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Genes implicated in familial Parkinson's disease provide a dual picture of nigral dopaminergic neurodegeneration, with mitochondria taking center stage

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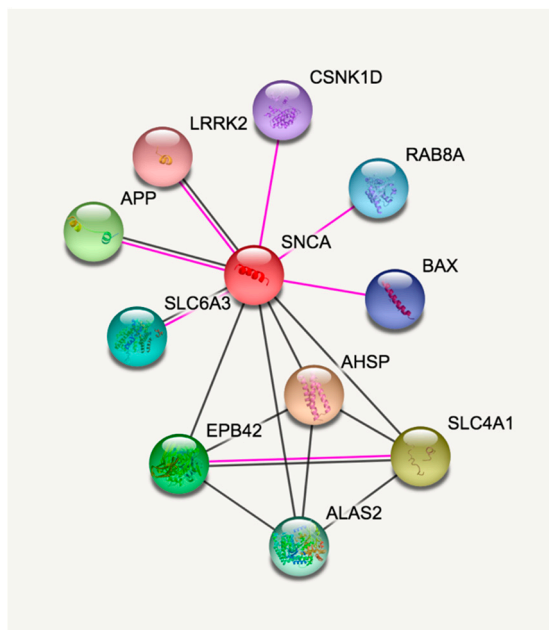
Supplementary Figure S1 and Table S1

Supplementary Figure S1.

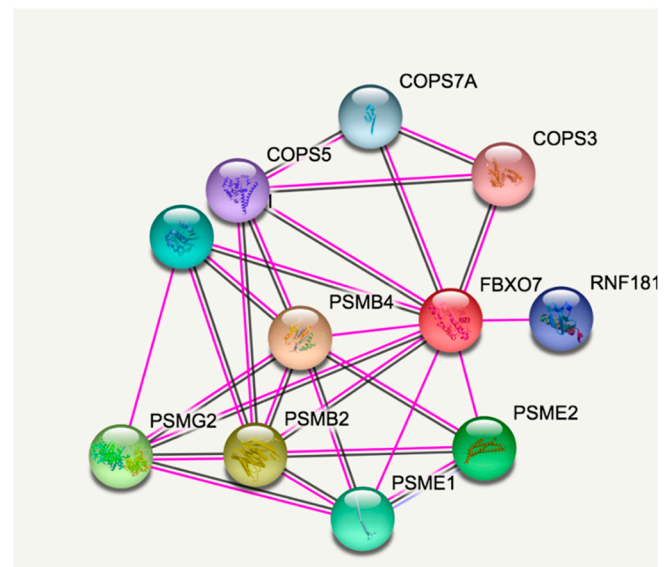
STRING analysis of connections of either SNCA (A), GBA (B), FBXO7 (C), ATP13A2 (D) and UCHL1 (E).

Line color code. Sky blue: known interactions from curated databases; magenta: experimentally determined interactions; green: predicted from neighborhood; red: predicted from gene fusions; blue: predicted from gene co-occurrence; pastel green: textmining; black: coexpression and clear violet: protein homology.

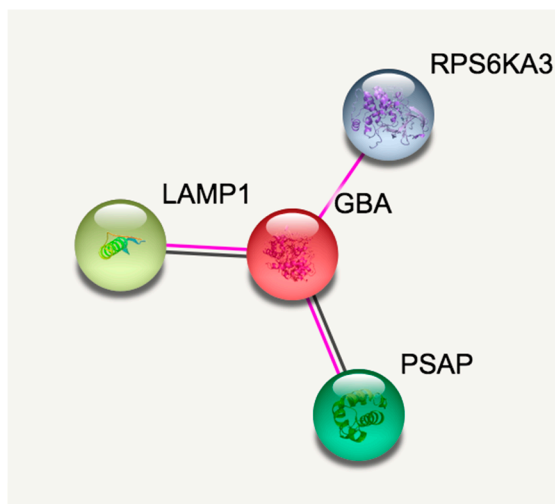
Panel A: SNCA



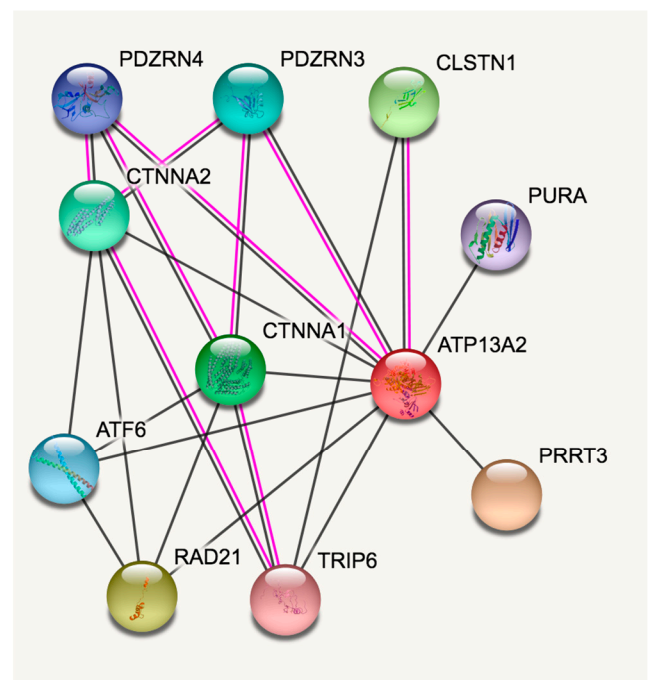
Panel C: FBXO7



Panel B: GBA



Panel D: ATP13A2



Panel E: UCHL1

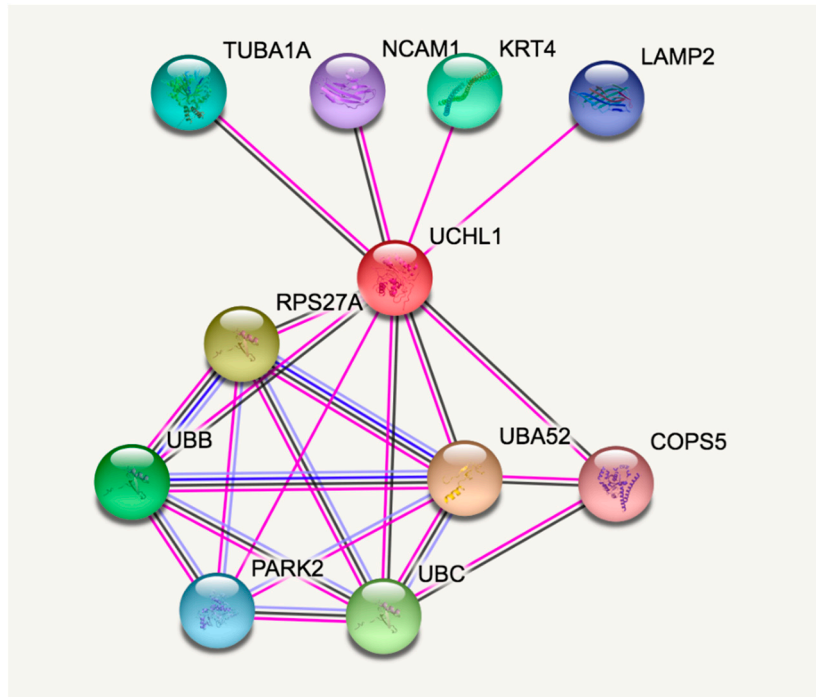


Table S1. Findings in animal models related to *Gba*, *Uchl1*, *Vps35*, *Atp13a2*, *Pla2g6*, *Dnajc6*, *Synj1*, *DJ-1/Park7* and *Fbxo7*

Gene	Animal model(s)	In vi vo	In vit ro	Expression level	Main findings	Reference
GBA	K-14Cre-positive <i>Gba^{lnl/lnl}</i>		X	<i>Gba</i> KO mice (except in skin)	• Strong similarities with Gaucher disease pathology	[1]
	B6;129S6- <i>Gba^{tm1Nsb}/J</i>		X	<i>Gba</i> KO mice	• Downregulation of neurotrophic factors	[2]
	n.s.n.		X	<i>Gba</i> KO mice	• Autophagic lysosome reformation dysfunction	[3]
	Mice resulting from crossing SNCA Tg/Tg line with <i>Gba</i> +/- line (n.s.n.)		X	SNCA overexpressing <i>Gba</i> KO mice	• Increased total α -syn accumulation • Altered lipid metabolism	[4]
	Mice resulting from crossing A53T α -synuclein transgenic line M83 with <i>Gba</i> KO line B6;129S6- <i>Gba^{tm1Nsb}/J</i>	X	X	A53T-SNCA overexpressing <i>Gba</i> KO mice	• Impact on PD disease onset	[5]
	B6;129S4- <i>Gbatm1Rlp/Mmnc</i>	X	X	L444P- <i>Gba</i> KI mice	• Increased total α -syn accumulation • Enhanced neuron vulnerability	[6]
	B6;129P2- <i>Uchl1^{tm1Dgen}/Mmnc</i>	X	X	<i>UCH-L1</i> KO mice	• Significantly decreased motor performance on the rotarod test	[7]
<i>UCHL1</i> ^{>}	Mice resulting from crossing B6;129P2- <i>Uchl1^{tm1Dgen}/Mmnc</i> line with Thy1-maSN line	X	X	<i>Snc</i> a overexpressing <i>Uchl1</i> KO mice	• Earlier-onset motor deficits	[8]
	B6.Cg- <i>Vps35^{tm1.2Mjff}/J</i>	X	X	D620N- <i>Vps35</i> KI mice	• Manifest tau neuropathology and dopaminergic neurodegeneration	[9]

	129S- <i>Prkn</i> ^{tm1Rpa} /J	X		<i>Prkn</i> KO mice	<ul style="list-style-type: none"> Insensibility to 6-OHDA and methamphetamine neurotoxicity 	[10]
VPS35	129S- <i>Prkn</i> ^{tm1Rpa} /J	X		<i>Prkn</i> KO mice	<ul style="list-style-type: none"> Do not exhibit robust signs of parkinsonism 	[11]
ATP13A2	Mice resulting from crossing B6N.129S6(Cg)- <i>Atp13a2</i> ^{tm1Pjsh} /J line with B6;DBA-Tg(Thy1-SNCA)61Ema line	X		<i>Atp13a2</i> KO mice overexpressing human SNCA	<ul style="list-style-type: none"> Impaired sensorimotor function 	[12]
	B6;129S6- <i>Pla2g6</i> ^{tm1Zyao} /J	X	X	<i>Pla2g6</i> KO mice	<ul style="list-style-type: none"> No evidence that leads to dyslipidemia Altered catabolism of TAG-rich lipoproteins 	[13]
	<i>iPLA2-VIA</i> -deficient flies (n.s.n.)	X	X	<i>iPLA2-VIA</i> KO Drosophila	<ul style="list-style-type: none"> Dysregulation in neuronal functions and α-syn 	[14]
	y w;; <i>iPLA2-VIA</i> Δ 174 y w;; <i>iPLA2-VIA</i> Δ 192	X	X	<i>iPLA2-VIA</i> KO Drosophila	<ol style="list-style-type: none"> 1. stability 2. Impaired retromer and lysosomal function in neurons 	[15]
PLA2G6	PLA2G6 ^{D331Y/D331Y}	X	X	D331Y- <i>Pla2g6</i> KI mice	<ul style="list-style-type: none"> Mitophagy impairment Mitochondrial dysfunction ER stress 	[16]
	B6.129- <i>Dnajc6</i> ^{tm1Legr} /Mmjax		X	<i>Dnajc6</i> KO mice	<ul style="list-style-type: none"> Endocytosis and clathrin-uncoating defects 	[17]
	C57BL/6- <i>Dnajc6</i> ^{em1Mcook} /J	X	X	R857G- <i>Dnajc6</i> KI mice	<ul style="list-style-type: none"> Impaired clathrin-mediated trafficking at the Golgi and at the synapse 	[18]
	UAS-aux ^{R16182} (aux RNAi, VDRC) UAS-aux ^{R103426} (aux RNAi, VDRC)	X	X	Reduced aux expression Drosophila	<ul style="list-style-type: none"> Reduced locomotion and longevity DA neuron loss at the PPM1/2 cluster Enhanced and accelerated α-syn-mediated DA neuron loss 	[19]
DNAJC6	B6;129- <i>Synj1</i> ^{tm1Pdc} /J		X	<i>Synj1</i> KO mice	<ol style="list-style-type: none"> 7. Synaptic vesicles still form from synaptic endosomes 	[20]
	B6;129- <i>Synj1</i> ^{tm1Pdc} /J		X	<i>Synj1</i> KO mice	<ol style="list-style-type: none"> 8. Defects in both endocytosis and post-endocytic vesicle 	[21]
	B6;129- <i>Synj1</i> ^{tm1Pdc} /J		X	<i>Synj1</i> KO mice	<ul style="list-style-type: none"> Exhibit neurological defects 	[22]
SYNJ1	B6;129- <i>Synj1</i> ^{tm1Pdc} /J		X	<i>Synj1</i> KO mice	<ol style="list-style-type: none"> 9. Die shortly after birth. 10. Larger excitatory postsynaptic amplitudes 	[23]
	Mice resulting from crossing B6;129- <i>Synj1</i> ^{tm1Pdc} /J line with AD model line Tg2576	X	X	<i>Synj1</i> KO + AD model mice	<ol style="list-style-type: none"> 11. Ameliorated AD-associated behavioral and synaptic deficits 	[24]
	Mice resulting from crossing B6;129- <i>Synj1</i> ^{tm1Pdc} /J line and B6.Cg-Tg(Lrrk2*G2019S)2Yue/J line	X	X	G2019S- <i>Lrrk2</i> overexpressing <i>Synj1</i> KO mice	<ul style="list-style-type: none"> Impaired sustained exocytosis in MB neurons Altered specific motor functions 	[25]
	n.s.n.		X	Overexpressing <i>Synj1</i> mice	<ol style="list-style-type: none"> 12. Altered specific motor functions 13. Enlarged endosomes 	[26]
	n.s.n.	X	X	Down 's syndrome mouse model overexpressing either <i>Synj1</i> or human SYNJ1	<ul style="list-style-type: none"> Altered behavior Brain dysfunction 	[27]
	SJ1 RQ-KI	X	X	R259Q- <i>Synj1</i> KI mice	<ul style="list-style-type: none"> Endocytic defects Elevated auxilin and parkin 	[28]
	B6.129- <i>Park7</i> ^{tm1Mak}	X	X	<i>Dj-1</i> KO mice	<ol style="list-style-type: none"> 14. Brain dysfunction 15. Elevated auxilin and parkin 16. Impaired running wheel and rotarod performance 	[29]
	B6.129P2- <i>Park7</i> ^{tm1Dsp} /Cnbc	X	X	<i>Dj-1</i> KO mice	<ul style="list-style-type: none"> Mitochondrial defects and more ROS production Altered autophagy 	[30]
	B6.129P2- <i>Park7</i> ^{tm1Dsp} /Cnbc	X	X	<i>Dj-1</i> KO mice	<ol style="list-style-type: none"> 17. Altered autophagy 18. Increased sensitivity to excitotoxicity and ischemia 	[31]
	B6.129P2- <i>Park7</i> ^{tm1Dsp} /Cnbc	X	X	<i>Dj-1</i> KO mice	<ul style="list-style-type: none"> DJ-1 is crucial for full 	[32]

DJ-1/PARK7					19. activation of AKT upon oxidative injury	
	B6.Cg- <i>Park7^{tm1Shn}/J</i>		X	<i>Dj-1</i> KO mice	20. Lower expression of UCP4	[33]
	B6.Cg- <i>Park7^{tm1Shn}/J</i>		X	<i>Dj-1</i> KO mice	21. Loss of SNc dopaminergic neurons.	[34]
	B6.Cg- <i>Park7^{tm1Shn}/J</i>	X	X	<i>Dj-1</i> KO mice	22. Mitochondrial oxidative stress	[35]
	B6.Cg- <i>Park7^{tm1Shn}/J</i>		X	<i>Dj-1</i> KO mice	<ul style="list-style-type: none"> Increased mitochondrial Trx activity Increased GSH and GSSG levels Increased mitochondrial glutaredoxin (GRX) activity 	[36]
	B6.Cg- <i>Park7^{tm1Shn}/J</i>		X	<i>Dj-1</i> KO mice	<ul style="list-style-type: none"> Declined dendritic complexity 	[37]
	B6.Cg- <i>Park7^{tm1Shn}/J</i>		X	<i>Dj-1</i> KO mice	<ul style="list-style-type: none"> Mitochondrial respiration not affected 	[38]
	B6.Cg- <i>Park7^{tm1Shn}/J</i>		X	<i>Dj-1</i> KO mice	<ul style="list-style-type: none"> Altered Ca²⁺ homeostasis in the skeletal muscle 	[39]
	B6.Cg- <i>Park7^{tm1Shn}/J</i>	X	X	<i>Dj-1</i> KO mice	<ul style="list-style-type: none"> Absence of dopaminergic neuronal degeneration 	[40]
	B6.Cg- <i>Park7^{tm1Shn}/J</i>	X	X	<i>Dj-1</i> KO mice	<ul style="list-style-type: none"> Absence of LTD in medium spiny neurons 	[41,42]
	B6.Cg- <i>Park7^{tm1Shn}/J</i>	X	X	<i>DJ-1</i> KO mice	<ul style="list-style-type: none"> Enhanced sensitivity to energy metabolism impairment 	[43]
	B6;129X1- <i>Park7^{tm1Cai}/Mmjax</i>	X	X	<i>Dj-1</i> KO mice	<ul style="list-style-type: none"> Retinal abnormalities Visual dysfunction 	[44]
	B6;129X1- <i>Park7^{tm1Cai}/Mmjax</i>	X	X	<i>Dj-1</i> KO mice	30. Increased oxidative stress in mice	[45]
	DAT-Ret; <i>Dj-1</i> mice resulting from crossing B6.Cg- <i>Park7^{tm1Shn}/J</i> line with DAT-Ret line	X	X	<i>Dj-1</i> KO + midbrain dopaminergic neurons <i>Ret</i> KO mice	<ul style="list-style-type: none"> Interaction between DJ-1 and Ret-mediated signaling DJ-1 promotes cell survival 	[46]
	B6.129- <i>Park7^{tm1Mak}</i> FVB/N- <i>Khdrbs2^{Tg(LRRK2* R1441G)135Cjli}/J</i>	X	X	- <i>Dj-1</i> KO mice -R1441G- <i>LRRK2</i> expressing mice	<ul style="list-style-type: none"> Modest impairments of motor behavior 	[47]
	B6.Cg- <i>Park7^{tm1Shn}/J</i>		X	- <i>Dj-1</i> KO mice - <i>DJ-1</i> -deficient SH-SY5Y cells	<ul style="list-style-type: none"> Inhibited S-nitrosylation of endogenous Parkin Mitochondrial dysfunction 	[48]
	B6.Cg- <i>Park7^{tm1Shn}/J</i> B6.129S4- <i>Park2^{tm1Shn}/J</i>		X	- <i>Dj-1</i> KO mice - <i>Prkn</i> KO mice	<ul style="list-style-type: none"> Changes in the expression of neurotransmitter receptors 	[49]
	Mice resulting from crossing B6.129S4- <i>Prkn^{tm1Shn}/J</i> line with B6.Cg- <i>Park7^{tm1Shn}/J</i> line and <i>Sod1</i> KO or <i>Sod2</i> KO line	X	X	Triple <i>Prkn</i> KO + <i>Dj-1</i> KO + <i>Sod1</i> or <i>Sod2</i> KO mice	<ul style="list-style-type: none"> Enhanced performance in locomotor tests 	[50]
	n.s.n.	X	X	<i>DJ-1</i> β mutants <i>Drosophila</i>	36. Elevated levels of dopamine in the striatum	[51]
FBXO7	n.s.n.	X	X	<i>Fbxo7</i> KO mice	<ul style="list-style-type: none"> Reduced proteasome activity Motor deficits Premature death 	[52]

n.s.n.: Non standard nomenclature

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