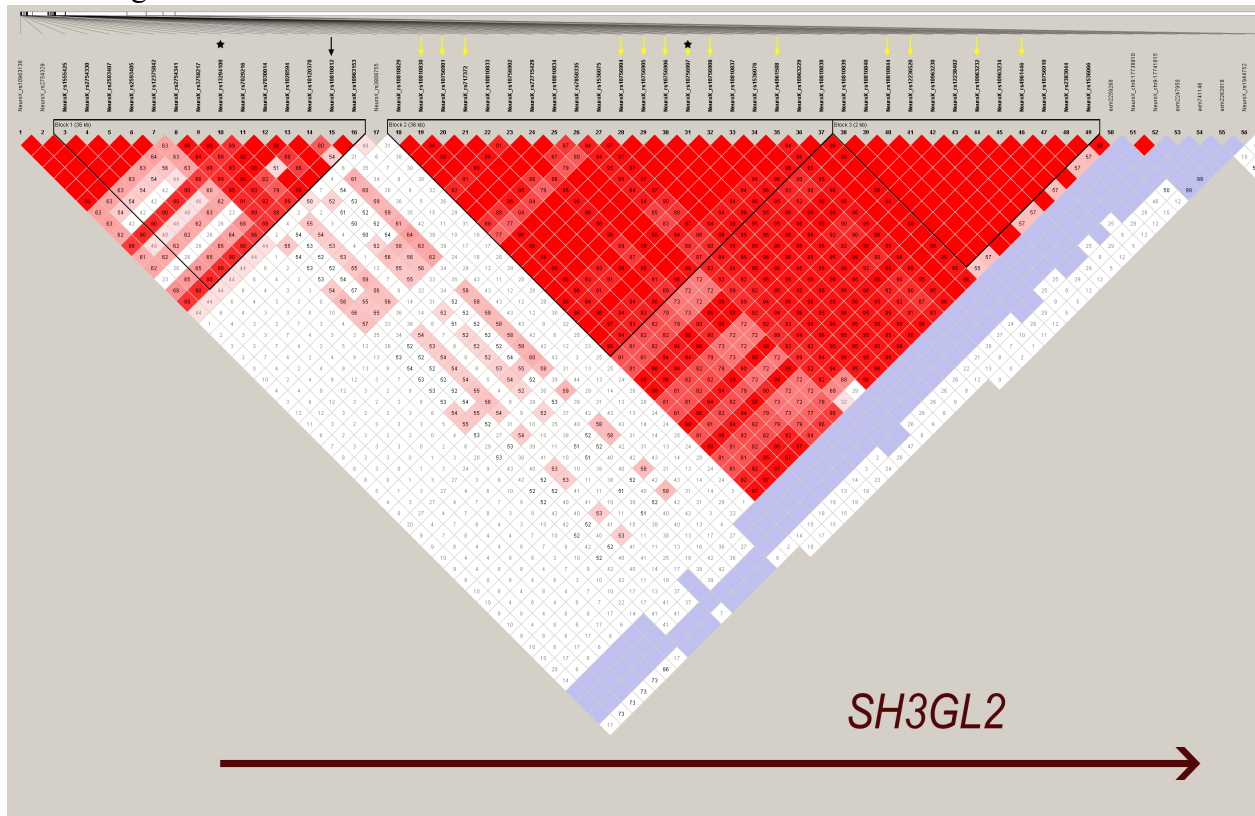


Supplementary Material

Axial Impairment Following Deep Brain Stimulation in Parkinson's Disease: A Surgicogenomic Approach

Supplementary Figure 1. LD-structure of the *SH3GL2* locus. The *SH3GL2* locus (based on the 150 investigated patients with Parkinson's Disease) is tagged by 13 SNPs (yellow arrows) belonging to a single LD-block, while rs10810812 (a black arrow) belongs to a different LD-block. Two SNPs (rs13294100, rs10756907) that were previously reported to be associated with PD at a GWAS-significant level are marked with a star.



Supplementary Table 1. A list of the 113 genes most recently reported to be Parkinson's disease loci.

Gene symbol	Gene Name	CYTOBAND
ASXL3	additional sex combs like 3, transcriptional regulator (ASXL3)	18q11
BAG3	BCL2 associated athanogene 3 (BAG3)	10q26.11
BIN3	bridging integrator 3 (BIN3)	8p21.3
BRIP1	BRCA1 interacting protein C-terminal helicase 1 (BRIP1)	17q23.2
BST1	bone marrow stromal cell antigen 1 (BST1)	4p15
C5orf24	chromosome 5 open reading frame 24 (C5orf24)	5q31.1
CAB39L	calcium binding protein 39 like (CAB39L)	13q14.2
CAMK2D	calcium/calmodulin dependent protein kinase II delta (CAMK2D)	4q26
CASC16	cancer susceptibility candidate 16 (non-protein coding) (CASC16)	16q12.1
CD19	CD19 molecule (CD19)	16p11.2
CHD9	chromodomain helicase DNA binding protein 9 (CHD9)	16q12.2
CHRNB1	cholinergic receptor nicotinic beta 1 subunit (CHRNB1)	17p13.1
CLCN3	chloride voltage-gated channel 3 (CLCN3)	4q33
CNTN1	contactin 1 (CNTN1)	12q12
CRHR1	corticotropin releasing hormone receptor 1 (CRHR1)	17q21.31
CRLS1	cardiolipin synthase 1 (CRLS1)	20p12.3
CTSB	cathepsin B (CTSB)	8p22
CUEDC2	CUE domain containing 2 (CUEDC2)	10q24.32
CYLD	CYLD lysine 63 deubiquitinase (CYLD)	16q12.1
DDRGK1	DDRGK domain containing 1 (DDRGK1)	20p13
DLG2	discs large MAGUK scaffold protein 2 (DLG2)	11q14.1
DNAH17	dynein axonemal heavy chain 17 (DNAH17)	17q25.3
DYRK1A	dual specificity tyrosine phosphorylation regulated kinase 1A (DYRK1A)	21q22.13
ELOVL7	ELOVL fatty acid elongase 7 (ELOVL7)	5q12.1
FAM171A2	family with sequence similarity 171 member A2 (FAM171A2)	17q21.31
FAM47E	family with sequence similarity 47 member E (FAM47E)	4q21.1
FAM47E-STBD1	FAM47E-STBD1 readthrough (FAM47E-STBD1)	4q21.1
FAM49B	family with sequence similarity 49 member B (FAM49B)	8q24.21
FBRSL1	fibrosin like 1 (FBRSL1)	12q24.33
FCGR2A	Fc fragment of IgG receptor IIa (FCGR2A)	1q23
FGD4	FYVE, RhoGEF and PH domain containing 4 (FGD4)	12p11.21
FGF20	fibroblast growth factor 20 (FGF20)	8p22
FYN	FYN proto-oncogene, Src family tyrosine kinase (FYN)	6q21
GAK	cyclin G associated kinase (GAK)	4p16
GALC	Galactosylceramidase (GALC)	14q31
GBA	glucosylceramidase beta (GBA)	1q21
GBAP1	glucosylceramidase beta pseudogene 1 (GBAP1)	1q21

GBF1	golgi brefeldin A resistant guanine nucleotide exchange factor 1 (GBF1)	10q24
GCH1	GTP cyclohydrolase 1 (GCH1)	14q22.2
GPNMB	glycoprotein nmb (GPNMB)	7p15
GRN	granulin precursor (GRN)	17q21.32
GS1-124K5.11	RAB guanine nucleotide exchange factor 1 pseudogene (GS1-124K5.11)	7q11.21
GXYLT1	glucoside xylosyltransferase 1(GXYLT1)	12q12
HIP1R	huntingtin interacting protein 1 related (HIP1R)	12q24
HLA-DRB5	major histocompatibility complex, class II, DR beta 5 (HLA-DRB5)	6p21.3
IGSF9B	immunoglobulin superfamily member 9B (IGSF9B)	11q25
INPP5F	inositol polyphosphate-5-phosphatase F (INPP5F)	10q26.11
IP6K2	inositol hexakisphosphate kinase 2 (IP6K2)	3p21.31
ITGA8	integrin subunit alpha 8 (ITGA8)	10p13
ITPKB	inositol-trisphosphate 3-kinase B (ITPKB)	1q42.13
KANSL1	KAT8 regulatory NSL complex subunit 1 (KANSL1)	17q21.31
KCNIP3	potassium voltage-gated channel interacting protein 3 (KCNIP3)	2q21.1
KCNS3	potassium voltage-gated channel modifier subfamily S member 3 (KCNS3)	2p24
KPNA1	karyopherin subunit alpha 1 (KPNA1)	3q21
KRTCAP2	keratinocyte associated protein 2 (KRTCAP2)	1q22
LCORL	ligand dependent nuclear receptor corepressor like (LCORL)	4p15.32
LINC00174	long intergenic non-protein coding RNA 174 (LINC00174)	7q11.21
LINC00693	long intergenic non-protein coding RNA 693 (LINC00693)	3p24.1
LOC100131289	uncharacterized LOC100131289 (LOC100131289)	6p22.1
LRRK2	leucine rich repeat kinase 2 (LRRK2)	12q12
MAP3K14	mitogen-activated protein kinase kinase kinase 14 (MAP3K14)	17q21
MAP4K4	mitogen-activated protein kinase kinase kinase kinase 4 (MAP4K4)	2q11.2
MAPT-AS1	MAPT antisense RNA 1 (MAPT-AS1)	17q21.31
MBNL2	muscleblind like splicing regulator 2 (MBNL2)	13q32.1
MCCC1	methylcrotonoyl-CoA carboxylase 1 (MCCC1)	3q27
MED12L	mediator complex subunit 12 like (MED12L)	3q25.1
MED13	mediator complex subunit 13 (MED13)	17q23.2
MEX3C	mex-3 RNA binding family member C (MEX3C)	18q21.2
MIPOL1	mirror-image polydactyly 1 (MIPOL1)	14q13.3-q21.1
NEK1	NIMA related kinase 1 (NEK1)	4q33
NFATC2IP	nuclear factor of activated T-cells 2 interacting protein (NFATC2IP)	16p11.2
NOD2	nucleotide binding oligomerization domain containing 2 (NOD2)	16q21
NSF	N-ethylmaleimide sensitive factor, vesicle fusing ATPase (NSF)	17q21

NUCKS1	nuclear casein kinase and cyclin dependent kinase substrate 1 (NUCKS1)	1q32.1
PAM	peptidylglycine alpha-amidating monooxygenase (PAM)	5q21.1
PRKN	parkin RBR E3 ubiquitin protein ligase (PARK2)	6q26
PARK7	Parkinsonism associated deglycase (PARK7)	1p36.23
PINK1	PTEN induced putative kinase 1 (PINK1)	1p36
PMVK	phosphomevalonate kinase (PMVK)	1q22
PRSS3	protease, serine 3 (PRSS3)	9p11.2
RAB29	RAB29, member RAS oncogene family (RAB29)	1q32
RETREG3	reticulophagy regulator family member 3	17q21.2
RIMS1	regulating synaptic membrane exocytosis 1 (RIMS1)	6q12-q13
RIT2	Ras like without CAAX 2 (RIT2)	18q12.3
RNF141	ring finger protein 141 (RNF141)	11p15.4
RPS12	ribosomal protein S12 (RPS12)	6q23.2
RPS6KL1	ribosomal protein S6 kinase like 1 (RPS6KL1)	14q24.3
SATB1	SATB homeobox 1 (SATB1)	3p23
SCAF11	SR-related CTD associated factor 11 (SCAF11)	12q12
SCARB2	scavenger receptor class B member 2 (SCARB2)	4q21.1
SEC23IP	SEC23 interacting protein (SEC23IP)	10q26.11-q26.12
SEMA4A	semaphorin 4A (SEMA4A)	1q22
SETD1A	SET domain containing 1A (SETD1A)	16p11.2
SH3GL2	SH3 domain containing GRB2 like 2, endophilin A1 (SH3GL2)	9p22
SIPA1L2	signal induced proliferation associated 1 like 2 (SIPA1L2)	1q42.2
SLC44A4	solute carrier family 44 member 4 (SLC44A4)	6p21.3
SMPD1	sphingomyelin phosphodiesterase 1 (SMPD1)	11p15.4
SNCA	synuclein alpha (SNCA)	4q21
SPPL2B	signal peptide peptidase like 2B (SPPL2B)	19p13.3
SPTSSB	serine palmitoyltransferase small subunit B (SPTSSB)	3q26.1
STK39	serine/threonine kinase 39 (STK39)	2q24.3
SYT17	synaptotagmin 1 7(SYT17)	16p12.3
TMEM163	transmembrane protein 163 (TMEM163)	2q21.3
TMEM175	transmembrane protein 175 (TMEM175)	4p16.3
TRIM40	tripartite motif containing 40 (TRIM40)	6p21.33
TXNDC15	thioredoxin domain containing 15 (TXNDC15)	5q31.1
UBAP2	ubiquitin associated protein 2 (UBAP2)	9p13.3
UBTF	upstream binding transcription factor, RNA polymerase I (UBTF)	17q21.3
VAMP4	vesicle associated membrane protein 4 (VAMP4)	1q24.3
VPS13C	vacuolar protein sorting 13 homolog C (VPS13C)	15q22.2
VPS35	VPS35, retromer complex component (VPS35)	16q12.7
WNT3	Wnt family member 3 (WNT3)	17q21
ZNF608	zinc finger protein 608 (ZNF608)	5q23.2

Cluster	NeuroX marker	Gene	Function	CHR	Position	A1	F_E	F_M	A2	CHISQ	P	OR
LT Axial	NeuroX_rs7244651	RIT2	intronic	18	40655156	C	0.050	0.191	T	4.82	0.028	0.2
LT Axial	NeuroX_rs11877437	RIT2	intronic	18	40658446	G	0.050	0.191	A	4.82	0.028	0.2
LT Axial	NeuroX_rs9948019	RIT2	intronic	18	40660098	G	0.050	0.191	A	4.82	0.028	0.2
LT Axial	NeuroX_rs868763	BST1;CD38	intergenic	4	15755905	C	0.050	0.203	T	5.43	0.020	0.2
LT Axial	NeuroX_rs9949064	RIT2	intronic	18	40678087	G	0.050	0.268	A	9.05	0.003	0.1
LT Axial	NeuroX_rs8096948	RIT2	intronic	18	40681293	C	0.050	0.268	T	9.05	0.003	0.1
LT Axial	NeuroX_rs12458426	RIT2	intronic	18	40679358	C	0.050	0.271	T	9.19	0.002	0.1
LT Axial	NeuroX_rs884474	BST1;CD38	intergenic	4	15756270	A	0.026	0.189	T	6.25	0.012	0.1
LT Axial	exm-rs6599389	TMEM175	intronic	4	939113	A	0.000	0.118	G	5.25	0.022	0.0
LT Axial	NeuroX_rs9468216	89	intergenic	6	27721304	T	0.000	0.103	C	3.86	0.049	0.0
LT Axial	exm-rs3132676	TRIM40	UTR3	6	30116078	T	0.000	0.114	C	5.05	0.025	0.0

A1, allele 1; A2, allele 2; Axial, Axial subscore of the Unified Parkinson's Disease Rating Scale; CHISQ, chi-square association test; CHR, chromosome; F_E, allele frequency in excellent outcome group; F_M, allele frequency in moderate/poor outcome subgroup; P, p value; OR, odds ratio; LEDD, levodopa equivalent daily dose (mg/day); LT, long-term (~5 years); ST, short-term (~1 year).

Supplementary Table 3. Comparison of baseline clinical characteristics for patients with and without the observed rare variants in IP6K2, PRSS3, and CRHR1 and between patients with AA vs GG genotype of rs10810812 in SH3GL2.

Preclinical variable	IP6K2			PRSS3			CRHR1			SH3GL2		
	median (N)	variants	non-variants	p	variants	non-variants	p	variants	non-variants	p	AA	GG
Age at onset (y)	60.0 (3)	45.0 (145)	0.21	42.0 (3)	45.0 (145)	0.83	48.0 (5)	45.0 (143)	0.25	45.0 (54)	48.0 (22)	0.37
Age at surgery (y)	66.0 (3)	58.0 (145)	0.11	63.0 (3)	58.0 (145)	0.33	66.0 (5)	58.0 (143)	0.03	57.5 (54)	60.5 (22)	0.07
Disease duration at surgery (y)	9.0 (3)	11.0 (145)	0.52	20.0 (3)	11.0 (145)	0.21	17.0 (5)	11.0 (143)	0.35	11.0 (54)	11.0 (22)	0.71
Pre-op UPDRS-III OFF L-dopa	39.5 (3)	39.0 (145)	0.77	38.5 (3)	39.5 (145)	0.87	41.0 (5)	39.0 (143)	0.43	40.0 (54)	39.3 (22)	0.26
Pre-op UPDRS-III ON L-dopa	16.0 (3)	15.0 (143)	0.64	14.0 (3)	15.0 (143)	0.43	14.0 (5)	15.0 (141)	0.70	15.0 (54)	13.5 (22)	0.39
L-dopa responsiveness (%)	57.6 (3)	62.2 (143)	0.51	69.3 (3)	61.5 (143)	0.74	57.1 (5)	61.8 (141)	0.95	63.7 (54)	61.2 (22)	0.83
Pre-op LEDD	970.0 (3)	1500 (144)	0.05	1680 (3)	1472 (144)	0.51	1650 (5)	1472 (142)	0.48	1560 (54)	1405 (22)	0.79
Pre-op axial subscore	6.50 (3)	8.0 (145)	0.20	10.0 (3)	8.0 (145)	0.29	9.0 (5)	8.0 (143)	0.51	8.3 (54)	6.3 (22)	0.09