



The analysis gene function and protein physicochemical property of LRRK2 protein

LRRK2蛋白基因功能和理化性质的生物信息学分析

Group members: Han Ge, Zeng Xin, Li Songlu, Li Wanhua

Adviser: Professor Luo Jingchu

Report date:2015.1.25

Group number: 17



Outline

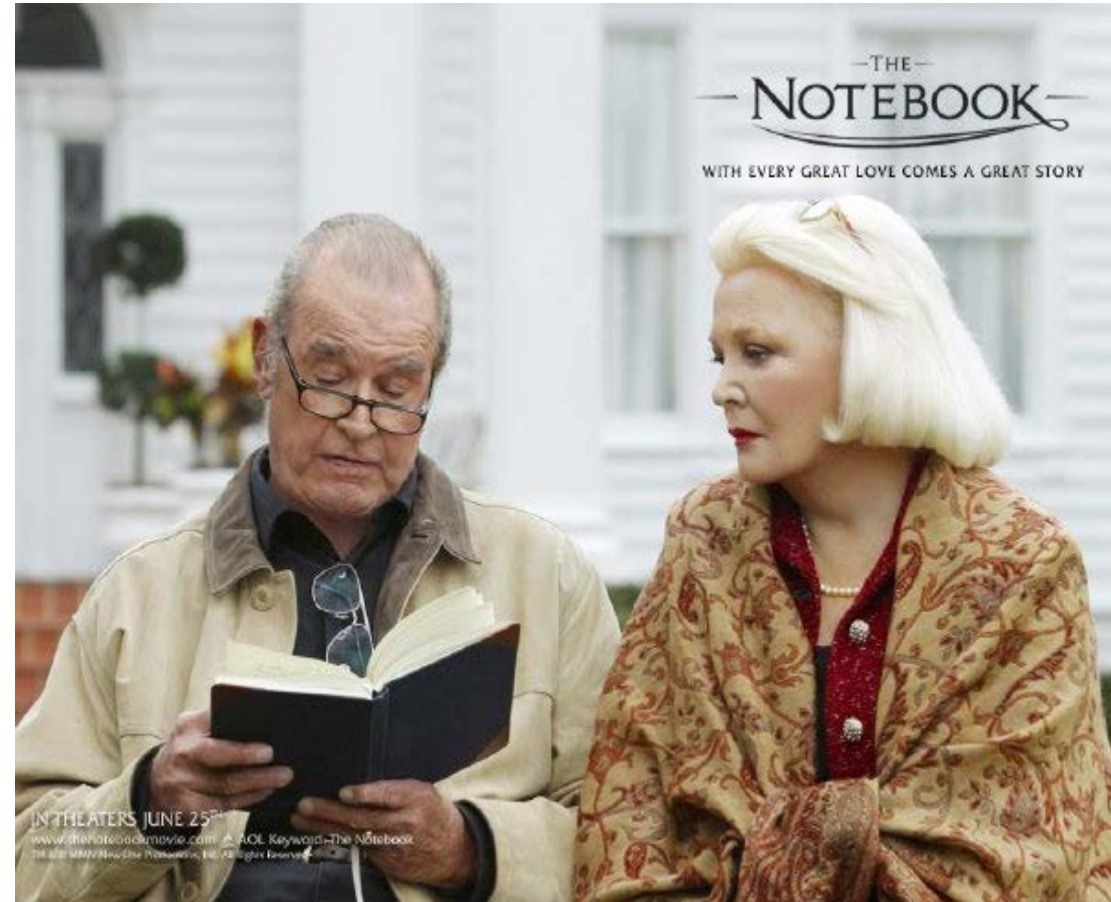
- Background
- Sequence analysis
- Physicochemical property analysis
- Protein structure analysis
- Function and pathway analysis

Background



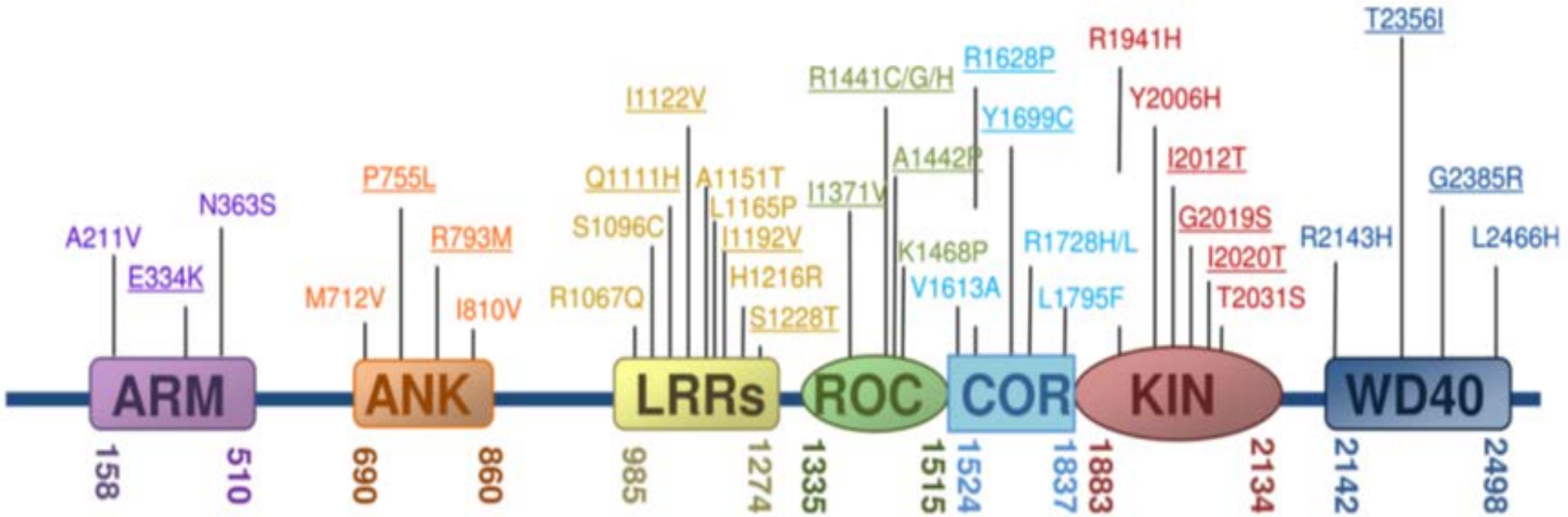
Background

Leucine-rich repeat kinase 2 (LRRK2), also known as dardarin (from the Basque word "dardara" which means trembling), is an enzyme that in humans is encoded by the PARK8 gene. LRRK2 is a member of the leucine-rich repeat kinase family. Variants of this gene are associated with an increased risk of Parkinson's disease and also Crohn's disease.





Background



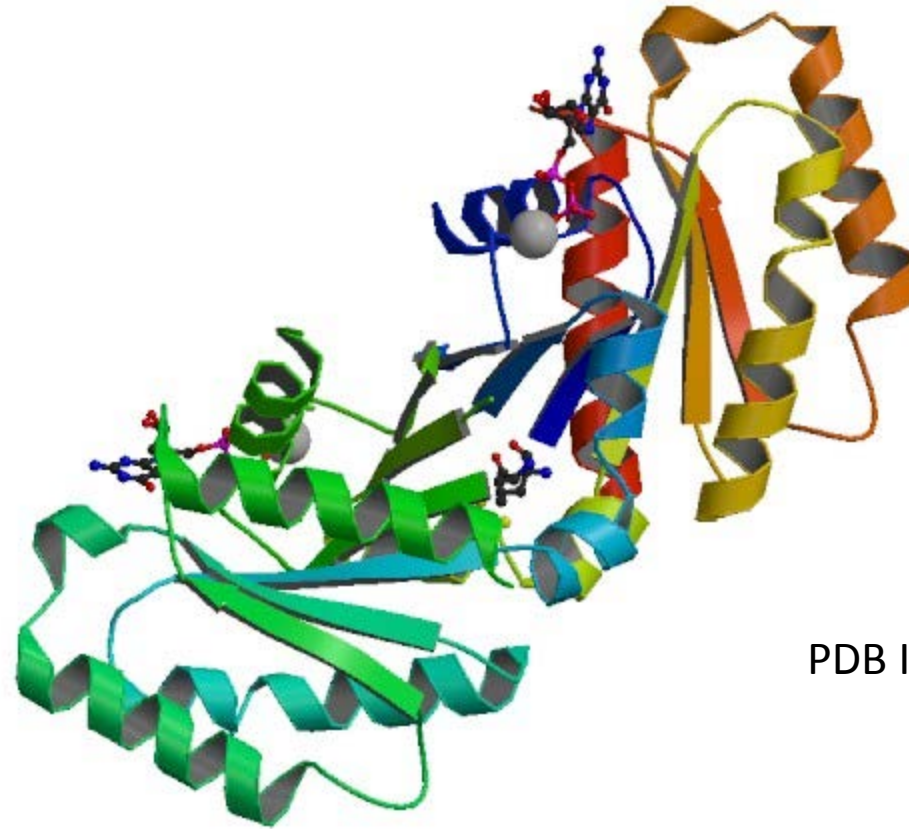
LRRK2: leucine-rich repeat kinase 2

Location: Chromosome 12:40.196.74-40.369.285 forward strand.

2527 amino acid



Background



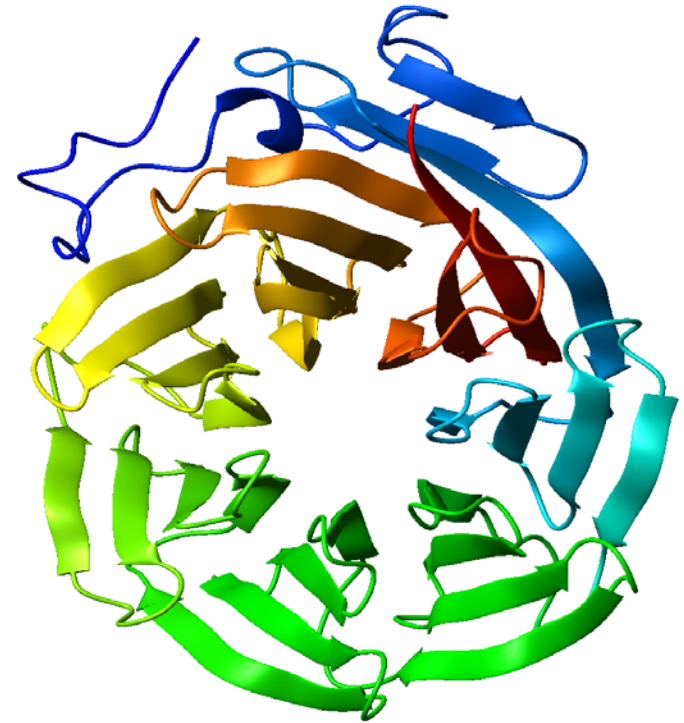
PDB ID: 2ZEJ

Structure of the ROC domain from the Parkinson's disease-associated leucine-rich repeat kinase 2 reveals a dimeric GTPase.



Background

The WD40 repeat (also known as the WD or beta-transducin repeat) is a short structure motif of approximately 40 amino acids, often terminating in a tryptophan-aspartic acid (W-D) dipeptide. Tandem copies of these repeats typically fold together to form a type of circular solenoid protein domain called the WD40 domain.



Sequence analysis



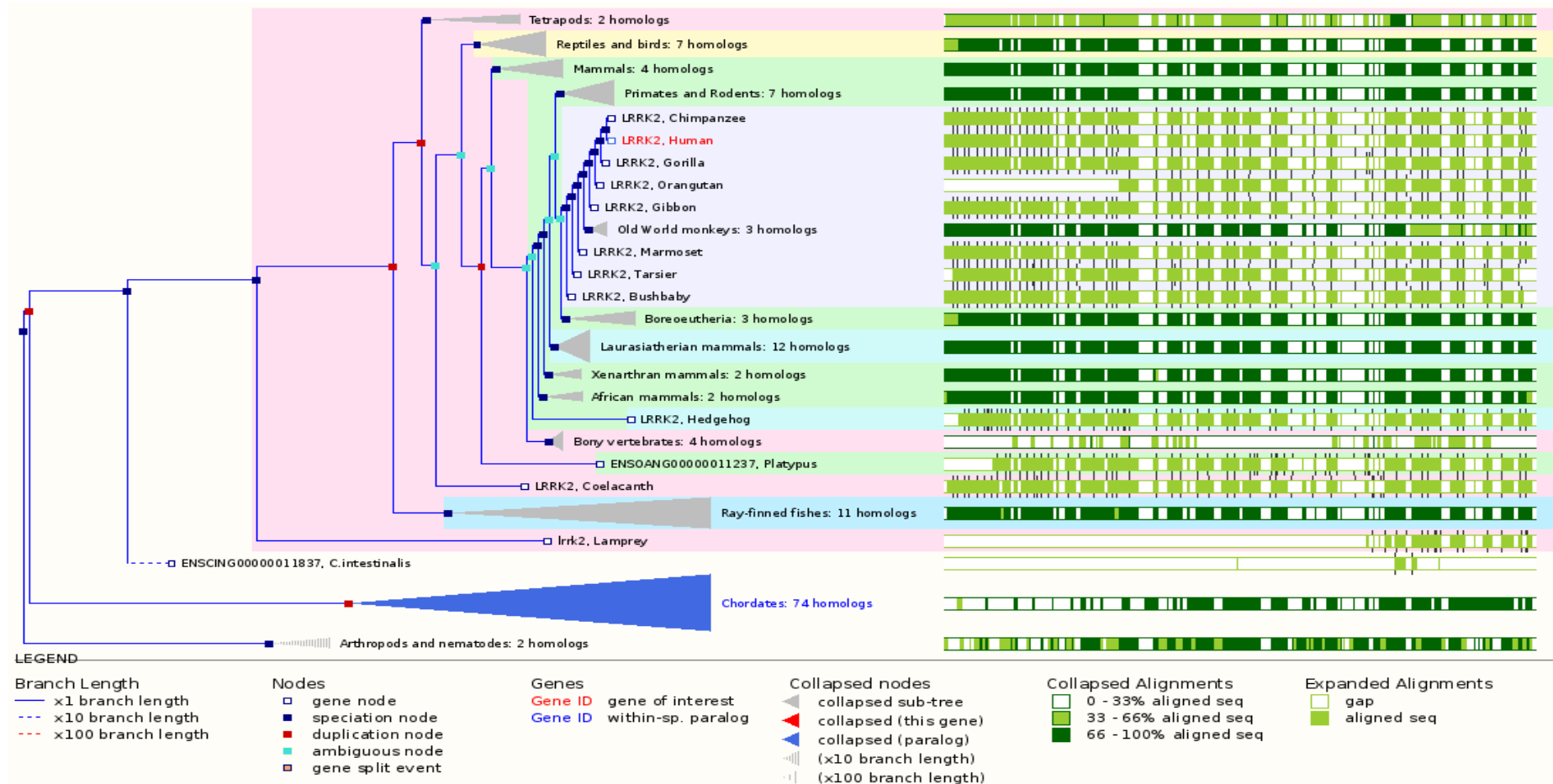
Transcripts

Name	Transcript ID	bp	Protein	Biotype	CCDS	RefSeq	Flags
LRRK2-004	ENST00000298910	9158	2527 aa	Protein coding	CCDS31774	NM_198578 NP_940980	TSL:1 GENCODE basic APPRIS PI
LRRK2-002	ENST00000343742	4740	1271 aa	Protein coding	-	-	TSL:5 GENCODE basic
LRRK2-001	ENST00000416796	1655	521 aa	Protein coding	-	-	CDS 3' incomplete TSL:3
LRRK2-005	ENST00000430804	6400	207 aa	Nonsense mediated decay	-	-	CDS 5' incomplete TSL:1
LRRK2-007	ENST00000481256	561	No protein	Processed transcript	-	-	TSL:4
LRRK2-003	ENST00000479187	8306	No protein	Retained intron	-	-	TSL:5
LRRK2-006	ENST00000474202	556	No protein	Retained intron	-	-	TSL:4

This gene has 7 transcripts. (splice variants)



Gene tree





Sequence alignment

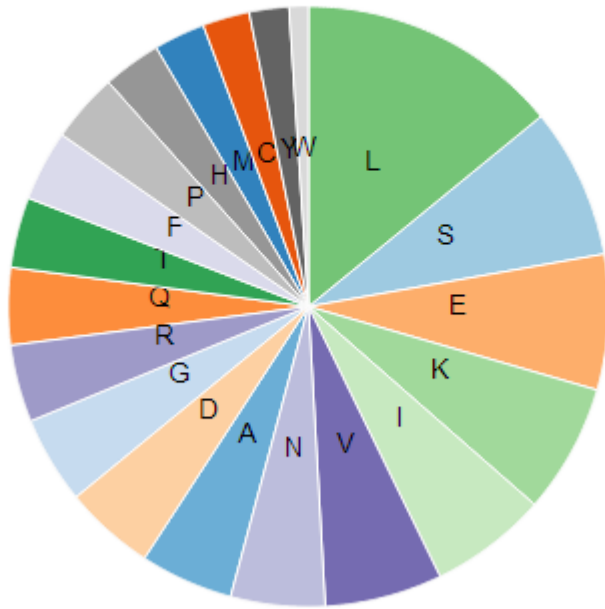
SPECIES	LENGTH	SCORE	IDENTITY	SIMILARITY	GAPS
Human/mouse	2529	11437.0	2189/2529 (86.6%)	2356/2529 (93.2%)	4/2529 (0.2%)
Human/Rat	2529	11446.0	2186/25279 (86.4%)	2363/2529 (93.4%)	5/2529 (0.2%)
Rat/Mouse	2527	12467.0	2400/2527 (95.0%)	2465/2527 (97.5%)	1/2527 (0.0%)

physicochemical property



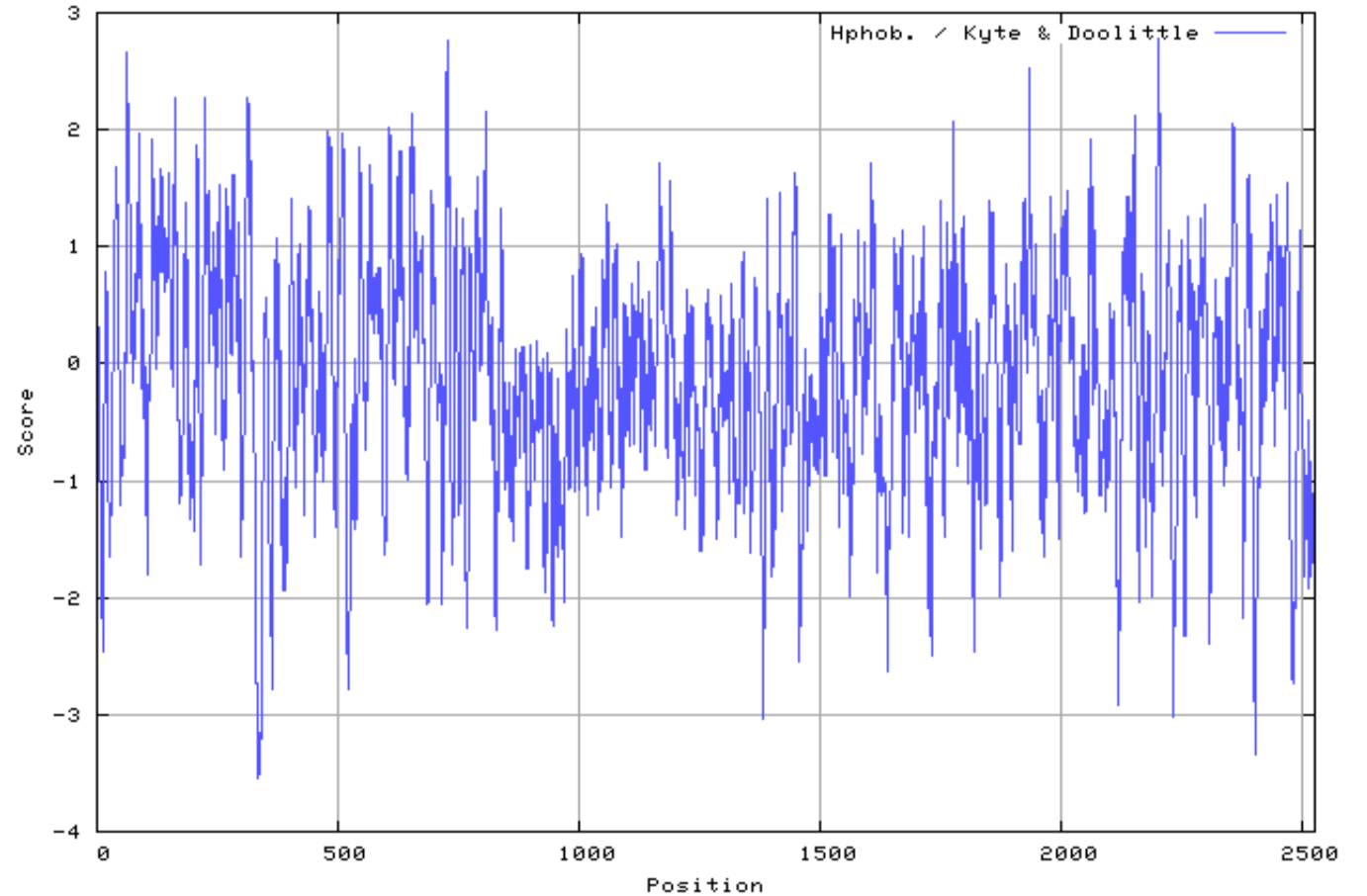
The properties of LRRK2

Amino Acid composition



L: 14.1% S: 8.1% E: 7.3% K: 7.0% I: 6.3%

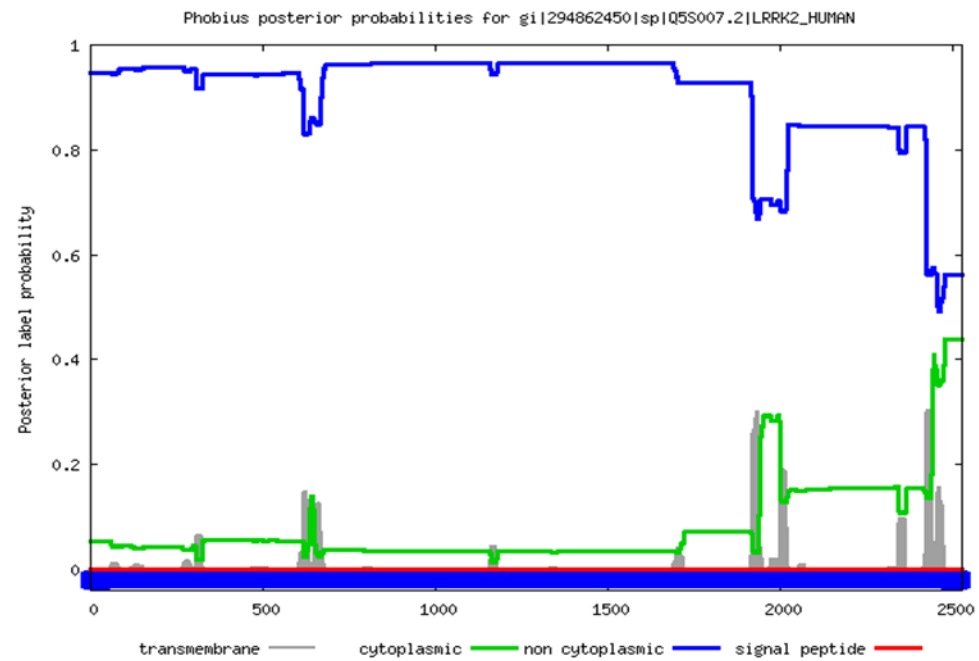
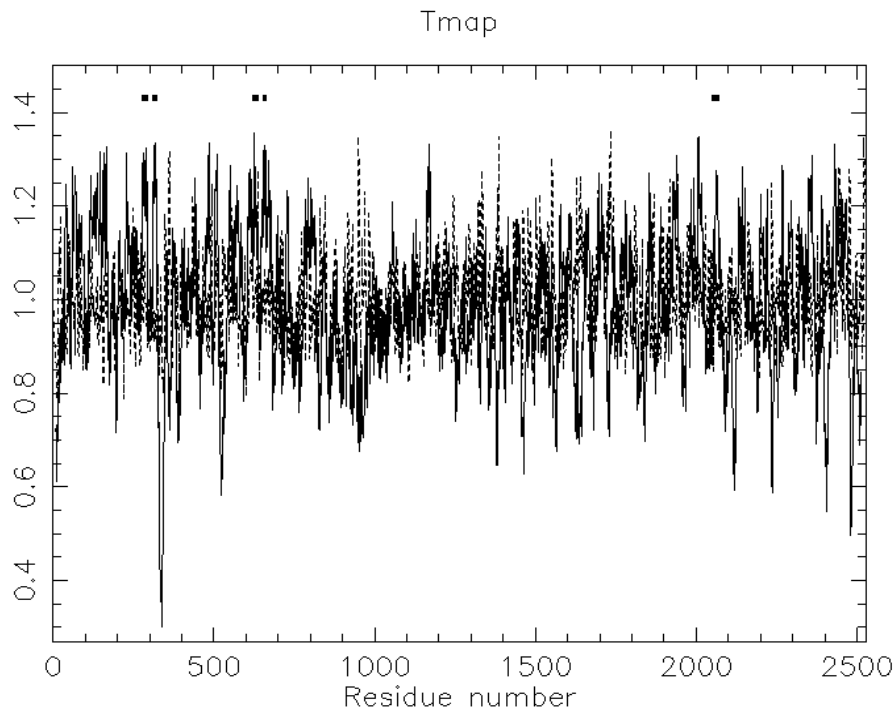
ProtScale output for user sequence



*Predict Protein
ExPASy*



The properties of LRRK2

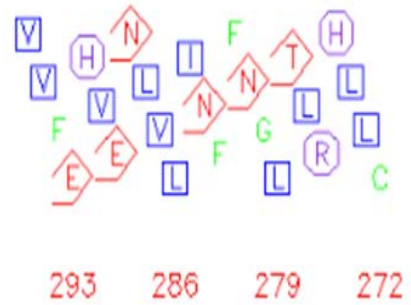




The properties of LRRK2

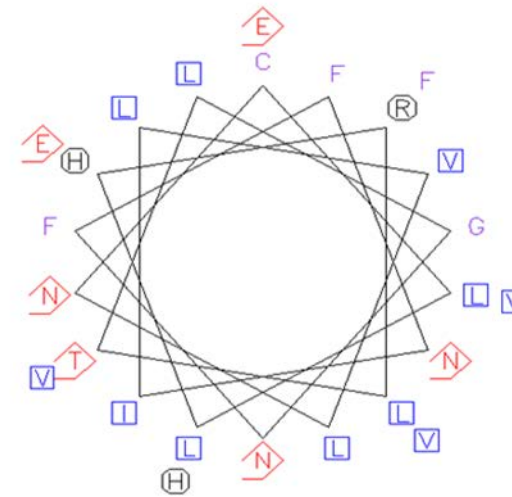
Helical net of fasta::LRRK2:LRRK2-HUMAN[272:296]

Thu 15 Jan 2015 10:41:26



Helical wheel of fasta::LRRK2:LRRK2-HUMAN[272:296]

Thu 15 Jan 2015 10:39:04



Protein structure analysis

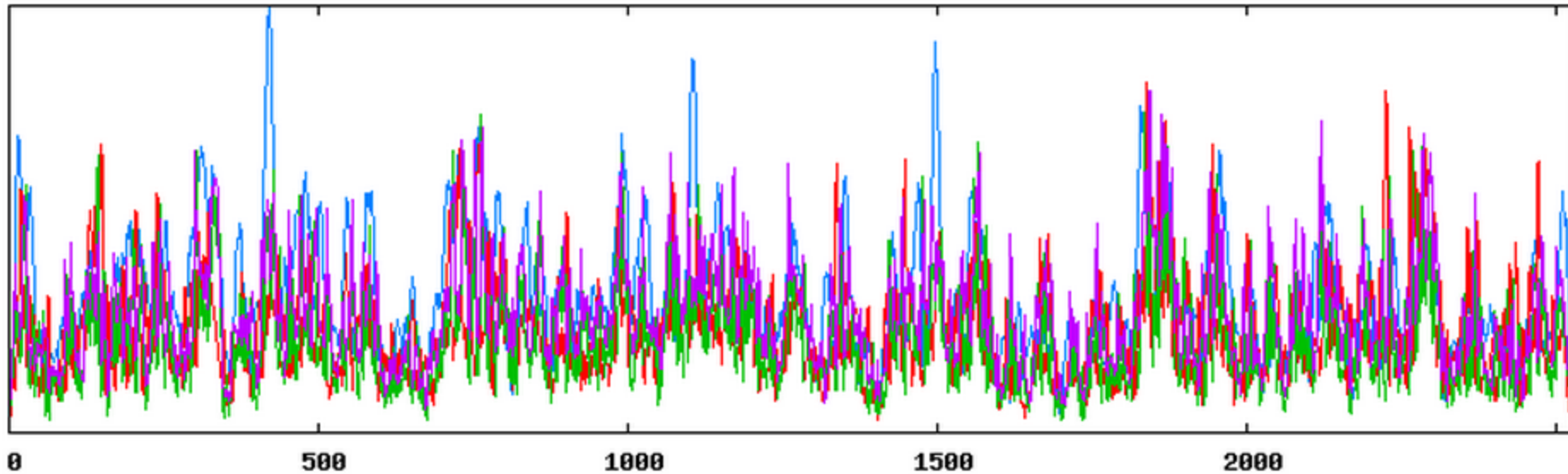
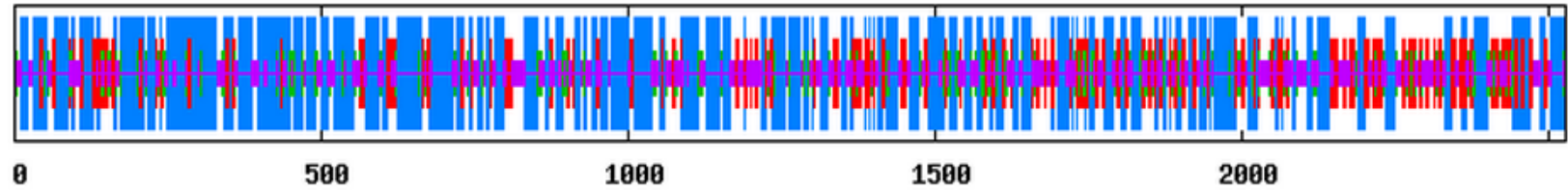


Secondary structure prediction

Sequence length : 2527

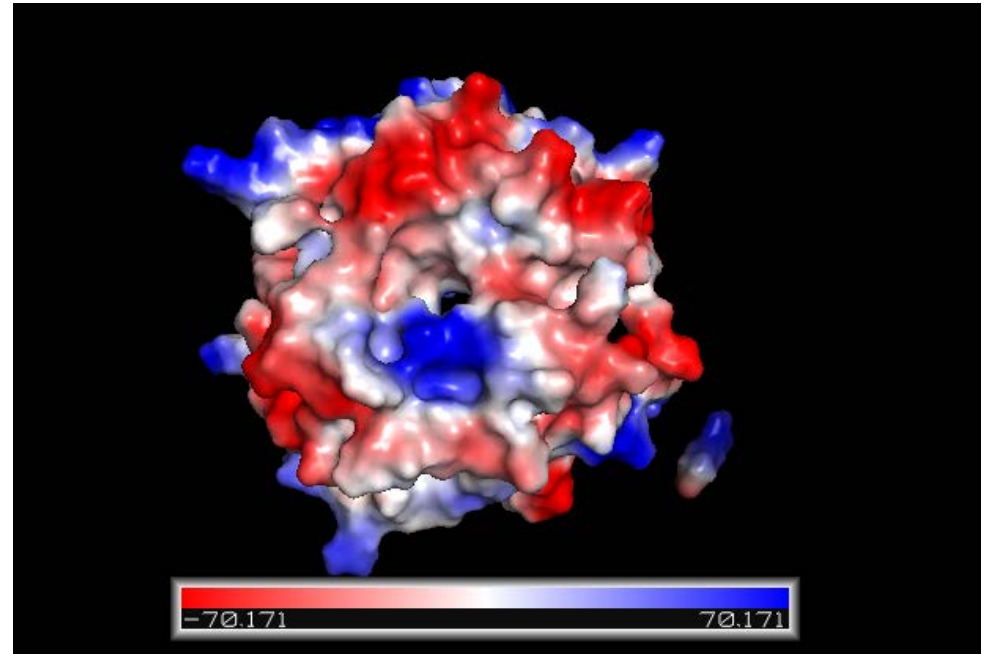
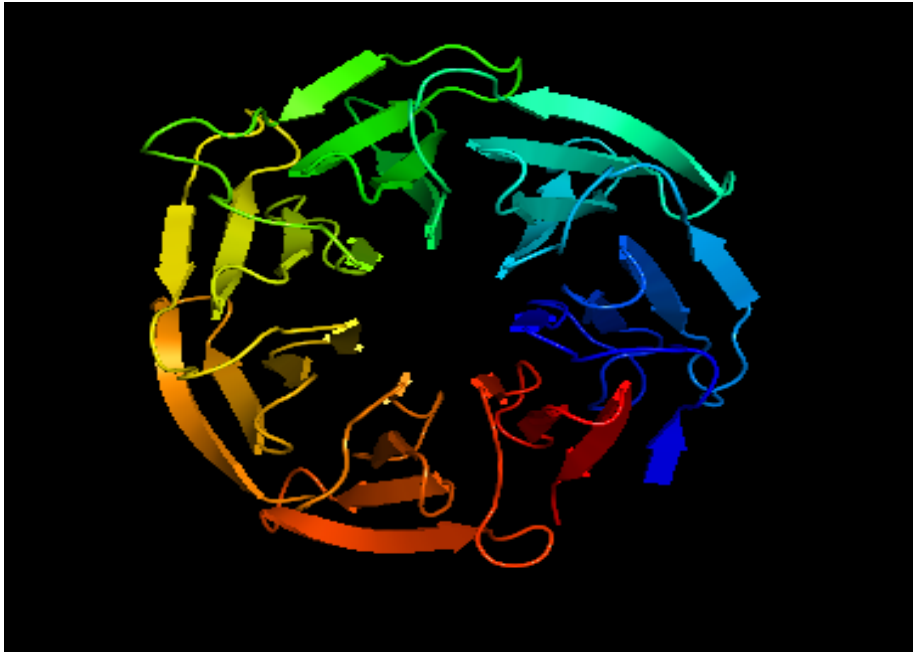
SOPMA :

Alpha helix	(Hh)	:	1196	is	47.33%
3_{10} helix	(Gg)	:	0	is	0.00%
Pi helix	(Ii)	:	0	is	0.00%
Beta bridge	(Bb)	:	0	is	0.00%
Extended strand	(Ee)	:	440	is	17.41%
Beta turn	(Tt)	:	208	is	8.23%
Bend region	(Ss)	:	0	is	0.00%
Random coil	(Cc)	:	683	is	27.03%
Ambiguous states (?)		:	0	is	0.00%
Other states		:	0	is	0.00%





The prediction of WD40 domain



Template PDB ID: 3DM0

Confidence:100.0%

Coverage:81%

Residue: 2142-2498

Phyre
Pymol

Function and pathway analysis

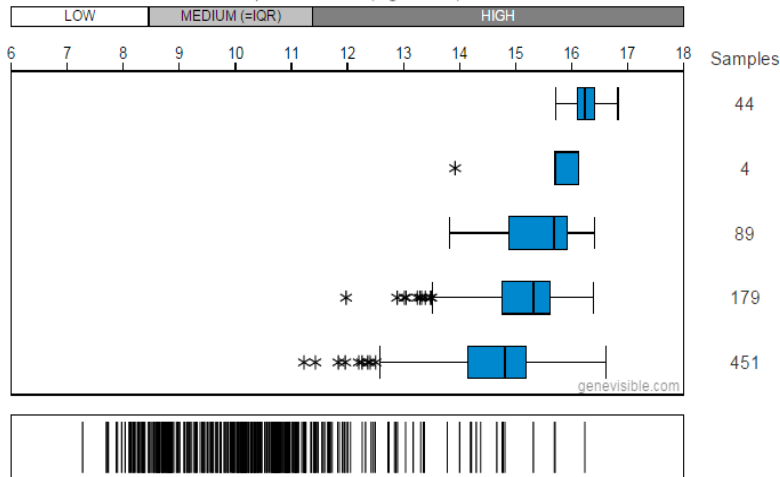


Tissue localization

Organism: **Homo sapiens** / Gene: **LRRK2** / Selected probe(set): **229584_at** / Platform: **Affymetrix Human Genome U133 Plus 2.0 Array**

TOP FIVE TISSUES

Expression level (log2 scale)



Expression of LRRK2 (229584_at) across 325 tissues tested by GENEVESTIGATOR

Neuron

Volume 44, Issue 4, 18 November 2004, Pages 601-607



Article

Mutations in *LRRK2* Cause Autosomal-Dominant Parkinsonism with Pleomorphic Pathology

Alexander Zimpr Lincoln⁴, Jennifer F. Pfeiffer⁷, Nadja Müller-Myhsok⁹, Wszolek ⁵, ⁶

Neuron

Volume 44, Issue 4, 18 November 2004, Pages 595-600



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doi:10.1016/j.neu

Under an Elsevier

Article

Cloning of the Gene Containing Mutations that Cause *PARK8*-Linked Parkinsonism

Coro Paisán Marcel van c Khan³, Jane Peña⁶, Roh Wood ², ¹

Show more

doi:10.1016/

Under an Elt



Original Articles

Localization of LRRK2 to membranous and vesicular structures in mammalian brain

Saskia Biskup MD, PhD^{1,2,†}, Darren J. Moore PhD ^{1,2,†}, Fulvio Celsi B:

Andrew B. West PhD¹ Kaisa Kurkinen PhD¹

Joseph M. Savitt MD, PhD⁶, Richard L. M. Emson PhD⁵, Reidu MD, PhD³, Ted M. D and Valina L. Dawso

PhD⁶, Richard L. M. Emson PhD⁵, Reidu MD, PhD³, Ted M. D and Valina L. Dawso

Dagmar Gatter PhD¹, Marie Westerlund MSc¹, Andrea Carmine PhD¹, Eva Lindqvist BSc¹, Olof Sydow MD, PhD² and Lars Olson PhD^{1,*}

Article first published DOI: 10.1002/ana.211

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Article first published online: 10 MAR 2006 DOI: 10.1002/ana.20808

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Brief Communication

LRRK2 expression linked to dopamine-innervated areas

Dagmar Gatter PhD¹, Marie Westerlund MSc¹, Andrea Carmine PhD¹, Eva Lindqvist BSc¹, Olof Sydow MD, PhD² and Lars Olson PhD^{1,*}

Article first published DOI: 10.1002/ana.20808

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Article first published online: 10 MAR 2006 DOI: 10.1002/ana.20808

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Annals of Neurology Volume 59, Issue 4, pages 714-719, April 2006



Subcellular localization

Currently selected additional filtering parameters:

aspect C

Count of Annotations per GO Identifier

Statistics for all 34 distinct GO IDs

Code	Name	%	Count	
GO:0030425	dendrite	6.33	5	■
GO:0005737	cytoplasm	6.33	5	■
GO:0043204	perikaryon	5.06	4	■
GO:0030424	axon	5.06	4	■
GO:0005794	Golgi apparatus	5.06	4	■
GO:0005783	endoplasmic reticulum	5.06	4	■
GO:0005768	endosome	5.06	4	■
GO:0005764	lysosome	5.06	4	■
GO:0005743	mitochondrial inner membrane	5.06	4	■
GO:0005741	mitochondrial outer membrane	5.06	4	■
GO:0031410	cytoplasmic vesicle	3.80	3	■
GO:0016020	membrane	3.80	3	■
GO:0005829	cytosol	3.80	3	■
GO:0005759	mitochondrial matrix	3.80	3	■
GO:0005739	mitochondrion	3.80	3	■
GO:0045202	synapse	2.53	2	■
GO:0043025	neuronal cell body	2.53	2	■
GO:0043005	neuron projection	2.53	2	■

Currently selected additional filtering parameters:

evidence IMP, IGI, IPI, IDA, IEP, EXP
aspect C

Count of Annotations per GO Identifier

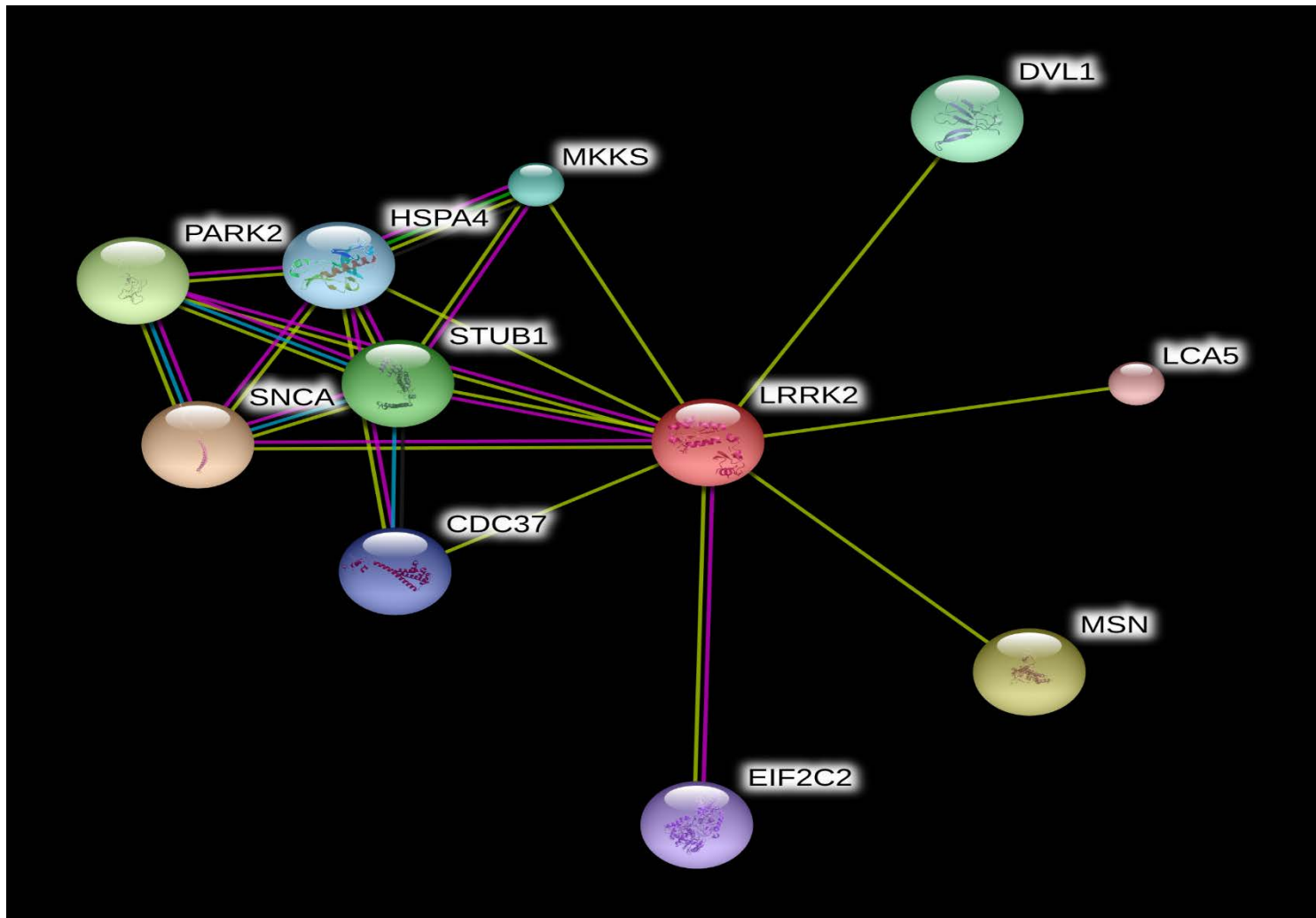
Statistics for all 14 distinct GO IDs

Code	Name	%	Count	
GO:0005829	cytosol	16.67	3	■
GO:0043025	neuronal cell body	11.11	2	■
GO:0005737	cytoplasm	11.11	2	■
GO:0070062	extracellular vesicular exosome	5.56	1	■
GO:0043204	perikaryon	5.56	1	■
GO:0043005	neuron projection	5.56	1	■
GO:0032839	dendrite cytoplasm	5.56	1	■
GO:0032473	cytoplasmic side of mitochondrial outer membrane	5.56	1	■
GO:0031966	mitochondrial membrane	5.56	1	■
GO:0030425	dendrite	5.56	1	■
GO:0030424	axon	5.56	1	■
GO:0016234	inclusion body	5.56	1	■
GO:0005739	mitochondrion	5.56	1	■
GO:0005615	extracellular space	5.56	1	■

Manual experimental

Quick GO

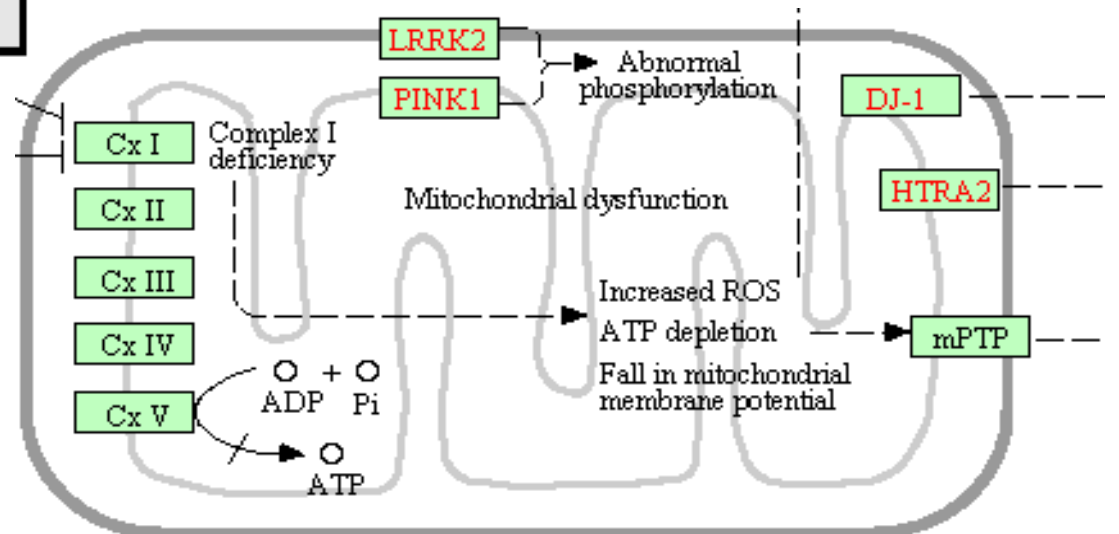
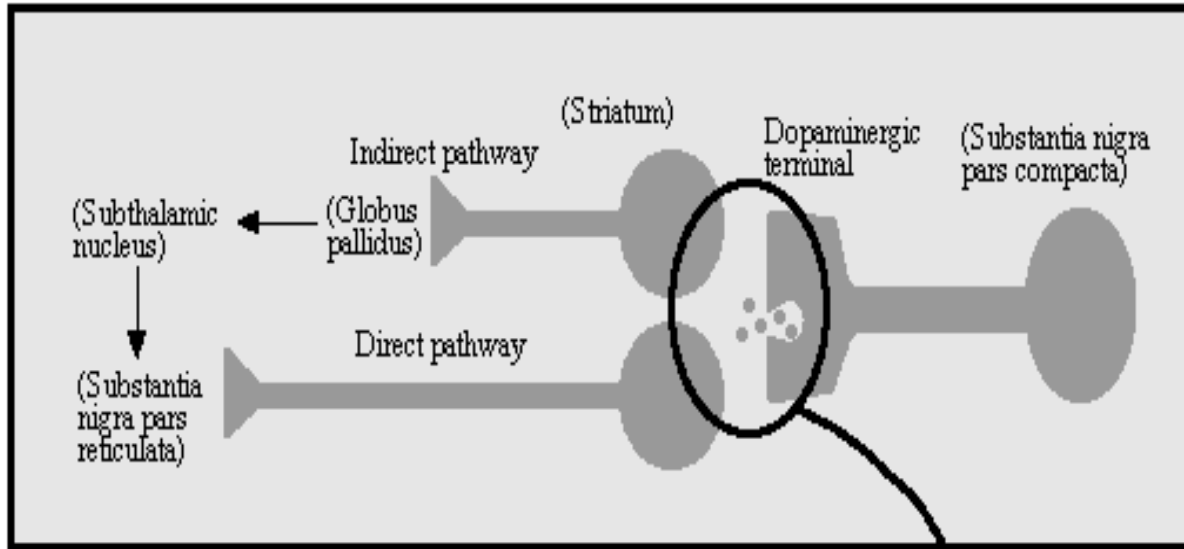
Protein protein interaction



STUB1: STIP1 homology and U-box containing protein 1; Modulates the activity of several chaperone complexes, including Hsp70, Hsc70 and Hsp90. Has E3 ubiquitin-protein ligase activity.

PARK2: May play a more general role in the ubiquitin proteasomal pathway by participating in the removal and/or detoxification of abnormally folded or damaged protein. Loss of this ubiquitin ligase activity appears to be the mechanism underlying pathogenesis of PARK2.

Pathway





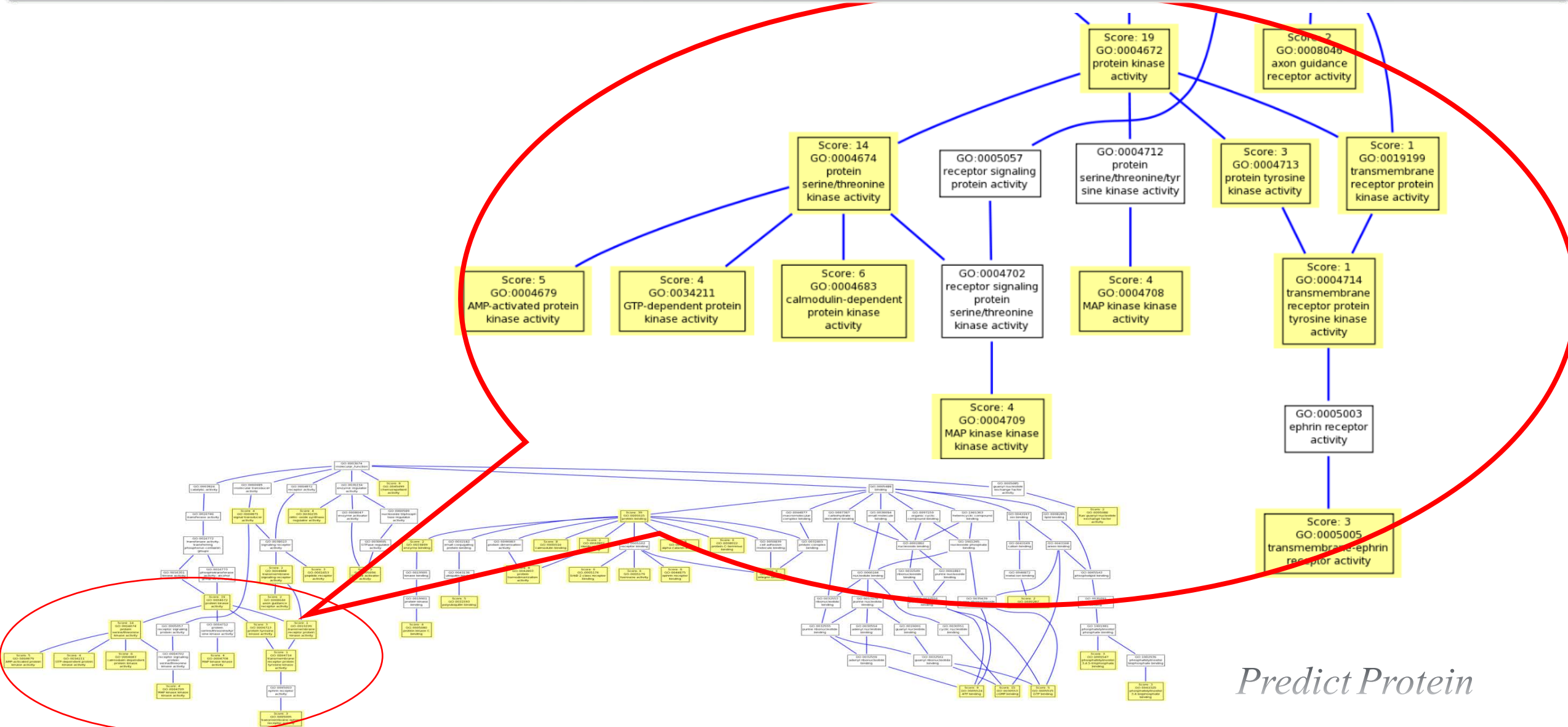
Go analysis

Molecular Function Ontology				
#	GO ID	GO Term	Reliability (%)	
1	GO:0005515	protein binding	39	<input checked="" type="checkbox"/>
2	GO:0004672	protein kinase activity	19	<input checked="" type="checkbox"/>
3	GO:0030553	cGMP binding	15	<input checked="" type="checkbox"/>
4	GO:0004674	protein serine/threonine kinase activity	14	<input checked="" type="checkbox"/>
5	GO:0008022	protein C-terminus binding	9	<input checked="" type="checkbox"/>
6	GO:0005524	ATP binding	9	<input checked="" type="checkbox"/>
7	GO:0045294	alpha-catenin binding	8	<input checked="" type="checkbox"/>
8	GO:0042803	protein homodimerization activity	8	<input checked="" type="checkbox"/>
9	GO:0005516	calmodulin binding	8	<input checked="" type="checkbox"/>
10	GO:0005178	integrin binding	6	<input checked="" type="checkbox"/>
11	GO:0005176	ErbB-2 class receptor binding	6	<input checked="" type="checkbox"/>
12	GO:0004683	calmodulin-dependent protein kinase activity	6	<input checked="" type="checkbox"/>
13	GO:0046875	ephrin receptor binding	6	<input checked="" type="checkbox"/>
14	GO:0045499	chemorepellent activity	6	<input checked="" type="checkbox"/>
15	GO:0005179	hormone activity	6	<input checked="" type="checkbox"/>
16	GO:0031593	polyubiquitin binding	5	<input checked="" type="checkbox"/>
17	GO:0004679	AMP-activated protein kinase activity	5	<input checked="" type="checkbox"/>
18	GO:0005525	GTP binding	5	<input checked="" type="checkbox"/>
19	GO:0004708	MAP kinase kinase activity	4	<input checked="" type="checkbox"/>
20	GO:0034211	GTP-dependent protein kinase activity	4	<input checked="" type="checkbox"/>

Biological Process Ontology				
#	GO ID	GO Term	Reliability (%)	
1	GO:0007264	small GTPase mediated signal transduction	26	<input checked="" type="checkbox"/>
2	GO:0031398	positive regulation of protein ubiquitination	24	<input checked="" type="checkbox"/>
3	GO:0040012	regulation of locomotion	21	<input checked="" type="checkbox"/>
4	GO:0006468	protein amino acid phosphorylation	20	<input checked="" type="checkbox"/>
5	GO:0046777	protein amino acid autophosphorylation	20	<input checked="" type="checkbox"/>
6	GO:0018105	peptidyl-serine phosphorylation	19	<input checked="" type="checkbox"/>
7	GO:0070997	neuron death	19	<input checked="" type="checkbox"/>
8	GO:0000186	activation of MAPKK activity	19	<input checked="" type="checkbox"/>
9	GO:0043068	positive regulation of programmed cell death	18	<input checked="" type="checkbox"/>
10	GO:0000910	cytokinesis	17	<input checked="" type="checkbox"/>
11	GO:0006979	response to oxidative stress	17	<input checked="" type="checkbox"/>
12	GO:0008340	determination of adult lifespan	16	<input checked="" type="checkbox"/>
13	GO:0006464	protein modification process	15	<input checked="" type="checkbox"/>
14	GO:0007165	signal transduction	10	<input checked="" type="checkbox"/>
15	GO:0007275	multicellular organismal development	9	<input checked="" type="checkbox"/>
16	GO:0023034	intracellular signaling pathway	9	<input checked="" type="checkbox"/>
17	GO:0007243	intracellular protein kinase cascade	9	<input checked="" type="checkbox"/>
18	GO:0045860	positive regulation of protein kinase activity	8	<input checked="" type="checkbox"/>
19	GO:0043507	positive regulation of JUN kinase activity	8	<input checked="" type="checkbox"/>
20	GO:0030154	cell differentiation	8	<input checked="" type="checkbox"/>



Molecular function



Predict Protein



Acknowledge

- **Thanks for my mentors Dr. Ye!**
- **Thanks for my group members!**
- **Thanks for ABC course teacher Dr. Luo and classmates !**



Acknowledge

Thanks for your attention!