinsonism/dementia complex, susceptibility to}
605978	VPS13A	200150	Choreoacanthocytosis
608879	VPS13C	616840	Parkinson disease 23, autosomal recessive, early onset
601501	VPS35	614203	{Parkinson disease 17}

300526	WDR45	300894	Neurodegeneration with brain iron accumulation 5
605237	XPR1	616413	Basal ganglia calcification, idiopathic, 6

Supplementary Table 2: Exome sequencing summary statistics

Sequence generated (Gb)	Average coverage	% uncovered	% covered ≥ 20x	Ts/Tv ratio	Number of SNVs per exome	Number of indels per exome	Number of variants called by Pindel per exome	Number of Exomedepth CNV calls per exome
11.4 (2.3)	139.1 (28)	0.1 (0.1)	97.6 (1.3)	2.6 (1)	67351.1 (1134.3)	5738.4 (193.1)	349.9 (132.7)	137.2 (33.7)

Values are given as mean (standard deviation) for 80 exomes included in the analysis.

Supplementary Table 3: Variants of unknown significance (VUS) in Mendelian PD genes

Gene	Variation nucleotide[a]	Variation amino acid[a]	dbSNP142	Frequency ExAC European (allele count/ total allele number)	Frequency gnomAD European (allele count/ total allele number)	Frequency in-house exomes[b] (allele count/ total allele number)	HGMD	ClinVar classification[c]	MDSGene classification	PDMutDB classification	M-CAP score	M-CAP 95% TPR	SIFT	PolyPhen
LRRK2	c.917C>T	p.Ala306Val	not found	not found	not found	not found	not found	not found	na	not found	0.047	possibly pathogenic	tolerated	benign
LRRK2	c.4192C>T	p.Arg1398Cys	rs373268136	2/66584	2/111322	1/16986	not found	not found	na	not found	0.118	possibly pathogenic	deleteriou s	benign
LRRK2	c.7067C>T	p.Thr2356Ile	rs113511708	17/66438	39/126416	10/16986	DM	uncertain significance	na	pathogenic nature unclear	0.009	likely benign	tolerated	benign
VPS35	c.2320C>A	p.Leu774Met	rs192419029	5/66728	13/126634	9/16986	DM?	not found	possibly pathogenic	na	0.055	possibly pathogenic	deleteriou s	possibly damaging

ExAC, Exome Aggregation Consortium, Cambridge, MA (http://exac.broadinstitute.org). gnomAD, genome Aggregation Database (http://gnomad.broadinstitute.org/). HGMD, Human Gene Mutation Database Professional release 2016.2. ClinVar, (www.ncbi.nlm.nih.gov/clinvar/). M-CAP, (http://bejerano.stanford.edu/mcap/). SIFT, PolyPhen, CADD, FATHMM, MutationTaster, and MutationAssessor: bioinformatics prediction tools accessed by Ensembl Variant Effect Predictor (www.ensembl.org/Tools/VEP). [a]numbering according to NCBI accessions NM_000113 and NP_000104 for *LRRK2* and NM_183357 and NP_899200 for *VPS35*. [b]consisting of 8,493 exomes with no neurological disease phenotype. [c]classification of variant in ClinVar referring to Parkinson's disease or parkinsonism. HGMD = classification of variant in HGMD database. MDSGene = classification of variant in MDSGene database. PDmutDB = classification of variant in PdmutDB. hom = homozygous, het = heterozygous, comp. het. = compound heterozygous. VUS = variant of unknown significance. DM, denotes a mutation reported by HGMD to be disease-causing (DM). DM?, denotes a mutation reported by HGMD as likely disease-causing, but with questionable pathogenicity. MutationAssessor classification: H (high) or M (medium) are predicted functional, L (low) or N (neutral) are predicted non-functional. na = information for gene not available in database. not found = variant not present in database.

Supplementary Table 3 continued

Gene	Variation nucleotide[a]	CADD	FATHMM	MutationTaster	Mutation Assessor	Assessment of variant frequency	Available data on functional characterisation
LRRK2	c.917C>T	20.8	tolerated	disease causing	L	Singleton variant – not reported in PD case series and PD case-control studies. Not reported in publicly available exome sequencing data (ExAC, gnomAD, 1000Genomes).	Located in ARM domain.[1] Variants in the ARM domain have been classified both as pathogenic and benign.[1] No experimental data on functional characterization available.
LRRK2	c.4192C>T	26.6	tolerated	disease causing	L	Not reported in PD case series and PD case-control studies. Very rare variant reported in publicly available exome sequencing data (ExAC, gnomAD, 1000Genomes).	Located in ROC domain.[1] Higher prevalence of pathogenic mutations.[1] No experimental data on functional characterization available.
LRRK2	c.7067C>T	16.32	tolerated	polymorphism	N	The variant was detected in PD case series.[2, 3] A PD case-control study reported equal frequencies in cases and controls.[4] Rare variant reported in publicly available exome sequencing data (ExAC, gnomAD, 1000Genomes) It is reported in the Wellderly study, a cohort of healthy individuals of age > 80 years where presence of PD symptoms was an exclusion criterion.[5]	Located in WD40 domain.[1] Experimental data indicates no impact of variant on kinase activity and on 14-3-3 binding.[6, 7] Mutant protein was classified as having properties similar to wildtype LRRK2.[8]
VPS35	c.2320C>A	24.2	tolerated	disease causing	M	Two case-control studies report frequency data[9, 10]: Zimprich et al.: found in 2 cases and 2 controls; Sharma et al.: found in 6 cases and 1 control, however, no statistically significant enrichment Very rare variant in reported in publicly available exome sequencing data (ExAC, gnomAD, 1000Genomes)	Located at C-terminal end which interacts with WASH complex.[9] Functional studies in Drosophila showed no or very weak effects for L774M transgenic flies compared to flies transgenic for the clearly pathogenic D620N variant.[11, 12]

ExAC, Exome Aggregation Consortium, Cambridge, MA (http://exac.broadinstitute.org). gnomAD, genome Aggregation Database (http://gnomad.broadinstitute.org/). SIFT, PolyPhen, CADD, FATHMM, MutationTaster, and MutationAssessor: bioinformatics prediction tools accessed by Ensembl Variant Effect Predictor (www.ensembl.org/Tools/VEP). [a]numbering according to NCBI accessions NM_000113 and NP_000104 for *LRRK2* and NM_183357 and NP_899200 for *VPS35*.

Supplementary Table 4: Annotation of heterozygous variants detected in *PARK2*

Variation nucleotide[a]	Variation amino acid[a] /deleted exons	M-CAP score	M-CAP 95% TPR	SIFT	PolyPhen	CADD	FATHMM	Mutation Taster	Mutation Assessor
c.245C>A	p.Ala82Glu	0.036	possibly pathogenic	tolerated(0.97)	benign(0.075)	0.029	D	N	N
c.1000C>T	p.Arg334Cys	0.046	possibly pathogenic	tolerated(0.05)	benign(0.057)	21.4	D	N	L
c.1204C>T	p.Arg402Cys	0.191	possibly pathogenic	deleterious(0.01)	probably_damaging(0.999)	29.4	D	D	M
c.823C>T	p.Arg275Trp	0.099	possibly pathogenic	deleterious(0)	probably_damaging(0.997)	34	D	N	M
c.247A>G	p.Thr83Ala	0.03	possibly pathogenic	tolerated(0.68)	benign(0.001)	0.001	D	N	N
c.(?-103)_(171+1_172-1)del	EX1-2DEL	na	na	na	na	na	na	na	na
c.(7+1_8-1)_(171+1_172-1)del	EX2DEL	na	na	na	na	na	na	na	na
c.(7+1_8-1)_(618+1_619-1)del	EX2-5DEL	na	na	na	na	na	na	na	na

M-CAP, (http://bejerano.stanford.edu/mcap/). SIFT, PolyPhen, CADD, FATHMM, MutationTaster, and MutationAssessor: bioinformatics prediction tools accessed by Ensembl Variant Effect Predictor (www.ensembl.org/Tools/VEP).). [a]numbering according to NCBI accessions NM_004562.2 and NP_004553.2. na = no prediction available.

Supplementary Table 5: Variants detected in PD genes with conflicting evidence

Gene	Variation nucleotide	Variation amino acid	dbSNP142	Frequency ExAC European (allele count/ total allele number)	Frequency gnomAD European (allele count/ total allele number)	Frequency in-house exomes[b] (allele count/ total allele number)	HGMD	ClinVar	M-CAP score	M-CAP 95% TPR	SIFT
DNAJC13	NM_015268.3:c.787G>A	p.Val263Ile	rs781283510	not found	2/111130	not found	not found	not found	0.007	likely benign	tolerated
DNAJC13	NM_015268.3:c.2021A>C	p.Asp674Ala	rs199541720	20/66240	59/123618	6/16986	not found	not found	0.041	possibly pathogenic	tolerated
DNAJC13	NM_015268.3:c.2855G>A	p.Arg952Gln	rs202174230	9/66628	23/126404	5/16986	not found	not found	0.042	possibly pathogenic	deleterious
EIF4G1	NM_198241.2:c.1904A>G	p.His635Arg	rs781077577	1/66068	3/111718	not found	not found	not found	0.014	likely benign	tolerated
EIF4G1	NM_198241.2:c.4258C>G	p.Gln1420Glu	rs770965114	1/66738	1/111720	not found	not found	not found	0.013	likely benign	deleterious
EIF4G1	NM_198241.2:c.1331C>T	p.Thr444Met	rs143014570	not found	1/126688	2/16986	not found	not found	0.005	likely benign	tolerated
EIF4G1	NM_198241.2:c.2416A>G	p.Ile806Val	rs62287499	23/66576	70/126704	15/16986	not found	not found	0.016	likely benign	deleterious
GIGYF2	NM_015575.3:c.536G>A	p.Arg179Lys	not found	not found	not found	not found	not found	not found	0.076	possibly pathogenic	deleterious
GIGYF2	NM_015575.3:c.1223C>T	p.Ala408Val	rs757412826	2/66286	3/111274	1/16986	not found	not found	0.041	possibly pathogenic	tolerated
GIGYF2	NM_015575.3:c.2092G>T	p.Ala698Ser	not found	not found	not found	not found	not found	not found	0.033	possibly pathogenic	tolerated
GIGYF2	NM_015575.3:c.3542C>T	p.Thr1181Ile	rs767282894	12/66706	28/126712	6/16986	not found	not found	0.059	possibly pathogenic	deleterious

Supplementary Table 5 continued

Gene	Variation nucleotide	Variation amino acid	PolyPhen	CADD	FATHMM	MutationTaster	Mutation Assessor	Our classification
DNAJC13	NM_015268.3:c.787G>A	p.Val263Ile	benign	14.14	T	N	L	likely benign
DNAJC13	NM_015268.3:c.2021A>C	p.Asp674Ala	benign	22.7	T	D	L	benign
DNAJC13	NM_015268.3:c.2855G>A	p.Arg952Gln	probably damaging	32	T	D	M	benign
EIF4G1	NM_198241.2:c.1904A>G	p.His635Arg	benign	11.38	T	D	L	likely benign
EIF4G1	NM_198241.2:c.4258C>G	p.Gln1420Glu	benign	22.3	T	D	M	likely benign
EIF4G1	NM_198241.2:c.1331C>T	p.Thr444Met	benign	4.902	T	N	N	likely benign
EIF4G1	NM_198241.2:c.2416A>G	p.Ile806Val	benign	23	T	D	L	benign
GIGYF2	NM_015575.3:c.536G>A	p.Arg179Lys	unknown	28.6	na	D	M	likely benign
GIGYF2	NM_015575.3:c.1223C>T	p.Ala408Val	unknown	14.61	na	D	L	likely benign
GIGYF2	NM_015575.3:c.2092G>T	p.Ala698Ser	unknown	23.4	na	N	N	likely benign
GIGYF2	NM_015575.3:c.3542C>T	p.Thr1181Ile	probably damaging	24	na	D	M	likely benign

ExAC, Exome Aggregation Consortium, Cambridge, MA (http://exac.broadinstitute.org). gnomAD, genome Aggregation Database (http://gnomad.broadinstitute.org/). HGMD, Human Gene Mutation Database Professional release 2016.2. ClinVar, (www.ncbi.nlm.nih.gov/clinvar/). M-CAP, (http://bejerano.stanford.edu/mcap/). SIFT, PolyPhen, CADD, FATHMM, MutationTaster, and MutationAssessor: bioinformatics prediction tools accessed by Ensembl Variant Effect Predictor (www.ensembl.org/Tools/VEP). hom = homozygous, het = heterozygous, comp. het. = compound heterozygous. VUS = variant of unknown significance. DM, denotes a mutation reported by HGMD to be disease-causing (DM). DM?, denotes a mutation reported by HGMD as likely disease-causing, but with questionable pathogenicity. MutationAssessor classification: H (high) or M (medium) are predicted functional, L (low) or N (neutral) are predicted non-functional. [b]consisting of 8,493 exomes with no neurological disease phenotype. not found = variant not present in database. na = no prediction available.

References:

1. Cardona F, Tormos-Perez M, Perez-Tur J. Structural and functional in silico analysis of LRRK2 missense substitutions. Molecular biology reports 2014;41(4):2529-2542.
2. Khan NL, Jain S, Lynch JM, et al. Mutations in the gene LRRK2 encoding dardarin (PARK8) cause familial Parkinson's disease: clinical, pathological, olfactory and functional imaging and genetic data. Brain 2005;128(Pt 12):2786-2796.
3. Johnson J, Paisan-Ruiz C, Lopez G, et al. Comprehensive screening of a North American Parkinson's disease cohort for LRRK2 mutation. Neuro-degenerative diseases 2007;4(5):386-391.
4. Ross OA, Soto-Ortolaza AI, Heckman MG, et al. Association of LRRK2 exonic variants with susceptibility to Parkinson's disease: a case-control study. The Lancet Neurology 2011;10(10):898--908.
5. Erikson GA, Bodian DL, Rueda M, Molparia B, Scott ERa. Whole-Genome Sequencing of a Healthy Aging Cohort. Cell 2016;165(4):1002--1011.
6. Jaleel M, Nichols RJ, Deak M, et al. LRRK2 phosphorylates moesin at threonine-558: characterization of how Parkinson's disease mutants affect kinase activity. The Biochemical journal 2007;405(2):307-317.
7. Nichols RJ, Dzamko N, Morrice NA, et al. 14-3-3 binding to LRRK2 is disrupted by multiple Parkinson's disease-associated mutations and regulates cytoplasmic localization. The Biochemical journal 2010;430(3):393-404.
8. Deng H-XH, Shi Y, Yang Y, et al. Identification of TMEM230 mutations in familial Parkinson's disease. Nat Genet 2016;advance on(7):733--739.
9. Zimprich A, Benet-Pags A, Struhal W, et al. A mutation in VPS35, encoding a subunit of the retromer complex, causes late-onset parkinson disease. American Journal of Human Genetics 2011;89(1):168--175.
10. Sharma M, Ioannidis JPA, Aasly JO, et al. A multi-centre clinico-genetic analysis of the VPS35 gene in Parkinson disease indicates reduced penetrance for disease-associated variants. Journal of medical genetics 2012;49(11):721--726.
11. Malik BR, Godena VK, Whitworth AJ. VPS35 pathogenic mutations confer no dominant toxicity but partial loss of function in Drosophila and genetically interact with parkin. Human Molecular Genetics 2015;24(21):6106--6117.
12. Wang HS, Toh J, Ho P, Tio M, Zhao Y, Tan EK. In vivo evidence of pathogenicity of VPS35 mutations in the Drosophila. Mol Brain 2014;7(1):73.