Supplementary Appendix

Supplementary table 1. Carriers of pathogenic variants

Patient ID	Variant identified	AAO	Gender	Family history	Tremor	Bradykinesia	Postural instability	Rigidity	Cognitive decline	Ethnicity
Likely genetically solved patients with (likely) pathogenic variants in the biallelic state for recessive or heterozygous state for dominant disorders										
L-8599	*PRKN* het p.R275W *PRKN* het Ex2-4del	17	M	n.a.	yes	yes	n.a.	no	yes, MCI	German
L-513	*PRKN* het p.Gln34Argfs*5 *PRKN* het Ex2-3del	32	F	yes	yes	n.a.	yes	yes	n.a.	German
L-3296	*PRKN* het p.Asn52Metfs*29 *PRKN* het Ex6-7Dupl	12	F	yes	n.a.	n.a.	n.a.	n.a.	n.a.	German
B-11	*PRKN* het Ex7 Del.+ het c.1072delT	64	M	yes	n.a.	n.a.	n.a.	n.a	n.a.	Italian
L-3035	*PRKN* het Ex3+4 Del + het Ex7-9 Dupl	31	M	no	yes	n.a.	n.a.	n.a.	n.a.	n.a.
L-3048	*PRKN* het p.A275T + het Ex4 Del	15	M	yes	n.a.	n.a.	n.a.	n.a.	n.a.	German
L-5415	*PRKN* het p.R275W + het p.C352R	>35	F	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	German
L-649	*PRKN* het p.R275W	16	M	yes	yes	yes	yes	yes	n.a.	German
L-1888	*PRKN* het p.R275W and Ex1dupl	19	F	no	yes	n.a.	n.a.	n.a.	n.a.	German
L-3043	*PRKN* het p.P37L and *SNCA* Dupl	33	F	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	German
L-1703	*PINK1* homo p.V170G	31	F	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	German
L-2122	*PINK1* homo p.Gln456*	61	F	yes	n.a.	n.a.	n.a.	n.a.	n.a.	German
L-2123	*PINK1* homo p.Gln456*	39	M	yes	n.a.	n.a.	n.a.	n.a.	n.a.	German
L-2124	*PINK1* homo p.Gln456*	53	F	yes	n.a.	n.a.	n.a.	n.a.	n.a.	German
L-2126	*PINK1* homo p.Gln456*	47	F	yes	n.a.	n.a.	n.a.	n.a.	n.a.	German

L-1355	*PLA2G6* het p.A781T *PLA2G6* het p.Y790*	24	F	no	n.a.	n.a.	n.a.	n.a.	n.a.	German
L-1706	*GBA* het p.R502C (p.R463C)	35	F	yes	n.a.	yes	yes	yes	no	German
L-1927	*GBA* het p.L483P (p.L444P)	30	M	no	yes	yes	yes	yes	yes, MCI	German
L-865	*GBA* het p.F252I (p.F213I)	35	F	n.a.	n.a.	n.a.	n.a.	n.a.	no	German
L-3512	*GBA* het p.N409S	39	M	no.	n.a.	n.a.	n.a.	n.a.	n.a.	German
L-295	*LRRK2* het p.R1441C	45	F	yes	n.a.	n.a.	n.a.	n.a.	n.a.	German
L-2501	*LRRK2* het p.R1441C	>32	M	yes	n.a.	n.a.	n.a.	n.a.	n.a.	German
L-7774	*LRRK2* het p.R1441S	51	M	no.	yes	yes	no	yes	no	German

Legend: AAO: age at onset, het: heterozygous, homo: homozygous, Dupl: duplication, Del: deletion, n.a.: not available, F: female, M: male, MCI: mild cognitive impairment

Supplementary table 2. List of GWAS loci investigated

Chr: Position	SNP	Gene
1:161469054	rs6658353	*FCGR2A*
1:171719769	rs11578699	*VAMP4*
1:226916078	rs4653767	*ITPKB*
2:102413116	rs34043159	*IL1R2*
2:166133632	rs353116	*SCN3A*
2:18147848	rs76116224	*KCNS3*
2:96000943	rs2042477	*KCNIP3*
3:122196892	rs55961674	*KPNA1*
3:151108965	rs11707416	*MED12L*
3:161077630	rs1450522	*SPTSSB*
3:18277488	rs4073221	*SATB1*
3:28705690	rs6808178	*LINC00693*
3:48748989	rs12497850	*NCKIPSD, CDC71*
3:52816840	rs143918452	*ALAS1, ITIH4, ITIH3, TLR9, DNAH1, BAP1, PHF7, STAB1*
4:114360372	rs78738012	*ANK2, CAMK2D*
4:170583157	rs62333164	*CLCN3*
4:17968811	rs34025766	*LCORL*
5:102365794	rs26431	*PAM*
5:134199105	rs11950533	*C5orf24*
5:60273923	rs2694528	*ELOVL7*
6:112243291	rs997368	*FYN*
6:133210361	rs75859381	*RPS12*
6:27681215	rs9468199	*ZNF184*
6:30108683	rs9261484	*TRIM40*
6:72487762	rs12528068	*RIMS1*

7:66009851	rs76949143	*GS1-124K5.11*
8:130901909	rs2086641	*FAM49B*
8:11707174	rs2740594	*CTSB*
8:22525980	rs2280104	*SORBS3, BIN3, C8orf58, PDLIM2*
9:17579690	rs13294100	*SH3GL2*
9:34046391	rs6476434	*UBAP2*
10:104015279	rs10748818	*GBF1*
10:15569598	rs10906923	*FAM171A1*
11:10558777	rs7938782	*RNF141*
12:46419086	rs7134559	*SCAF11*
13:133065768	rs11610045	*FBRSL1*
13:49927732	rs9568188	*CAB39L*
13:97865021	rs4771268	*MBNL2*
14:37989270	rs12147950	*MIPOL1*
14:75373034	rs3742785	*RPS6KL1*
14:88472612	rs8005172	*GALC*
16:28944396	rs2904880	*CD19*
16:50736656	rs6500328	*NOD2*
16:19279464	rs11343	*COQ7*
16:52599188	rs4784227	*TOX3*
16:58587672	rs200564078	*CNOT1*
17:40698158	rs601999	*ATP6V0A1, PSMC3IP, TUBG2*
17:42294337	rs2269906	*UBTF*
17:42434630	rs850738	*FAM171A2*
17:59917366	rs61169879	*BRIP1*
17:76425480	rs666463	*DNAH17*
17:7355621	rs12600861	*CHRNB1*
18:31304318	rs1941685	*ASXL3*

18:48683589	rs8087969	*MEX3C*
20:6006041	rs77351827	*CRLS1*

Chr: chromosome, Position: hg19, Gene: HUGO nomenclature

Supplementary table 3. List of variants identified in 61 nominated genes

Gene	Chr	Position (hg19)	Ref	Alt	SNP	Amino acid change	ExAC	GnomAD	CADD score	Cases (n)	Controls (n)
SCN3A	2	165984439	C	G	rs147300771	SCN3A:NM_001081676: exon18:c.2948G>C:p.R983T	$8.25x10^{-3}$	$1.59x10^{-5}$	18.87	1	
SCN3A	2	166032720	G	A	n.a.	SCN3A:NM_001081676: exon3:c.185C>T:p.P62L	n.a.	n.a.	28.6		1
ALAS1	3	52237963	A	G	n.a.	ALAS1:NM_001304443: exon4:c.512A>G:p.Q171R	n.a.	n.a.	15.3	1	
DNAH1	3	52404770	G	T	rs375219203	DNAH1:NM_015512: exon41:c.6454G>T:p.D2152Y	0.0004	0.0002082	25.8	1	
DNAH1	3	52426643	G	A	rs201752275	DNAH1:NM_015512: exon64:c.10216G>A:p.V3406I	0.0031	0.002509	18.1	1	
DNAH1	3	52380680	G	C	n.a.	DNAH1:NM_015512: exon11:c.1849G>C:p.D617H	n.a.	n.a.	16.7	1	
DNAH1	3	52396410	C	T	rs17052097	DNAH1:NM_015512: exon31:c.4987C>T:p.R1663C	0.0068	$3.57x10^{-6}$	20.8	1	
DNAH1	3	52429022	G	A	rs138940904	DNAH1:NM_015512: exon68:c.10915G>A:p.A3639T	0.0016	0.001262	34	3	
DNAH1	3	52410004	G	A	rs201299120	DNAH1:NM_015512: exon46:c.7193G>A:p.R2398H	0.0005	0.00203	23.9	1	
DNAH1	3	52384594	A	G	rs61734644	DNAH1:NM_015512 :exon16:c.2717A>G:p.D906G	0.0008	0.004475	24.5	1	
DNAH1	3	52424975	C	G	rs200158571	DNAH1:NM_015512: exon61:c.9646C>G:p.L3216V	n.a.	0.0006666	23.5		1
DNAH1	3	52398697	C	T	rs61739896	DNAH1:NM_015512: exon33:c.5288C>T:p.S1763L	0.0679	0.006287	27.8	1	
DNAH1	3	52422300	C	T	rs61731638	DNAH1:NM_015512: exon57:c.9121C>T:p.R3041C	0.0811	0.006178	35	1	
DNAH1	3	52400807	G	T	rs200859252	DNAH1:NM_015512: exon36:c.5669G>T:p.G1890V	n.a.	0.002275	27	1	
DNAH1	3	52378570	A	G	rs76591348	DNAH1:NM_015512: exon9:c.1351A>G:p.K451E	0.0005	0.0009621	20.4	1	

ITIH3	3	52836533	G	A	rs74320783	ITIH3:NM_002217: exon12:c.1567G>A:p.G523R	0.0087	0.007854	33	1	
ITIH3	3	52833078	G	A	rs199634029	ITIH3:NM_002217: exon7:c.760G>A:p.V254M	0.0003	0.0002686	31	1	
ITIH4	3	52857988	C	T	rs74971919	ITIH4:NM_001166449: exon10:c.1204G>A:p.V402M	0.0013	0.001455	25	1	
NISCH	3	52522297	G	A	rs150644559	NISCH:NM_007184: exon16:c.2789G>A:p.R930H	0.007	0.008041	17.21	1	
SATB1	3	18458436	G	T	n.a.	SATB1:NM_001131010: exon3:c.346C>A:p.L116M	n.a.	n.a.	24.9	1	
STAB1	3	52548194	C	T	rs139838594	STAB1:NM_015136: exon33:c.3511C>T:p.R1171C	0.0022	0.001995	16.71	1	
STAB1	3	52547252	A	G	rs41292856	STAB1:NM_015136: exon30:c.3265A>G:p.S1089G	0.0003	0.001815	15.29	2	
TLR9	3	52255901	C	T	rs201411213	TLR9:NM_017442: exon2:c.2431G>A:p.D811N	$8.48x10^{-3}$	$2.13x10^{-5}$	26.7	1	
ANK2	4	114279628	T	C	rs36210417	ANK2: NM_001148: exon38:c.9854T>C:p.I3285T	0.0082	0.008634	25		1
ANK2	4	114278578	C	A	n.a.	ANK2:NM_001148: exon38:c.8804C>A:p.S2935Y	n.a.	n.a.	19.71	1	
ANK2	4	114286207	T	A	rs66785829	ANK2: NM_001148: exon41: c.10901T>A: p.V3634D	0.0027	0.002367	24.7	4	
ANK2	4	114254358	G	C	n.a.	ANK2:NM_001148: exon29:c.3373G>C:p.D1125H	n.a.	$1.061x10^{-5}$	26.2	1	
ANK2	4	114279597	G	A	n.a.	ANK2:NM_001148: exon38:c.9823G>A:p.D3275N	n.a.	$1.19x10^{-5}$	24.6	1	
ANK2	4	114275451	G	T	n.a.	ANK2:NM_001148: exon38:c.5677G>T:p.V1893L	n.a.	n.a.	22.5	1	
ANK2	4	114279549	T	C	n.a.	ANK2:NM_001148: exon38:c.9775T>C:p.S3259P	n.a.	n.a.	21.4		1
ANK2	4	114294462	C	T	rs121912706	ANK2: NM_001148: exon43: c.11716C>T: p.R3906W	0.0011	0.001066	20.9	2	
CLCN3	4	170641112	G	A	rs149400550	CLCN3:NM_173872: exon14:c.G2497G>A:p.G833S	0.0043	0.004556	21.5	1	
PAM	5	102309844	A	G	rs111855745	PAM:NM_000919: exon14:c.1187A>G:p.K396R	0.0001	$7.98x10^{-5}$	20.9	1	
PAM	5	102282589	C	T	rs78753846	PAM:NM_000919: exon7:c.575C>T:p.P192L	0.0081	0.00674	27.8	1	
RIMS1	6	72678706	C	T	n.a.	RIMS1:NM_014989: exon2:c.185C>T:p.A62V	$3.31x10^{-2}$	$2.00x10^{-5}$	17.15	1	
ZNF184	6	27420048	G	C	rs61736956	ZNF184:NM_007149: exon6:c.1290C>G:p.H430Q	0.0097	0.009688	19.9	1	
C8orf58	8	22458457	C	G	rs145988500	C8orf58:NM_001013842: exon2:c.103C>G:p.R35G	0.0095	0.009268	27	1	

SORBS3	8	22423972	C	G	rs150705192	SORBS3:NM_001018003: exon2:c.39C>G:p.D13E	0.0036	0.003543	27	1	
SH3GL2	9	17793463	G	T	rs150543523	SH3GL2:NM_003026: exon8:c.G827T:p.G276V	0.0035	0.003668	24.4	3	
UBAP2	9	33956096	G	T	rs200331065	UBAP2:NM_018449: exon11:c.847C>A:p.H283N	0.0004	0.0003825	17.16	1	
FAM171A1	10	15296725	C	T	n.a.	FAM171A1:NM_001010924: exon4:c.572G>A:p.G191E	n.a.	n.a.	16.23	1	
FAM171A1	10	15262960	A	C	rs780797236	FAM171A1:NM_001010924: exon6:c.854T>G:p.M285R	$8.26X10^{-3}$	$1.195x10^{-5}$	28.9	1	
RNF141	11	10546851	T	C	rs61760882	RNF141:NM_016422: exon4:c.322A>G:p.K108E	0.0026	0.002802	18.21	1	
SCAF11	12	46320272	C	T	rs146183261	SCAF11:NM_004719: exon11:c.3212G>A:p.R1071H	0.0001	7.077E-06	19.83	1	
SCAF11	12	46345447	C	T	rs201119358	SCAF11:NM_004719: exon4:c.283G>A:p.E95K	0.0009	0.0008595	23.6	1	
NOD2	16	50750810	A	G	rs104895467	NOD2: NM_022162: exon6:c.2555A>G:p.N852S	0.0012	0.001092	18.52	1	
NOD2	16	50745929	C	T	rs5743277	NOD2: NM_022162: exon4:c.2107C>T:p.R703C	0.0033	0.003167	16.15	1	
NOD2	16	50756540	G	C	rs2066845	NOD2:NM_022162: exon8:c.2722G>C:p.G908R	0.0099	0.0002015	23	2	
NOD2	16	50746086	C	T	rs61747625	NOD2: NM_022162: exon4:c.2264C>T:p.A755V	0.0023	0.002519	24.4	1	
TOX3	16	52497869	G	A	rs201752610	TOX3:NM_001080430: exon3:c.385C>T:p.L129F	0.0007	0.0006746	22.4		1
FAM171A2	17	42433912	G	T	rs150823411	FAM171A2:NM_198475: exon4:c.484C>A:p.R162S	0.0017	0.001046	22.2	1	
PSMC3IP	17	40729267	C	A	rs139657728	PSMC3IP:NM_013290: exon3:c.189G>T:p.K63N	0.0005	0.0005303	26.6	1	
ASXL3	18	31326012	T	G	rs144534810	ASXL3:NM_030632: exon12:c.6200T>G:p.L2067R	0.0063	0.006666	16	1	
CRLS1	20	5986989	G	A	rs756560223	CRLS1:NM_019095: exon1:c.97G>A:p.A33T	n.a.	0.001086	15.2	1	

Legend: Chr: chromosome;Ref:reference allele; Alt: alternate allele; SNP: single nucleotide polymorphism; ExAC frequency: Exome Aggregation Consortium; GnomAD: Genome Aggregation Database CADD score: combined annotation dependent depletion score; Nr. of cases: numbers of cases; Nr. of controls: numbers of controls

Supplementary table 4. Double mutation carriers and clinical course

MUTATION	ID	Sex	Age	AAO	FH	Population	Pathogenic variants	Median AAO of mutation carrier**	Initial signs/symptoms of mutation carrier**
DNAH1 p.A3639T	L-295	female	n.a.	45	yes.	German	*LRRK2* het p.R1441C	58	Tremor (50% of patients)
	L-2501	male	n.a.	n.a.	yes.	German	*LRRK2* het p.R1441C	58	Tremor (50% of patients)
STAB1 p.S1089G	L-2124	female	68	53	yes	German	*PINK1* homo p.Gln456*	37	Bradykinesia (36% of patients)
	L-2126	female	72	47	yes	German	*PINK1* homo p.Gln456*	37	Bradykinesia (36% of patients)
ANK2 p.V3634D	L-3035	male	40	35	no	n.a.	*PRKN* het Ex3-4 Del.+ het Ex7-9 Dupl[%]	34	Tremor (50% of patients)
SH3GL2 p.G276V	L-649	male	n.a.	16	yes	German	*PRKN* het p.R275W[$]	41	Tremor (50% of patients)
NOD2 p.G908R	L-1888	female	25	19	no	German	*PRKN* het p.R275W and Ex1 Dupl[%]	33	Tremor (42% of patients)

**Data obtained from MDSGene database, filtering for the specific pathogenic variants identified for summary clinical statistics. [$]=could not filter for heterozygous patients only as the database did not contain any heterozygous mutation carriers, thus filtered for homozgous. [%]filtered for any patient with compound heterozygous variants that include the specific pathogenic mutation of interest

Supplementary table 5. Single variant association testing

Chr	Gene	Position (hg19)	Ref	Alt	Amino acid change	OR	95% CI	p -value
3	*DNAH1*	52429022	G	A	p.A3639T	1.20	0.52 to 2.76	0.08
3	*STAB1*	52547252	A	G	p.S1089G	2.87	1.61 to 5.13	0.0008
4	*ANK2*	114286207	T	A	p.V3634D	1.59	0.95 to 2.66	0.08
4	*ANK2*	114294462	C	T	p.R3906W	1.42	0.72 to 2.81	0.30
9	*SH3GL2*	17793463	G	T	p.G276V	2.08	1.40 to 3.08	0.0009
16	*NOD2*	50756540	G	C	p.G908R	3.45	2.77 to 4.28	<0.0001

PD vs. healthy individuals are compared in this table. Legend: Chr: chromosome; Ref:reference allele; Alt: alternate allele; OR: odds ratio; CI: confidence interval

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