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Supplementary Online Content

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Supplementary Note Methods

Figure 1, Supplementary Table 1 and Supplementary Table 4
Euclidean distances from idiopathic Parkinson's disease was calculated based on 29 factors for the 22 genetic forms (see **Supplementary Table 4 for data on the distance metrics**). Data were plotted versus average age of onset for all variants. The size of each circle represents the relative frequency of the genetic forms. To aid in visualization, the radius of the circles are scaled relative to the most common form by subtracting the log2 value of the observed prevalence from the log2 value of the least-common form. These factors allowed for easier visualization of the relative frequency over the observed range. However, it should be noted that the scale is not linear with respect to the actual observed frequencies and the reader is referred to Supplementary Table 1 for more detail. Because there are varying degrees of robustness of neuropathological data, color shades was used to reflect this as follows: dark blue indicates Lewy body pathology in all cases; medium blue indicates variable findings with the majority of cases showing Lewy body pathology; light blue indicates Lewy body pathology in only a few cases; yellow indicates Lewy body pathology was not found but the data is sparse or incomplete; orange indicates no data was available. The area between the grey hashed lines indicates early-onset parkinsonism and below the bottom grey hash line, juvenile (<20y) parkinsonism.

Supplementary Figure 1A-C, Supplementary Table 5
We accessed STRING DB and exported the protein interaction network for all human proteins. We visualized the protein interaction networks from this data for three groupings of genes found in **Supplementary Table 1** as described in the text and figure legend. We used the HUGO terms in STRING DB to identify the gene products and interactors. Knowledge Explorer ™ (available from IO Informatics) was used to visualize the protein interaction network from STRING DB for the gene products of interest (**Figures 1A-C**). The list of proteins that interact with the highly validated MLBD associated genes *LRRK2, GBA, SNCA* are shown in Figure 1C and can be found in **Supplementary Table 5**. The full list of protein interactions for genes with mutations that are known to cause parkinsonism but do not always manifest with the same neuropathological findings are shown in **Figure 1A** (*LRRK2, GBA, SNCA, VPS35, DJ-1, PINK1, PARK2* and *DNAJ13C*), and can be found at http://www.thepi.org/scientific-resources/.

Supplementary Table 1: Genes implicated in Multisystem Lewy body disease and parkinsonism

HUGO gene name, symbol, locus, reference sequence	Mutation types causing primary disease	Inheritance and name of primary disease	Age at onset in years (mean, SD or SEM)	Clinical presentation	Neuropathology	Peripheral autonomic involvement
A. Multisystem Lewy body disease: Mutations in genes causative for Parkinson's disease-like syndrome, with the neuropathological hallmark of Lewy bodies, and evidence of peripheral autonomic nervous system involvement						
Synuclein, alpha (non A4 component of amyloid precursor), *SNCA*,chr4q21-22, NM_000345.3	Five point mutations described: c.88G>C (p.Ala30Pro)[1,2], c.136G>A (p.Glu46Lys)[3], c.150T>G (p.His50Gln)[4,5], c.152G>A (p.Gly51Asp)[6-9], c.157G>A (p.Ala53Thr)[10-15], gene duplication[16-20] and gene triplication[21-24], partial trisomy chromosome 4q[25]	Autosomal Dominant	p.Ala53Thr: 47 (SD 12), p.Ala30Pro: 60 (SD 11), p.Glu46Ly: 60 (SD 7), dup: 50 (SD 11), trip: 40 (SD 14)[26]	Present with parkinsonian motor features, but may have more rapid motor progression and frequent dementia	All cases have alpha-synuclein positive Lewy bodies, Lewy neurites and neuronal cells loss in the substantia nigra and other areas in a distribution similar to that seen in MLBD[27]. Additional neuropathological findings include, 5 cases with glial cytoplasmic inclusions reminiscent of multiple system atrophy[27], variable distribution of tau pathology in 9 cases[27], one case with TDP-43 inclusions consistent with frontotemporal dementia (FTLD)[27].	Cardiac MIBG scintigraphy scan suggesting cardiac denervation in c.136G>A (p.Glu46Lys)[28,29], SNCA duplication[30] and triplication[31]
B. Mixed: Multisystem Lewy body disease in some but not all: Mutations in genes causative for Parkinson's disease-like syndrome, neuropathological hallmark of Lewy bodies in some cases but also pleomorphic pathology, and some evidence of peripheral autonomic nervous system involvement						
Leucine-rich repeat kinase 2, *LRRK2,* chr12q12, NM_198578.3	Seven pathogenic mutations described: c.4309C>A (p.Asn1437His[32]), c.4321C>T (p.Arg1441Cys)[33], c.4321C>G (p.Arg1441Gly)[34], c.4883G>C (p.Arg1628Pro)[35,36], c.5096A>G (p.Tyr1699Cys)[34], c.6055G>A (p.Gly2019Ser)[37], c.6059T>C (p.Ile2020Thr)[33], c.7153G>A (p.Gly2385Arg)[38,39]	Autosomal dominant with high, but incomplete penetrance (67%)[40,41]	Mean 58.1 (SD14)[42]	Present with parkinsonian motor features, but motor and non-motor symptoms are more benign compared to idiopathic PD[42]	35 of 37 LRRK2-related PD cases show neuronal loss in the substantia nigra (2 cases had no data), 17 LRRK2 cases had alpha-synuclein positive Lewy bodies similar to that seen in MLBD, 20 cases had no Lewy body pathology[43]. Furthermore, 14 cases with LRRK2 p.Gly2019Ser has been described elsewhere[44-47] with alpha-synuclein positive Lewy bodies similar to that seen in MLBD. Additional neuropathological findings include tau inclusions (22/28 reported cases) and TDP-43 inclusions in three cases[27].	Cardiac MIBG scintigraphy scan suggesting cardiac denervation in 3 of 6 cases[48]
C. Parkinson's disease, but Multisystem Lewy body disease has not been ruled out due to lack of data: Mutations in genes associated with other diseases, but carriers as well as disease subjects at risk for developing Parkinson's disease-like syndrome and have the neuropathological hallmark of Lewy bodies, but data lacking on peripheral autonomic nervous system involvement.						
Glucosidase, beta, acid, *GBA*, chr1q22, NM_000157.3	Nearly 300 mutations detected of which four common mutations detected in 89% of Gaucher Disease patients[49]: c.1226A>G (p.Asn370Ser) c.1448T>C (p.Leu444Pro) c.84_85insG, (p.Leu29Alafs*18)	Autosomal Recessive, Gaucher disease	Slightly earlier onset (~5 years earlier, mean 59.39 (SEM	*GBA* mutation carriers and patients with Gaucher disease are both at risk (5-6 fold increase in risk) of developing parkinsonian motor features; may present	From four studies, 10 autopsies from subjects with Gaucher disease and parkinsonism had alpha-synuclein positive Lewy bodies, Lewy neurites and cells loss in the substantia nigra and other areas in a distribution similar to that seen in MLBD. 77 of 80 GBA heterozygote carriers and parkinsonism showed alpha-synuclein	No data to confirm or refute

	c.115+1G>A		2.1)[50 51]	with more prominent hyposmia and cognitive decline[50,51]	positive Lewy bodies, no consistent detailed reports on cell loss in the substantia nigra[27,52-54]	
D. Likely MLBD, but more data needed: Mutations in genes causative for Parkinson's disease-like syndrome, limited histopathological phenotype of Lewy body Parkinson's Disease, minimal or no evidence of peripheral autonomic nervous system involvement limited or lacking						
PTEN induced putative kinase 1, *PINK1*, chr1p35-36, NM_032409.2	Over 80 variants resulting in deletions and missense, nonsense, frameshift, and copy number mutations[55]	Autosomal Recessive	36.0 (SD 6.9)[56-58]	Parkinsonian motor features with earlier onset	Only one case has been reported with alpha-synuclein positive Lewy bodies and Lewy neurites and cells loss in the substantia nigra, with sparing of the locus coeruleus which is less common in MLBD[59]	Cardiac MIBG scintigraphy scan suggesting cardiac denervation in 1 of 2 brothers[48]
DnaJ (Hsp40) homolog, subfamily C, member 13, *DNAJC13*, chr3q22.1, NM_015268.3	c.2564A>G (p.Asn855Ser)[60,61]	Autosomal Dominant	67.0 (SD 9.5)[60]	Parkinsonian motor features; Note: to date only one missense mutation has been reported; pedigree shows partial segregation with two mutation negative PD cases (phenocopies)[60]; p.Asn855Ser found in 2 patients with essential tremor[62]	Three mutation carrier with clinical diagnosis of Parkinson's disease from one family (SK1) have alpha-synuclein positive Lewy bodies, Lewy neurites and cells loss in the substantia nigra and other areas in a distribution similar to that seen in MLBD[61], in the same family one case with atypical parkinsonism and without p.Asn855Ser mutation showed PSP pathology [61]	No data to confirm or refute
E. Majority are parkinsonism, but unlikely MLBD: Mutations in genes causative for Parkinson's disease-like syndrome, majority of neuropathology reports show absence of Lewy bodies, and little evidence of peripheral autonomic involvement.						
Parkin RBR E3 ubiquitin protein ligase, *PARK2*, chr6q25.2-p27 NM_004562.2	Over 180 variants described: point mutations (~50% of cases) and copy number variants (~50% of cases)[63]	Autosomal Recessive	Mean 29.2 (SD 10.4)[42], if age at onset <20, PARKIN mutations found in up to 77% of cases, range 8-58[64]	Parkinsonian motor features, benign slow course[65]	Of 21 total published cases with mutations on both alleles, 15 cases with neuronal loss in substantia nigra pars compacta and no Lewy body pathology, 5 cases reported alpha-synuclein positive Lewy bodies and/or Lewy neurites and cell loss in the substantia nigra and other areas, 1 had basophilic LB-like inclusions, brainstem transitional Lewy Body disease[27,66-78]. Of 3 cases with mutations on one allele, 2 cases are reported as typical alpha-synuclein positive Lewy bodies, Lewy neurites and cells loss in the substantia nigra and other areas in a distribution similar to that seen in MLBD[79,80] and 1 case showed PSP pathology[81].	MIGB abnormal in 1 of 4 cases[48], normal MIBG in 2 patients with homozygous exon 4 deletion and corresponding LB-negative autopsy[71], 8 *PARK2* cases less pronounced changes in MIGB compared to iPD[68]
Vacuolar protein sorting 35 homolog (S. cerevisiae), *VPS35*,	c.1858G>A (p.Asp620Asn)[82,83] (overall 29 affected mutation carriers reported[84]	Autosomal Dominant	51.4 (SD 8.6)[84-86]	Parkinsonian motor features	Pathology on limited brain tissue (cortex and basal ganglia) staining for alpha-synuclein was negative[87] with no neuronal loss, gliosis, senile plaques, neurofibrillary tangles or intraneuronal inclusions.	No data to confirm or refute

chr16q11.2, NM_018206.4						
Daisuke-Junko 1, *DJ-1* chr1p36 NM_001123377.1	Multiple point mutations[88]	Autosomal Recessive	34.8 (SD 10.4)[89]	Parkinsonian motor features but earlier onset, similar to PARKIN, fewer cases identified and studied	No pathology reported[27]	No data to confirm or refute
GTP cyclohydrolase 1, *GCH1,* Chr14q22.1-22.2, NM_000161.2	More than 100 point mutations and copy number variants[90]	Autosomal-dominant or recessive with incomplete penetrance; DOPA-responsive dystonia (DRD, DYT5)	Mean 6 for DRD, in cases with parkinsonism 61.0 (SD10.9)	Two distinct clinical presentations: 1. Dystonia in limbs, typically foot dystonia (equinovarus posture) resulting in gait disturbance, later development of parkinsonism, dramatic sustained response to L-Dopa[91], 2. Parkinsonian motor features [92]	In DRD cases, marked reduction or melanin pigment and dopamine content in nigrostriatal neurons, but no evidence of nigral cell loss or degeneration[93]; only 1 case has been reported with alpha-synuclein positive Lewy bodies and cell loss in the substantia nigra and concomitant tau-immunoreactive neurofibrillary tangles[94]	No data to confirm or refute
F. Other neurological disease with additional concomitant parkinsonism, MLBD cannot be ruled out: Mutations in genes associated with other diseases that can have a parkinsonian component and may also cause or be a risk factor for Parkinson's disease, but Lewy body pathology is documented in three or fewer cases and data lacking on peripheral autonomic nervous system involvement.						
Ataxin 2, *ATXN2*, chr12q24.12, NM_002973.3	CAG-repeat (normal: 15–32; expanded: 33–64), in 2.34% of familial PD in Japan intermediate repeat lengths (25-35)[95]	Autosomal dominant; Spino cerebellar ataxia-2 (SCA-2)	Parkinsonism: mean 49.9 (SD 16.1)[59,95,96], CAG repeat length 36.2 +/- 1.1; SCA2 mean 26.9 (SD 11.0) and 43.1 +/- 3.2)[97]	progressive ataxia, dysarthria/dysphagia, some patients present with parkinsonism[98-100]	Two cases reported: first case presents with alpha-synuclein positive Lewy bodies and Lewy neurites and cells loss in the substantia nigra and other areas in a distribution similar to that seen in typical idiopathic PD[59]; second case presented with atrophy of olivo-ponto-cerebellar system and substantia nigra which compatible to SCA2 and Lewy body related pathological changes in the substantia nigra, the locus coeruleus, the dorsal motor nuclei of vagus (same patient also shows Lewy body pathology in the periphery)[101]	Lewy body related pathological changes in myocardial sympathetic nerve; cardiac MIBG scan suggesting cardiac denervation in patient with 38/40 repeats[101]; reduced MIBG in SCA-2 cases, not as prominent as in MLBD[102]
22q11 deletion	1.5 Mb to 3Mb deletion on chromosome 22q11	Spontaneous; Di George syndrome	40.8 (SD 6.7)[103]	Di George syndrome with risk for early onset parkinsonism[104-106], 7 cases total reported but only seen in subjects carrying the 3Mb deletion, precise gene unknown	Alpha-synuclein positive Lewy bodies and Lewy neurites and cells loss in the substantia nigra and other areas in a distribution similar to that seen in MLBD reported in 3 or 3 cases[103]	No data to confirm or refute
Chromosome 19	missense, nonsense,	Autosomal	Mean 10.1	Pallido-pyramidal	Neurodegeneration with Brain Iron	No data to confirm or

open reading frame 12, *C19orf12*, chr19q12, NM_001282931.1	frameshift, copy number variants [107]	recessive; pallido-pyramidal syndrome	(SD 4.0)[107], parkinsonism mean 26.75 (SD1.8)[107,108]	syndrome, parkinsonism in ~40% of cases, dementia[108,109], hereditary spastic paraplegia-43[110]	Accumulation (NBIA)[107], *one case* had in addition to NBIA alpha-synuclein positive Lewy bodies and Lewy neurites in globus pallidus, substantia nigra, striatum, hippocampus, and neocortex. Lewy body pathology was much more pronounced than in sporadic Lewy body disease[109].	refute
G. Complex disorder with parkinsonism as only one component (neuropathological hallmark of Lewy bodies is rare, absent or unknown)						
Phospholipase A2, group VI (cytosolic, calcium-independent), *PLA2G6*, chr22q13.1, NM_003560.2	Nonsense, frameshift, splice-site, copy number variants[111]	Autosomal recessive, pallido-pyramidal syndrome	Mean 16.7 (SD 10.5)[112-114]	Adult-onset dystonia parkinsonism with absence of iron deposition on MRI[112,115], Karak syndrome, early-onset progressive dystonia, spasticity, parkinsonism, neuropsychiatric abnormalities, and optic atrophy or retinal degeneration[116]	In 6/6 cases alpha-synuclein positive Lewy bodies particularly severed in neocortex and tau pathology[114], neurodegeneration with brain iron accumulation type 2 (NBIA2)[114,117].	No data to confirm or refute
Pantothenate kinase 2, *PANK2* chr20p13, NM_153638.2	About 100 mutations identified, partial- and whole gene deletions[118]	Autosomal recessive, pallido-pyramidal syndrome	Mean 10.5 (SD 11.2)[119,120]	Dystonia, rigidity, choreoathetosis; Imaging: 'Eye of the tiger' sign on T_2-weighted MRI (≥1.5 Tesla), atypical Pantothenate Kinase-Associated Neurodegeneration presenting with lower-limb dystonia, bradykinesia and rest tremor similar to PARKIN parkinsonism	Neurodegeneration with brain iron accumulation type 1 (NBIA1); globus pallidus and variably in adjacent structures[114,121], alpha-synuclein positive Lewy bodies are not present in genetically confirmed cases[120].	No data to confirm or refute
Dynactin 1, *DCTN1*, chr2p13, NM_004082.4	Several pathogenic point mutations[122]	Autosomal dominant, Perry Syndrome[123]	Mean 53.3 (SD 6.9)[124-130]	Perry syndrome (parkinsonism, hypoventilation, depression, weight loss, mean disease duration 5 years, range 2-10 years), Pet imaging showed both striatal dopaminergic and widespread cortical/subcortical serotonergic dysfunction[131], can clinically also present as lower motor neuron disease[132,133], ALS[134,135], or FTD[124]	Severe neuronal loss in the substantia nigra with no Lewy bodies, TDP-43 positive neuronal inclusions[127]	MIBG showed markedly reduced uptake in one case[125]
TAF1 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 250kDa, *TAF1*[136], chrXq13.1, NM_004606.4	Few disease-specific single-nucleotide changes and deletion[137]	X-linked; DYT3, Lubag disease, founder effect on Panay Islands, Philippines	Mean 39.5 (SD 8.4)[136]	Severe progressive torsion dystonia followed by parkinsonism, deficits in sense of smell	Varying degrees of atrophy of the caudate nucleus and putamen (six cases)[136], two other independent cases with similar pathology reported[138,139]. No cases of Lewy body pathology described.	No data to confirm or refute
Ataxin 3, *ATXN3*, chr14q32.12, NM_004993.5	CAG repeat (normal, <44, intermediate 45-51, abnormal 52-86 repeats	Autosomal dominant, spino-cerebellar ataxia 3 (Machado-	Between 20-70 depending on CAG	Progressive cerebellar ataxia and pyramidal signs associated to a variable degree with a dystonic-rigid extrapyramidal syndrome or	Marked degeneration of subthalamopallidal (inner segment) system, the dentatorubral system, and the nuclei of cranial nerves[146].	No data to confirm or refute

		Joseph disease)	repeat length; for parkinsonism 39.9 (SD 9.9)[140-145]	peripheral amyotrophy[100], cases reported with predominant parkinsonism (all reported cases with abnormal repeat lengths)[140,142-145]	No cases of Lewy body pathology described.	
H. Complex disorder with parkinsonism (neuropathology unknown)						
ATPase type 13A2, *ATP13A2*, chr1p36, NM_022089.3	~30 mutations reported, missense, nonsense, frameshift, splice-site mutations, exon deletion[147-150]	Autosomal recessive, Kufor-Rakeb syndrome, pallido-pyramidal syndrome	Mean 23.7 (SD 13.5)[150]	Progressive dystonia, spasticity, L-Dopa responsive parkinsonism, neuropsychiatric abnormalities, optic or retinal degeneration; initial symptoms included bradykinesia, dystonia, gait disturbance, mental retardation, anxiety, postural instability, and rest tremor, uni- or bilateral Babinski sign was present in 27 of 37 patients, patients with neuronal ceroid lipofuscinoses (NCLs), a lysosomal storage disease[150]	1 NCL case described with abundant neuronal and glial lipofuscinosis involving the cortex, basal nuclei, cerebellum, but sparing the white matter, with whorled lamellar inclusions typical of NCL in electron microscopy. Lipofuscin deposits were confirmed in the retina[151].	No data to confirm or refute
F-box protein 7, *FBXO7*, chr22q12-q13, NM_012179.3	c.1132C>G (p.Arg378Gly)[152], c.1492 C>T (p.Arg498X)[153-155], c.1144 +1G>T[155]; c.65C>T (p.Thr22Met)[155]	Autosomal recessive, pallido-pyramidal syndrome	Mean 14.3 (SD 3.0)	Early-onset pallido-pyramidal syndrome, can include tics and chorea[153]	Unknown	No data to confirm or refute
DnaJ (Hsp40) homolog, subfamily C, member 6, *DNAJC6* chr1p31.3, NM_001256864.1	c.801-2A>G homozygous[156], c.2200C>T (p.Gln734X) homozygous[157]	Autosomal recessive	Mean 9.8 (SD 1.4)	Palestinian family with early-onset progressive parkinsonism[156] and Turkish family with juvenile parkinsonism that presented with mental retardation, pyramidal signs and epilepsy[157]	Unknown	No data to confirm or refute
Synaptojanin 1, *SYNJ1* chr21q22.11, NM_203446.2	c.773G>A (p.Arg258Gln) homozygous[158-160]	Autosomal recessive	Mean 24.3 (SD 3.4)	Early-onset parkinsonism with generalized seizures in Iranian family[158] and dementia in two Italian families[159,160], neuroimaging studies revealed severe nigrostriatal dopaminergic defects, mild striatal and very mild cortical hypometabolism[159]	Unknown	No data to confirm or refute
Solute carrier family 6 (neurotransmitter transporter),	~15 mutations reported, missense, splice-site, insertion/deletion[161-163]	Autosomal recessive, Infantile parkinsonism-	Mean 3.7 (SD3.5)[161-163]	Infantile parkinsonism-dystonia, presenting with hyperkinesia, parkinsonism, or a mixed hyperkinetic and hypokinetic movement	Unknown	No data to confirm or refute

member 3, *SLC6A3* chr5p15.33, NM_001044.4		dystonia, dopamine transporter deficiency syndrome (DTDS)		disorder[161,163]		

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Supplementary Table 2: LRRK2 mutant rodent models			
Ref	Paper	Model	Phenotype
1	Li et al. 2007. **Leucine-rich repeat kinase 2 (LRRK2)/PARK8 possesses GTPase activity that is altered in familial Parkinson's disease R1441C/G mutants.**	C57BL/6J Mouse BAC $Tg^{FLAG\text{-}LRRK2}$	• Kidney, Lung, Spleen and brain expression • Cerebral cortex, ventral tegmental area, amygdala, and hippocampus dopaminergic neurons of substantia nigra
2	Wang et al. 2008. **The chaperone activity of heat shock protein 90 is critical for maintaining the stability of leucine-rich repeat kinase 2.**	C57BL/6J Human cDNA $Tg^{HA\text{-}\ LRRK2(G2019S)}$ X $Tg^{(pPrP)\text{–}tetR}$ / $Tg^{(CaMKII)\text{–}tTA}$	• No neuropathological abnormalities or motor dysfunctions in Tg mice at 12 mo • LRRK2 interacts with Hsp90 • TetOff and PUH71 rescue G2019S axon length deficit.
3	Tong et al. 2009. **R1441C mutation in LRRK2 impairs dopaminergic neurotransmission in mice.**	C57BL/6J knockin $LRRK2^{R1441C/R1441C}$	• no dopaminergic (DA) neurodegeneration or alterations in steady-state levels of striatal dopamine at up to 2 years of age. • No change in Tau phosphorylation/accumulation • reductions in amphetamine-induced locomotor activity and stimulated catecholamine release in cultured chromaffin cells (amperometric recordings). • $LRRK2^{R1441C/R1441C}$ impairs dopamine D2 receptor function by decreased responses in locomotor activity to the inhibitory effect of D2 receptor agonist, quinpirole (open field). • firing of nigral neurons show reduced sensitivity to suppression induced by quinpirole, dopamine, or AMPH (brain slice electrophysiology).
4	Parisidou et al. 2009. **Phosphorylation of ezrin/radixin/moesin proteins by LRRK2 promotes the rearrangement of actin cytoskeleton in neuronal morphogenesis.**	C57BL/6J $LRRK2^{-/-}$ $Tg^{HA\text{-}\ LRRK2(G2019S)\ 2}$	• Increase in pERM-positive and F-actin-enriched filopodia in cultured neurons derived from LRRK2 G2019S transgenic mice, which correlates with the retardation of neurite outgrowth. • $LRRK2^{-/-}$ decreased pERM and F-actin contents in filopodia and promoted neurite outgrowth. • Inhibition of ERM phosphorylation or actin polymerization rescued the G2019S-dependent neuronal growth defects.
5	Andres-Mateos et al. 2009. **Unexpected lack of hypersensitivity in LRRK2 knock-out mice to MPTP.**	C57BL/6J $LRRK2^{-/-}$	• dopaminergic system is normal by HPLC for DA and its metabolites and no change in TH+ in young and aged mice • no significant difference in the susceptibility of $LRRK2^{-/-}$ and wild-type mice to MPTP
6	Li et al. 2009. **Mutant LRRK2(R1441G) BAC transgenic mice recapitulate cardinal features of Parkinson's disease**.	FVB Human BAC $Tg^{LRRK2(R1441G)}$	• Transgene expression was detected in the cortex, cerebellum, striatum and ventral midbrain (immunoblot) • Beaded and fragmented TH+ axons in striatum and piriform, with dystrophic neurites and decrease in number of tyrosine hydroxylase positive dendrites in the substantia nigra pars reticulate • hypokinesia in cylinder test, home cage and open field test; reversed with L-dopa • reduction of nomifensine induced extracellular, intrastriatal dopamine (microdialysis) • increased Tau p202/205 (AT8) by IHC of dystrophic neurites and immunoblot of dorsal striatum and piriform cortex
7	Zhou et al. 2009. **Developing tTA transgenic rats for inducible and reversible gene expression.**	Sprague Dawley $Tg^{(CAG\text{-}tTA)}$ X $Tg^{(TRE\text{-}HA\text{-}LRRK2)}$	• Expressed in cortex, cerebellum, brainstem, spinal cord, muscle, heart, lung liver
8	Lin et al. 2009. **Leucine-rich repeat kinase 2 regulates the progression of neuropathology induced by Parkinson's-disease-related mutant alpha-synuclein.**	C57BL/6J Human $cDNA^2$ -Tg^{LRRK2} -$Tg^{LRRK2(G2019S)}$ -$Tg^{LRRK2(inactive)}$ $LRRK2^{-/-}$ X Human $cDNA^2$ $Tg^{\alpha syn(A53T)}$	• Tg LRRK2 mainly detected at the olfactory bulb, cerebral cortex, hippocampus, and striatum • $Tg^{LRRK2(G2019S)}$ performed normally in rotarod test with significantly increased ambulatory activities at 12mo • $Tg^{\alpha syn(A53T)}$ weighed significantly less at 4mo with increased ambulatory activities at 2 mo, and elevated rearing activities at 6mo • $Tg^{\alpha syn(A53T)}$ causes 30% fewer striatal neurons • $Tg^{LRRK2(G2019S)}$ exacerbates A53T-mediated striatal neurodegeneration, with increased GFAP and Iba1 staining in at 1mo and A53T at 20mo, • 1mo $Tg^{A53T/G2019S}$ increase JadeC and caspase 3 staining in striatum • Tg^{LRRK2} did not accelerate APP-mediated astrocytosis and microgliosis $Tg^{APP/G2019S}$ mice • $Tg^{A53T/G2019S}$ a reduction of α-syn phosphorylation at S129 • $Tg^{A53T/G2019S}$ *cis*- and *trans*-golgi fragmentation neurons at 1mo
9	Melrose et al. 2010. **Impaired dopaminergic neurotransmission**	FVB Human Bac	• High expression in hippocampus and no TH+ loss • Low base line dopamine and enhanced response to amphetamine in

	and microtubule-associated protein tau alterations in human LRRK2 transgenic mice.	-Tg^{LRRK2} -$Tg^{LRRK2(G2019S)}$	Tg^{G2019S} (microdialysis) • Abnormal exploratory behavior (decreased thigomotaxis, increased mean path, decreased time in innermost zone (anxiety) • Increase Tau Ser202 (CP13), 396/404(PHF), 262/365 12E8
10	Dachsel et al. 2010. **A comparative study of Lrrk2 function in primary neuronal cultures.**	FVB Human BAC Tg - Tg^{LRRK2} - $Tg^{LRRK2(G2019S)}$ - $Tg^{LRRK2(Y1699C)}$ C57BL/6J $LRRK2^{G2019S/G2019S}$ $LRRK2^{-/-}$	In cultured hippocampal neurons: • $Tg^{LRRK2(Y1699C)}$ and $Tg^{LRRK2(G2019S)}$ decrease neurite outgrowth and branching • $LRRK2^{-/-}$ shows increased neurite outgrowth and branching • $LRRK2^{G2019S/G2019S}$ no change neurite outgrowth and branching
11	Li et al. 2010. **Enhanced striatal dopamine transmission and motor performance with LRRK2 overexpression in mice is eliminated by familial Parkinson's disease mutation G2019S.**	C57BL/6J Mouse BAC $Tg^{FLAG-LRRK2}$ $Tg^{FLAG-LRRK2\ (G2019S)}$	• 12 months, LRRK2-G2019S mice had 25% lower levels of DA and HVA, TH protein levels, enzymatic activity, and posttranslational modification of the TH protein associated with its activity • In $Tg^{FLAG-LRRK2}$ and not $Tg^{FLAG-LRRK2\ (G2019S)}$, increased rearing and movement in open field and decreased falls and slips on challenge beam task, longer strides and hind limb-forelimb diagonal distance in gait tests • Fast-scan cyclic voltammetry (FSCV) single pulse evoked DA in striatal slices 25% higher in $Tg^{FLAG-LRRK2}$ (enhanced release) and 35% lower in LRRK2-G2019S (decreased uptake) • $Tg^{FLAG-LRRK2}$ decreased pS396/pS404 (PHF-1) and pS202/T205 (CP13)
12	Tong et al. 2010 **Loss of leucine rich repeat kinase 2 causes impairment of protein degradation pathways, accumulation of synuclein and apoptotic cell death in aged mice**	C57BL/6J $LRRK2^{-/-}$	• No changes in TH+ neurons or DA and its metabolites in the striatum. • Age dependent renal atrophy with increased a-synuclein and ubiquinated protein accumulation, impaired autophagy(LC3I and p62 accumulation)
13	Winner et al. 2011. **Adult neurogenesis and neurite outgrowth are impaired in LRRK2 G2019S mice.**	FVB Human Bac $Tg^{LRRK2(G2019S)}$	• Decreased cell proliferation in DG SVZ and Olfactory bulb • Decreased dendrite length and branching points
14	Herzig et al. 2011. **LRRK2 protein levels are determined by kinase function and are crucial for kidney and lung homeostasis in mice.**	C57BL/6J $LRRK2^{-/-}$ Knockin $LRRK2^{G2019S/G2019S}$ $LRRK2^{D1994/D1994S}$	• No overt neuropathology and normal locomotor responses to dopamine agonists/antagonists in $LRRK2^{-/-}$ and $LRRK2^{D1994/D1994S}$ • $LRRK2^{-/-}$ and $LRRK2^{D1994S/D1994S}$ but not $LRRK2^{G2019S/G2019S}$ and WT mice developed dark kidneys • microvacuolization by accumulation of small isometric vacuoles in epithelial cells of the proximal tubules in both cortex and outer medulla • tubular degeneration and extracellular deposition of lipofuscin • 22mo $LRRK2^{-/-}$ females and 18mo $LRRK2^{-/-}$ males developed proteinuria; not in 20mo KI males and also diastolic hypertenstion • $LRRK2^{-/-}$ but not $LRRK2^{D1994/D1994S}$ or $LRRK2^{G2019S/G2019S}$ show microvacuolation in lung type II pneumocytes, within MUC1 positive alveolar-septal walls • $LRRK2^{-/-}$ 6wk kidney proximal tubules have increased numbers of secondary lysosomes, (LAMP1; IHC and EM) with typical stacked, whorled membranes, lipid and fine granular electron dense homogenous material. • $LRRK2^{-/-}$ show increased size and number of Lamellar bodies (by EM) in lung type II pneumocytes • $LRRK2^{D1994/D1994S}$ increased AKT, decreased mTOR; $LRRK2^{G2019S/G2019S}$ increased TSC2, increased mTOR, $LRRK2^{-/-}$ no change in 4EBP or LC3II. • $LRRK2^{D1994/D1994S}$ and inhibitor treatment decreases LRRK2 accumulation in kidney (Immunoblot)
15	Zhou et al. 2011. **Temporal expression of mutant LRRK2 in adult rats impairs dopamine reuptake.**	Sprague Dawley $Tg^{CAG-tTA}$ X $Tg^{TRE-HA-LRRK2\ 7}$	• Increased locomotor in open field distance traveled and decreased amphetamine and nomifensine evoked activity • Impaired DA reuptake by DAT, increased basal DA (release) and impaired amphetamine stimulated release
16	Ramonet et al. 2011. **Dopaminergic neuronal loss, reduced neurite complexity and autophagic abnormalities in transgenic mice expressing G2019S mutant LRRK2.**	C57BL/6J Human cDNA pCMV/PDGFβ $Tg^{LRRK2(R1441C)}$ $Tg^{LRRK2(G2019S)}$	• Age dependent 20% decrease in TH neurons of $Tg^{LRRK2(G2019S)}$ but not $Tg^{LRRK2(R1441C)}$ • Slight akinesia in $Tg^{LRRK2(R1441C)}$ open field but not in $Tg^{LRRK2(G2019S)}$? • Reduced neurite and dendrite complexity of midbrain DA neurons • Increased autophagic vacuoles in the cerebral cortex and mitochondrial condensation in $Tg^{LRRK2(G2019S)}$
17	Gillardon et al. 2012. **Parkinson's**	FVB	• Microglial cultures from $Tg^{LRRK2(R1441G)}$ mice show increased TNFα,

	disease-linked leucine-rich repeat kinase 2(R1441G) mutation increases proinflammatory cytokine release from activated primary microglial cells and resultant neurotoxicity.	$Tg^{LRRK2(R1441G)\ 6}$	IL1β and IL-6 with decreased IL-10 after LPS treatment
18	Friedman et al. 2012. **Disrupted autophagy leads to dopaminergic axon and dendrite degeneration and promotes presynaptic accumulation of α-synuclein and LRRK2 in the brain.**	$ATG7^{fl/fl}$ (Nestin Cre)	• Increased LRRK2 accumulation in purkinje layer of $ATG7^{-/-}$ and $ATG5^{-/-}$ MEFs.
19	Moehle et al. 2012. **LRRK2 inhibition attenuates microglial inflammatory responses.**	C57BL/6J $LRRK2^{-/-10}$	• Intra striatal and SN LPS injection increases LRRK2 expression on microglia
20	Maekawa et al. 2012. **The I2020T Leucine-rich repeat kinase 2 transgenic mouse exhibits impaired locomotive ability accompanied by dopaminergic neuron abnormalities.**	C57BL/6J Human cDNA CMV $Tg^{LRRK2(I2020T)}$	• Expressed in the SN, VTA and olfactory bulb. • $Tg^{LRRK2(I2020T)}$ show impaired locomotor activity by increased slips in in beam test and decreased latency to fall in rotarod test and increased rearing in cylinder test • Reduced striatal DOPAC and HVA content in DA and VTA • Golgi fragmentation and increased microtubule polymerization. • primary midbrain neurons exhibited decreased outgrowth and branches with increased TUNEL staining
21	Daher et al. 2012. **Neurodegenerative phenotypes in an A53T α-synuclein transgenic mouse model are independent of LRRK2.**	C57BL/6J $LRRK2^{-/-5}$ X $Tg^{ASYN(A53T)\ 22}$ $Tg^{LRRK2(G2019S)\ 16}$ X $Tg^{ASYN(A53T)\ 22}$	• no change in TH numbers from αSyn or LRRK2 mutation • $Tg^{LRRK2(G2019S)}$ nor $LRRK2^{-/-}$ modify the premature mortality, hyperkinesia or startle response, of $Tg^{ASYN(A53T)}$ • $LRRK2^{-/-}$ suppresses synuclein accumulation (pSer129 pathology) in the reticular formation • PrP promoter driven α-synuclein and CMVe-PDGFβ driven LRRK2
23	Herzig et al. 2012. **High LRRK2 levels fail to induce or exacerbate neuronal alpha-synucleinopathy in mouse brain.**	C57BL/6 Human cDNA mThy1 LRRK2 cDNA Tg^{LRRK2} & $Tg^{LRRK2(G2019S)}$ X Human cDNA mThy1 Tg^{Syn} & Tg^{A53T}	• Tg^{LRRK2} & Tg^{G2019S} do not modify Tg^{A53T} pathology by synuclein aggregation (immunoblot and TR-FRET oligomer assay), survival curve, latency to fall on rotorod, except a slight delay in motor deficit survival curve in female A53T/G2019S mice or increased microgliosis, • No changes in motor behavior relevant tests cocaine-induced hyperlocomotion; behavior in the open field, homecage running wheel performance, or movement; anxiety-relevant tests in the open field, the dark/light box and the elevated plus-maze; or hippocampus-dependent spatial reference learning in the Morris watermaze. • Tg expression in cortex, striatum, hippocampus, cerebellum, brainstem, spinal cord, none in SN • no changes in αSyn, αSyn pS129, Tau or Tau p202 in 15 mo LRRK2(G2019S) mice compared to wild-type littermate brain
24	Chen et al. 2012. **(G2019S) LRRK2 activates MKK4-JNK pathway and causes degeneration of SN dopaminergic neurons in a transgenic mouse model of PD.**	FVB Human BAC LRRK2 cDNA CMV/PDGFβ $Tg^{LRRK2(G2019S)}$	• 50% decrease in TH in SN and striatal terminals at 16 mo • Dopa responsive akinesia (Pole test and open field) • Expression in cortex, cerebellum, SN and striatum • Increased pTau 202/205 in GS • Decreased DAT in [99mTc]-TRODAT microSPECT imaging. • Increased MKK4/JNK/Jun phosphorylation and Caspase 9, 8 and 3 in in PD of 12mo SN
25	Hinkle et al. 2012. **LRRK2 knockout mice have an intact dopaminergic system but display alterations in exploratory and motor co-ordination behaviors.**	C57BL/6J $LRRK2^{-/-}$	• Less open field exploring and increased thigmotaxis (increased anxiety), increased rotorod performance, normal gait • No change in DA system: TH+ or DA neurochemistry, microdialysis, 3H-dopamine uptake • Increased LC3-II and p62 with age • Progressive kidney damage with increased lipofuscin
26	Tong et al. 2012. **Loss of leucine-rich repeat kinase 2 causes impairment of protein degradation pathways, accumulation of α-synuclein, and apoptotic cell death in aged mice.**	C57BL/6J $LRRK2^{-/-}$	• no change in TH+ neurons or • no change in DA or its metabolites or astrocytes or microglia • increased aggregation of α-synuclein and ubiquitinated proteins at 20 mo kidneys. • Increased oxidative species, apoptotic activity, accumulation of lipofuscin granules and decreased LC3-II and increased p62 indicating altered autophagy
27	Dzamko et al. 2012. **The IκB Kinase Family Phosphorylates the Parkinson's Disease Kinase LRRK2 at Ser935 and Ser910 during Toll-Like Receptor**	C57BL/6J $LRRK2^{-/-4}$	• IL-6, keratinocyte chemoattractant, RANTES, IL-1β, Monocyte chemoattractant protein 1, IL-10, TNFα and IL-12 (p40) not changed in $LRRK2^{-/-}$ BMDM

	Signaling		
28	Paus et al. 2013. **Enhanced dendritogenesis and axogenesis in hippocampal neuroblasts of LRRK2 knockout mice.**	C57BL/6J LRRK2 $^{-/-}$	• LRRK2 $^{-/-}$ no change in new cell proliferation or survival in DG but increased immature neuroblasts in hippocampus • LRRK2 $^{-/-}$ neuroblasts have increased dendritic length and arborization. • increased axonal mossy fiber projections dentate granule cells to CA3 pyramidal neurons in LRRK2 $^{-/-}$
29	Bichler et al. 2013. **Non-motor and motor features in LRRK2 transgenic mice.**	FVB Tg$^{LRRK2(R1441G)\ 6}$	• Decreased locomotor activity: 20mo, Tg reared less in cylinder; equal accelerated rotarod, similar muscular tonus capacity in mean latency to fall from inverted cage lid (grip strength test); open filed test-decreased rearing at 16mo (a), less active at 16-20mo photobeam horizontal activity decreased, less activity in the center of the apparatus (c), and increased total number of fine activities 3-6mo. • No anxiety behaviors elevated plus maze, tail suspension and forced swimming • Normal sensory responses late aged block test and buried test • Good learning abilities passive avoidance task • Similar sensory response to pain formalin test • Gastrointestinal dysfunction changes in stool water content and dry weight.
30	Dranka et al. 2013. **Diapocynin prevents early Parkinson's disease symptoms in the leucine-rich repeat kinase 2 (LRRK2^{R1441G}) transgenic mouse.**	FVB Tg$^{LRRK2(R1441G)\ 6}$	• No change in SN TH • Decreased latency to fall (rotarod); no change in open field or gait • No IBA-1 positive microglia • Diapocynin prevents (200mg/kg, 3X/wk) restores deficits in motor coordination
31	Sepulveda et al. 2013. **Short- and long-term effects of LRRK2 on axon and dendrite growth.**	C57BL/6J Tg$^{LRRK2\ 11}$ Tg$^{LRRK2G2019S\ 11}$ LRRK2$^{-/-\ 4}$	• LRRK2 Tg decreased axonal and dendritic motility on laminin • LRRK2 Tg showed reduced axonal and dendritic motility in LRRK2 TG and increased motility in LRRK2 LRRK2$^{-/-}$
32	Bailey et al. 2013. **LRRK2 phosphorylates novel tau epitopes and promotes tauopathy.**	FVB Tg$^{LRRK2(G2019S)\ 9}$ x FVB Tg$^{TauP301L/tTA\ 33}$	• LRRK2 expression highest in hippocampus and cortex • increased aggregation of insoluble tau and phosphorylation at T149, T153, T205, and S199/S202/T205
34	Baptista et al. 2013 **Loss of leucine-rich repeat kinase 2 (LRRK2) in rats leads to progressive abnormal phenotypes in peripheral organs.**	Long-Evans LRRK2$^{-/-}$	• increased lamellar body formation in TypeII pneumocytes of the lung • progressive abnormal kidney pathology with increased brown pigmentation, lipofuscin staining, hyaline droplets, lysosomal markers and kidney injury marker. • high serum phosphorous, creatinine, cholesterol and sorbital dehydrogenase and lower sodium and chloride • alterations in urine specific gravity, volume, potassium, creatinine, sodium and chloride
35	Yang et al. 2014. **Mitochondrial dysfunction driven by the LRRK2-mediated pathway is associated with loss of Purkinje cells and motor coordination deficits in a diabetic rat model.**	streptozotocin (STZ)-diabetic rats	• LRRK2 expression increased in Purkinkje cells of diabetic model
36	Sanchez et al. 2014. **Unaltered striatal dopamine release levels in young Parkin knockout, Pink1 knockout, DJ-1 knockout and LRRK2 R1441G transgenic mice.**	Parkin $^{-/-}$ Pink1 $^{-/-}$ DJ-1 $^{-/-}$ FVB human BAC Tg$^{LRRK2(R1441G)\ 6}$	• No change in DA release or uptake using fast scan cyclic voltammetry in, 6–8 week striatal sections (single, paired pulses and trains)
37	Miklavc et al. 2014. **Surfactant secretion in LRRK2 knock-out rats: changes in lamellar body morphology and rate of exocytosis.**	Long-Evans LRRK2 $^{-/-}$	• 50% larger laemellar bodies of TypeII pneumocytes cells with • ATP stimulation increased LB exocytosis and increased intracellular Ca2+ release

38	Parisiadou et al. 2014. **LRRK2 regulates synaptogenesis and dopamine receptor activation through modulation of PKA activity.**	C57BL/6J LRRK2$^{-/-}$ [4] LRRK2$^{R1441C/R1441C}$ [3]	• decreased number of mature spines in striatal projection neurons • SPNs had substantially longer dendritic spines, whereas the spine heads were smaller • reduction of PSD95 protein in P15 and P21 Lrrk2$^{-/-}$ striatum • moderately increased amplitude of mEPSCs but decreased frequency of mEPSCs of glutamatergic (mEPSCs) in striatal slices from P15 Lrrk2$^{-/-}$ by whole-cell voltage-clamp recordings • increased PKA phosphorylation of cofillin and GLur1 • LRRK2 confines PKARIIb to dendritic shafts • Similar effects of LRRK2$^{R1441C/R1441C}$ and Lrrk2$^{-/-}$ on GluR1 phosphorylation (S845) • Lrrk2$^{-/-}$ mice showed substantially increased ambulatory, grooming and rearing • defect in synaptogenesis from P5-15
39	Chou et al. 2014. **LRRK2 causes early-phase dysfunction of SNpc dopaminergic neurons and impairment of corticostriatal long-term depression in the PD transgenic mouse.**	FVB LRRK2 Tg$^{LRRK2(G2019S)}$ [24]	• Decrease in spontaneous firing frequency of SN from 8 mo Tg$^{LRRK2(G2019S)}$ mice (whole cell patch clamp in SN brain slices) • Impaired evoked dopamine release in dorsolateral striatum (carbon fiber electrode amperometry in striatal slices from 8-9m Tg^{G2019S} • Tg^{G2019S} failed to induce long term depression in corticostriatal EPSCs in 8-9m MSN
40	Caesar et al. 2014. **Changes in matrix metalloprotease activity and progranulin levels may contribute to the pathophysiological function of mutant leucine-rich repeat kinase 2.**	FVB Tg$^{LRRK2(R1441G)}$ [6]	• Decreased rearings and increased proportion of falls on beam test • Decreased progranulin and matrix-metalloprotease
41	Longo et al. 2014. **Genetic and pharmacological evidence that G2019S LRRK2 confers a hyperkinetic phenotype, resistant to motor decline associated with aging**	C57BL/6J LRRK2$^{G2019S/G2019S}$ LRRK2$^{D1994S/D1994S}$	• SN or DA analysis • LRRK2$^{G2019S/G2019S}$ showed hyperkinesia with decrease in age related immobility (bar test), increased steps in drag test and decreased immobility time and increased in total distance traveled in open field. • Phenotypes not seen in LRRK2$^{D1994S/D1994S}$ and is reversed with LRRK2 inhibitor Nov-LRRK2-11
42	Beccano-Kelly et al. 2014. **LRRK2 overexpression alters glutamatergic presynaptic plasticity, striatal dopamine tone, postsynaptic signal transduction, motor activity and memory.**	C57BL/6J LRRK2$^{-/-}$ [25] Human bac Tg^{LRRK2} [9]	• LRRK2$^{-/-}$ exhibit no change in glutamate transmission (mESPC) or short-term plasticity (PPR) in whole cell patch clamp of brain slices • LRRK2$^{-/-}$ show no loss of TH+, DA or striatal synaptic function in striatal projection neurons (SPN) • LRRK2$^{-/-}$ show no behavioral abnormalities in large male only cohort, open field, cylinder and novel object recognition • Tg^{LRRK2}show hypoactivity and long-term recognition memory impairment without anxiety • Tg^{LRRK2} Presynaptic D2R mediated short term synaptic plasticity defect (decreased paired pulse response) • altered DARP32 signaling. • Tg^{LRRK2} 35% decrease in dopamine tone (microdialysis), no change in re-uptake
43	Beccano-Kelly et al. 2014. **Synaptic function is modulated by LRRk2 and glutamate release is increased in cortical neurons of G2019S knockin mice.**	C57BL/6J LRRK2$^{-/-}$ Tg^{LRRK2} LRRK2$^{G2019S/G2019S}$	• In 21d cortical cultures LRRK2$^{-/-}$ Trend toward decreased synapse release frequency (mEPSC) with trend toward decreased synaptic proteins (PSD-95 and Syn1) • OE increased synaptic density with trend toward increased mESPC frequency • knockin LRRK2$^{G2019S/G2019S}$ no change in synaptic density with a significant increase in mEPSC frequency
44	Daher et al. 2014 **Abrogation of α-synuclein-mediated dopaminergic neurodegeneration in LRRK2-deficient rats.**	Long Evans LRRK2$^{-/-}$	• LRRK2$^{-/-}$ rats have less SN loss after LPS or AAV mediated αSyn overexpression compared to control • LRRK2 expression increased in CD68+/iNOS+ positive myeloid cells in SN
45	Tsika et al 2014 **Conditional expression of Parkinson's disease-related R1441C LRRK2 in midbrain dopaminergic neurons of mice causes nuclear abnormalities without neurodegeneration.**	C57BL/6J cDNA LRRK2^{R1441C} ROSA26promoter X BAC-DAT-iCre	• No change in motor or nigrostriatal system • Age related nuclear envelope abnormalities
46	Lee et al. 2015 **Behavioral,**	Sprague-Dawley	• No change in striatal DA or its metabolites up to 12mo

	neurochemical, and pathologic alterations in bacterial artificial chromosome transgenic G2019S leucine-rich repeated kinase 2 rats	Human Bac $Tg^{LRRK2(G2019S)}$	• Increases postural instability and increased rearings (cylinder) • Increased thiol oxidation and protein nitrosylation, iNOS expression and elongated morphology of TH+ neurons.
	PrP=prion promoter; DA=dopamine; SN=substantia nigra; TH=tyrosine hydroxylase; HVA=homovanilic acid; DOPAC=3,4-dihydroxyphenylacetic acid; CAG=cytomegalovirus/chicken beta-actin promoter; tTA=driving tetracycline regulated transactivator.		

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Supplementary Table 3: Critical factors of intrinsic and extrinsic variability for iPS cell modeling

***In vitro* culture conditions can result in**							
Clonal Variability affecting	Growth Rate	Morphology	Transcript Expression	Viability	Cell Adherence	Differentiation Potential	
Sources of Intrinsic Variability							
Donor background	Age, Gender, Ethnicity	Disease type (e.g. MLDB, PD, parkinsonism) genetic or idiopathic	Clinical manifestation: Age at onset, distribution of symptoms, severity, disease duration	Genetic background modifiers, independent of disease causing mutation	Imaging, Neuropathology	Environmental Exposure and lifestyle	**Solution:** Systematic collection and documentation of demographics, clinical phenotype, and longitudinal data; collection of matching controls, generation of genetically engineered isogenic lines
Sources of Extrinsic Variability							
Derivation of primary tissue culture	Source of donor tissue (e.g. fibroblasts, blood cells, renal epithelial cells)	Derivation of Primary Cell Culture	Passaging and Passage number: Enzymatically or manual dissection	Media/defined Conditions	Extracellular Matrix	Cryopreservation	**Solution:** Consistent method and protocol, minimal exposure to enzymatic treatment
Reprogramming Process	Nuclear reprogramming method: 1. Integrating viral vectors[1-3], 2. Non-integrating viral vectors (Adenovirus[4,5], Sendai virus[6,7]), 3. Non-integrating non-viral vectors (episomal vectors[8], human artificial chromosome vectors[9], piggyBac[10]), 4. mRNA transfection[11-13], 5. protein transfection[14]	Supplemental chemical compounds and selection for optimizing efficiency of reprogramming[2,15-18]	Passaging Enzymatically or manual dissection, feeder/feeder-free conditions	Media/defined Conditions	Extracellular Matrix (Matrigel, geltrex, polyornithine/laminin, human recombinant laminin LN521[19])	Cryopreservation	**Solution:** Consistent methods and protocols, documentation of lot numbers for tissue culture supplies, consistent use of plastic consumables; frequent karyotyping

Neuronal Differentiation Protocols	1. Spontaneous differentiation 2. Stromal feeder layer co-culture (SDIA)[20,21] 3. Co-culture with astrocytes 4. Embryoid body differentiation[22,23]/ neurosphere generation[24], 5. Differentiation using small molecule inhibitors and recombinant proteins[25-28] 6. Use of engineered cell lines with forced expression of midbrain transcription factors[29]	Duration, Plating cell density	Passaging Manual dissection or Enzymatic disruption with either collagenase vs. Accutase	Media/defined Conditions (NSC, DA1, DA2)	Extracellular Matrix (MEFs, matrigel, geltrex, polyornithine /laminin, LN521[19])	Cryopreservation (10% FBS/Media, Bambanker)	**Solution:** Consistent methods and protocols, documentation of lot numbers for tissue culture supplies, consistent use of plastic consumables; unbiased measures of number of dopaminergic neurons, midbrain specificity, neurophysiology

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Supplementary Table 4: 21 clinical symptoms and eight categories derived from Supplementary Table 1

Clinical Category	Gene	Neuropathology	Age onset (Mean)	Estimated Prevalence	Euclidian distance	F1	F2	F3	F4	F5	F6	cat A	cat B	cat C	cat D	cat E	cat f	cat G	cat H	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18	F19	F20	F21
		defining color of bubbles				Rigidity	Tremor	Bradykinesia	Cell loss	Lewy bodies	PAS									Dementia	Ataxia	Di George	PPS	NBIA	Dystonia	chore oathetosis	hypoventilation	Weight loss	torsion dystonia	hyperkinesia	seizures	pyramidal signs		tics	optic degenerat
Idiopathic PD			61.0 yrs (SD 10.9 yrs)	1000/100,000	0																													
Category A: MLBD = **idiopathic PD**																																		
	SNCA	LB = dark blue	p.Ala53Thr: 47 yrs (SD 12), p.Ala30Pro: 60 yrs (SD 11), p.Glu46Lys: 60 yrs (SD 7), dup 50 yrs (SD 11), trip: 40 yrs (SD 14)	2/100,000	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Category B: Mixed MLBD																																		
	LRRK2	mixed LB = blue	58.1 yrs (SD 14)	10/100,000	2	1	1	1	0.5	0.5	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0.5	0	0	0	0	0	0	0	0	0
Category C: PD, but MLBD not ruled out																																		
	GBA	LB = dark blue	59.39 yrs (SEM 2.1)	15/100,000	2	1	1	1	1	1	2	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Category D: Likely MLBD, but more data needed																																		
	PINK1	LB (1 case) = light blue	36.0 yrs (SD 6.9)	5/100,000	2.82	1	1	1	1	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
	DNAJC13	LB (1 family) = light blue	67.0 yrs (SD 9.5)	unknown	2.64	1	1	1	1	1	2	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Category E: Parkinsonism, but unlikely MLBD																																		
	PARK2	mixed LB = blue	29.2 yrs (SD 10.4)	40/100,000	2.44	1	1	1	1	0.5	1	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
	VPS35	no LB = yellow	51.4 yrs (SD 8.6)	unknown	3.6	1	1	1	0	0	2	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	PARK7	unknown = orange	34.8 yrs (SD 10.4)	<1/1,000,000	4.35	1	1	1	2	2	2	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	GCH-1	LB (1 case) = light blue	61.0 yrs (SD 10.9)	unknoown	2.82	1	1	1	1	1	2	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Category F: other neurological disease c parkinsonism																																		
	ATXN2	LB (2 cases) = light blue	49.9 yrs (SD 16.1)	1-2/100,000	3.31	1	1	1	1	1	1	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
	22q11	LB (3 cases) = light blue	40.8 yrs (SD 6.7)	unknown	2.82	1	1	1	1	1	2	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
	C19orf12	NBIA; LB (1 case) = light blue	10.1 yrs (SD 4.0)	unknown	3	0.5	0.5	0.5	1	1	2	0	0	0	0	0	1	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0
Category G: complex disorder c parkinsonism as only one component																																		
	PLA2G6	NBIA; LB (1 case) = light blue	16.7 yrs (SD 10.5)	<1/1,000,000	-3	1	1	1	0.5	0.5	2	0	0	0	0	0	0	1	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0
	PANK2	NBIA, no LB = yellow	10.5 yrs (SD 11.2)	unknown	-3.87	1	1	1	0	0	2	0	0	0	0	0	0	1	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0
	DCTN1	no LB = yellow	53.3 yrs (SD 6.9)	<1/1,000,000	-3.74	1	1	1	1	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0
	TAF1	no LB = yellow	39.5 yrs (SD 8.4)	<1/1,000,000, 4.7/100,000 Panay	-3.74	1	1	1	0	0	2	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
	ATXN-3	no LB = yellow	39.9 yrs (SD 9.9)	unknown	-3.6	1	1	1	0	0	2	0	0	0	0	0	0	1	0	0	1	0	0	0	1	0	0	0	0	0	0	1	0	0
Cateogry H: complex disorder c parkinsonism, no neuropathology																																		
	ATP13A2	unknown = orange	23.7 yrs (SD 13.5)	<1/1,000,000	-4.79	1	1	1	2	2	2	0	0	0	0	0	0	0	1	1	0	0	0	0	1	0	0	0	0	0	0	1	0	1
	FBX07	unknown = orange	14.3 yrs (SD 3.0)	unknown	-4.69	1	1	1	2	2	2	0	0	0	0	0	0	0	1	0	0	0	1	0	0	1	0	0	0	0	0	0	1	0
	DNAJC6	unknown = orange	9.8 yrs (SD 1.4)	<1/1,000,000	-4.58	1	1	1	2	2	2	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0
	SYNJ1	unknown = orange	24.3 yrs (SD 3.4)	<1/1,000,000	-4.58	1	1	1	2	2	2	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0
	SLC6A3	unknown = orange	3.7 yrs (SD 3.5)	unknown	-4.58	1	1	1	2	2	2	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	1	0	1	0	0

Legend

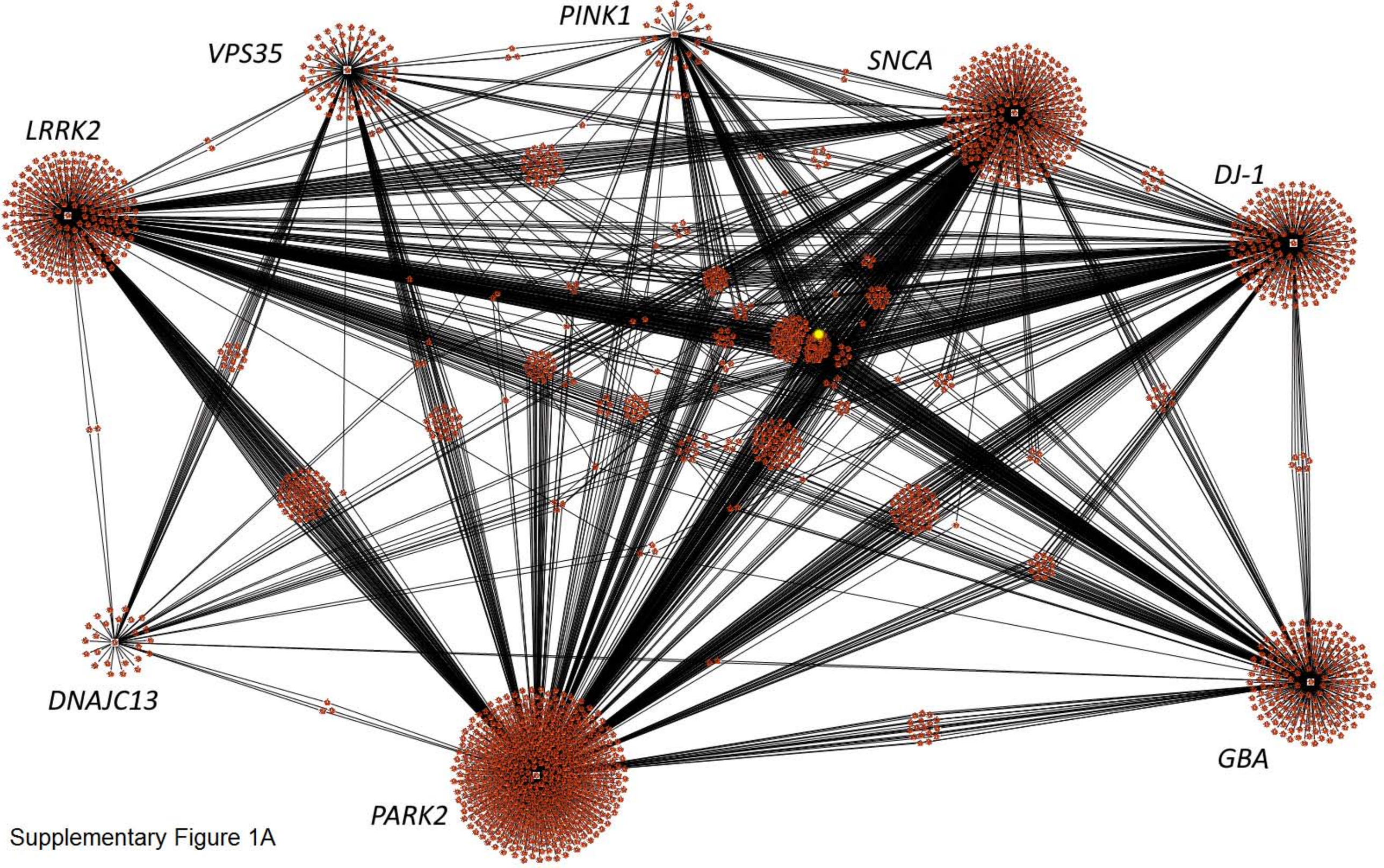
LB= Lewy bodies
mixed LB= not all autopsy cases present with Lewy body pathology
no LB= no Lewy bodies
NBIA= neurodegeneration with brain iron degeneration

0= no
0.5= partial
1= yes
2= not known

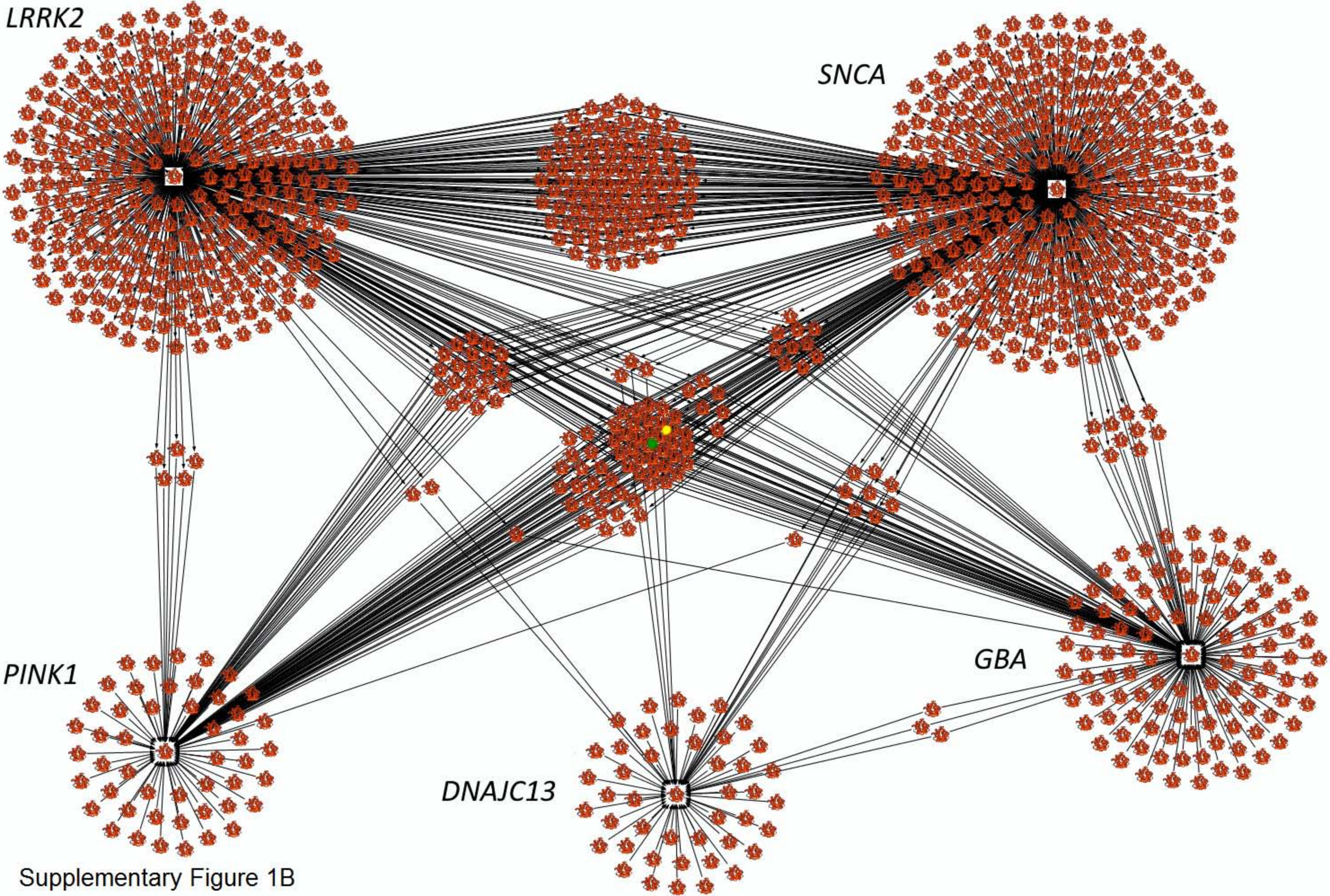
Supplementary Table 5: MLBD protein interaction networks

LRRK2, SNCA and GBA				SNCA and LRRK2				LRRK2 and GBA	GBA and SNCA
2DA2 HUMAN	CYP3A4	IKBKAP	SLC45A3	ACTB	DRD2	PTEN	TH	CCL18	AGA
A30	CYP3A43	KCNJ6	SLC6A3	ACTG1	DYRK1A	PTPN2	TNS1	CD1B	ALPL
ACMSD	CYP3A5	LRRK2	SNCA	AKT1	EPS15	RAB7L1	TOR1A	CHRNA4	ALPP
ADH1A	CYP4X1	MAOB	SNCAIP	ALS2	FBXW7	RANBP2	TP53	CTSS	ALPPL2
ADH1B	DGKQ	MAPT	SNCB	APP	FGF20	RBBP9	UBE2G1	CYP1A2	APOA2
APOE	FBXO7	MC1R	SOD2	ATG5	FGR	RGPD3	UBE2G2	DIF	CFTR
ATP13A2	FLJ42946	MCCC1	SRGAP2	BACE1	FHIT	RING1	UBE2H	IL1B	CKAP5
ATXN2	GAK	NAT2	STK39	BAG5	GDNF	RING1p	UBE2I	PAH	DNAH8
ATXN3	GAPDH	NGF	SYT11	BDNF	GFAP	RPS27A	UBE2K	PPARG	GSK3B
CACNA1S	GBA	NOS1	SYT12	CALU	GPR37	SEPT5	UBE2L3	RNASEH2	HERPUD1
CAT	GIGYF2	NR4A2	TBP	CASP3	GRN	SH3GL1	UBE2S	TMEM163	LYZ
CCDC62	GSTO1	NUCKS1	TFDP1	CASP9	HDAC4	SH3GL2	VCP		PANK2
CHRNB2	GSTO2	PARK2	TRAPPC4	CDK5R1	HLA-DRB1	SH3GL3	VDAC1		RAB1A
COMT	HIP1R	PARK7	TSPO	CHM	HLA-DRB5	SLC18A2	VIM		SKAP2
CYP1B1	HLA-DQA2	PDXK	UBA52	CSN1S1	HTT	SOD1	VPS35		SKP1
CYP20A1	HLA-DXA	PINK1	UBC	CSNK1A1	MFN2	SORL1	WWOX		SRGAP3
CYP2A6	HLA-DQA2	PLA2G6	UCHL1	CTNND1	PACRG	SPG11			TGM1
CYP2B6	HRAS	PM20D1	USP24	CUL1	PIK3CB	SPR			
CYP2C19	HSP90AA1	PRNP		CYCS	PIK3CD	SQSTM1			
CYP2D6	HSPA4	PSEN1		DDC	PITX3	STUB1			
CYP2D7P1	HTR2A	SEMA5A		DNM1L	PSEN2	TARDBP			
CYP2J2	HTRA2	SLC41A1		DRB1	PSMA7	TGFBI			

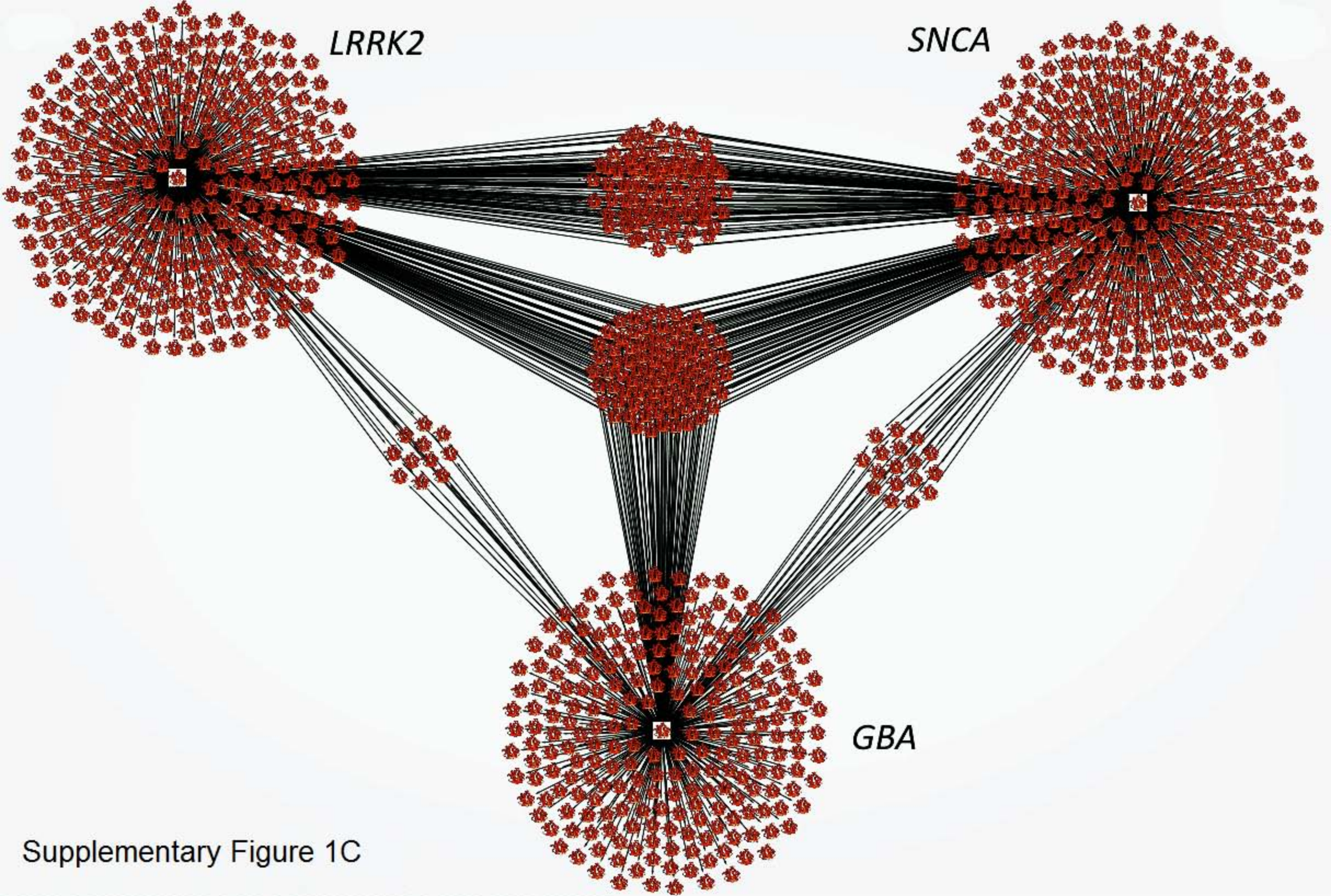
Protein IDs are based on the STRING database: http://string-db.org/



Supplementary Figure 1A



Supplementary Figure 1B



Supplementary Figure 1C