Introduction to Parkinson's disease

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- 1.5h lecture
- Break
- 1h workshop
- Clinic to bench
- Definitions:
- Pathology, Etiology, Symptoms, Syndroms, Phenotype

Neurodegenerative diseases
Prevalence in US

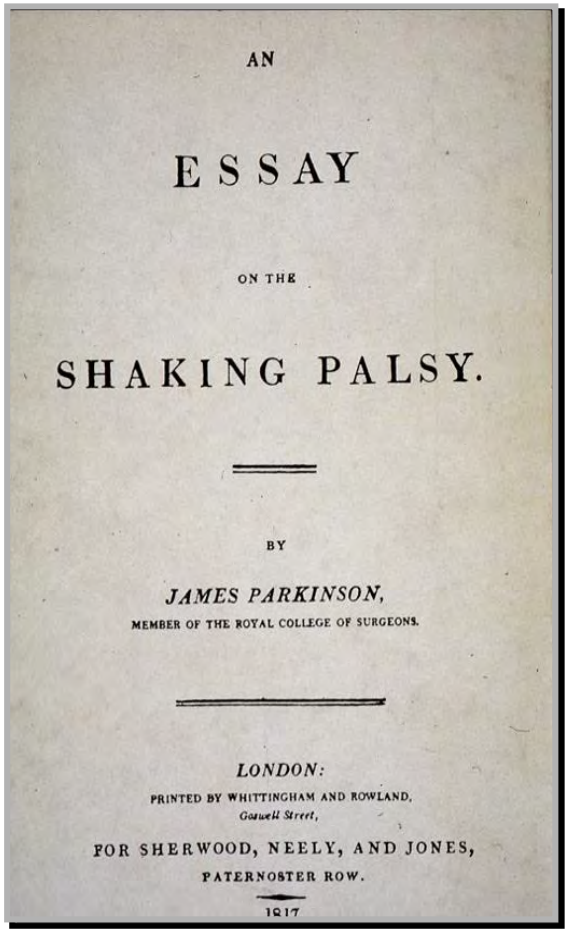
		# per 100,000
Alzheimer's disease	4,000,000	1,450
Parkinson's disease	*1,000,000*	*360*
Frontotemporal dementia	40,000	14
Pick's disease	5,000	2
Progressive supranuclear palsy	15,000	5
Amyotrophic lateral sclerosis	20,000	7
Huntington's disease	30,000	11
Prion disease	400	<1

Economic

…Thus, in the current state, the recurrent direct costs per patient adds up to 2,500 or 13,000 EUR per three months, depending on the disease stage of the patient (Dodel, Reese et al. 2008)…

…The current costs associated with PD in Europe are currently estimated to be at €13.9 billion annually (Gustavsson, 2011). Strikingly, the development of a treatment with the ability to only delay the progression of PD by 6 months would reduce the costs to the healthcare system (particularly for nursing) by an amount that is equivalent to the entire costs that are current spend on the symptomatic treatment for PD every year (Vossius et al., 2009).

Parkinson's Disease History



AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,
Goswell Street,

FOR SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW.

1817

- Best described as "shaking palsy" by James Parkinson in 1817
- "Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured."

Olanow CW et al. *Neurology*. 2001;56 (suppl 5):S1-S88. National Parkinson Foundation Web site. www.parkinson.org. Marttila RJ, Rinne UK. *Acta Neurol Scand*. 1991;84(suppl 136):24-28. DeStefano AL et al. *Am J Hum Genet*. 2002;70:1089-1095.

“As the disease proceeds towards its last stage, the trunk is almost permanently bowed…”

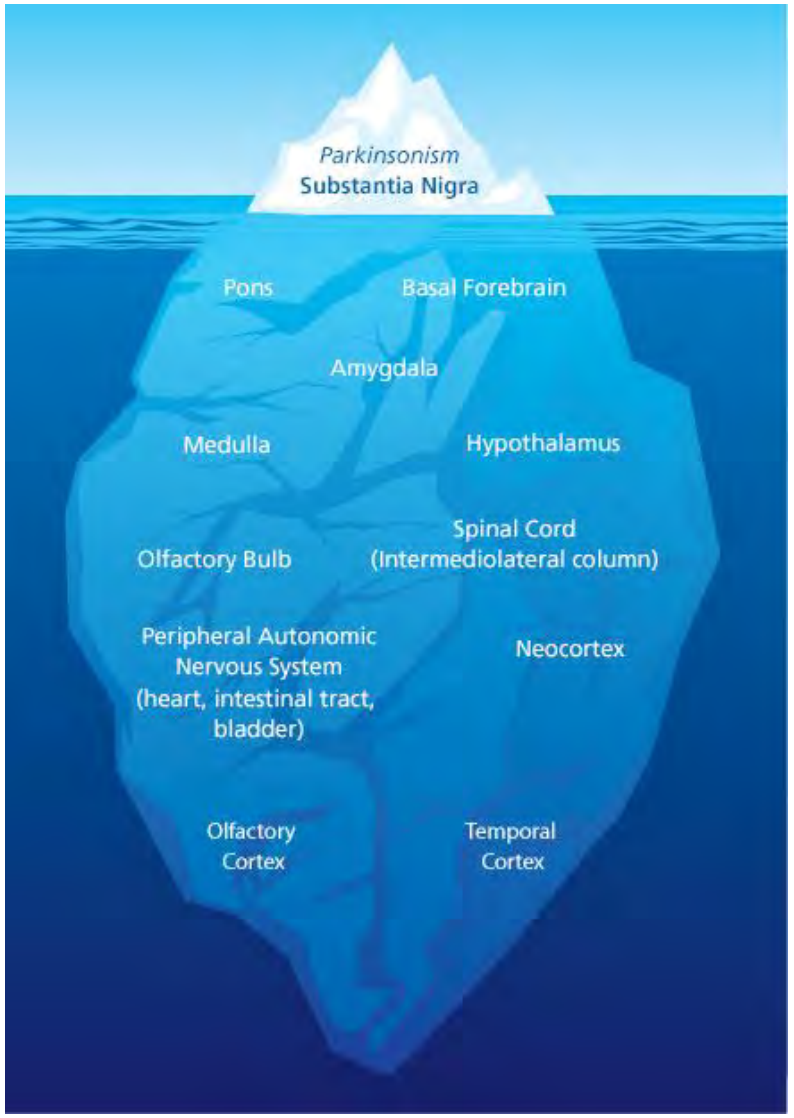
Motor Symptoms

- Tremor at rest
- Bradykinesia
- Rigidity
- Postural instability
- Decreased arm swing when walking
- Micrographia
- Hypophonia
- Masked face
- Slow, shuffling gait
- Stooped posture

Olanow CW, Watts RL, Koller WC.. *Neurology*. 2001;56 (suppl 5):S1-S88.
Waters CH. *Diagnosis and Management of Parkinson's Disease*. 3rd ed. 2002.
National Parkinson Foundation. http://www.parkinson.org.

Non-Motor

- Cognitive, mood, and behavioral dysfunction
- Olfactory disturbance
- Sleep disturbance
- Constipation
- Seborrheic dermatitis
- Pain
- Autonomic disturbances



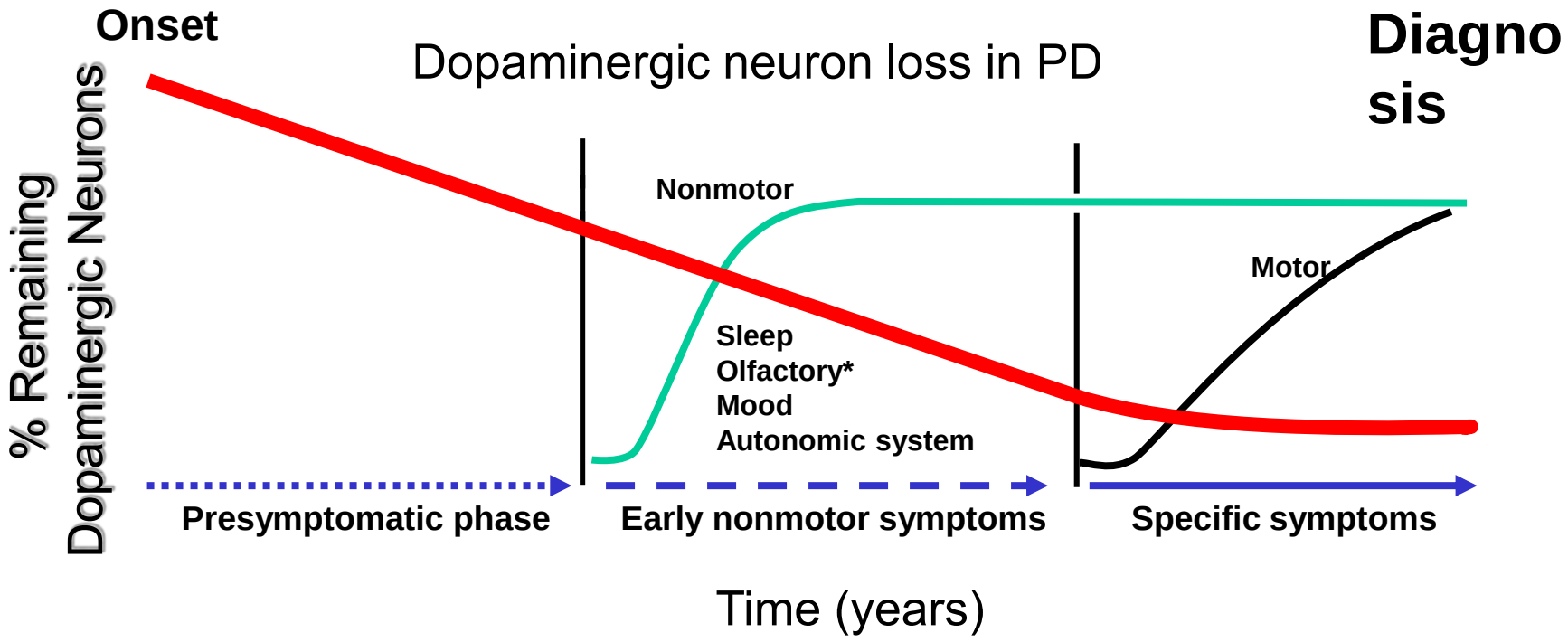
Nutt JG, Wooten GF. *N Engl J Med*. 2005;353:1021-1027.
Parkinson's Disease Foundation Web site. www.pdf.org.

Strange forerunner syndrome:

REM-sleep behaviour disorder

(Carlos H Schenck, Minneapolis)

Dynamic of symptoms



Halperin et al. *Neurotherapeutics*. 2009;6:128-140.
Lang. *Neurology*. 2007;68:948-952.
Ross et al. *Ann Neurol*. 2008;63:167-173.

Risk of Parkinson's Disease

Increased risk

- Age
- High Body Mass Index
- Male gender
- Family history
  - Genetics
- Depression
- Environment factors
  - rural living; pesticide exposure
  - well-water drinking
  - head injury, trauma, inflammation

Decreased risk

- Caffeine intake
- Smoking cigarettes
- Anti-oxidants in diet

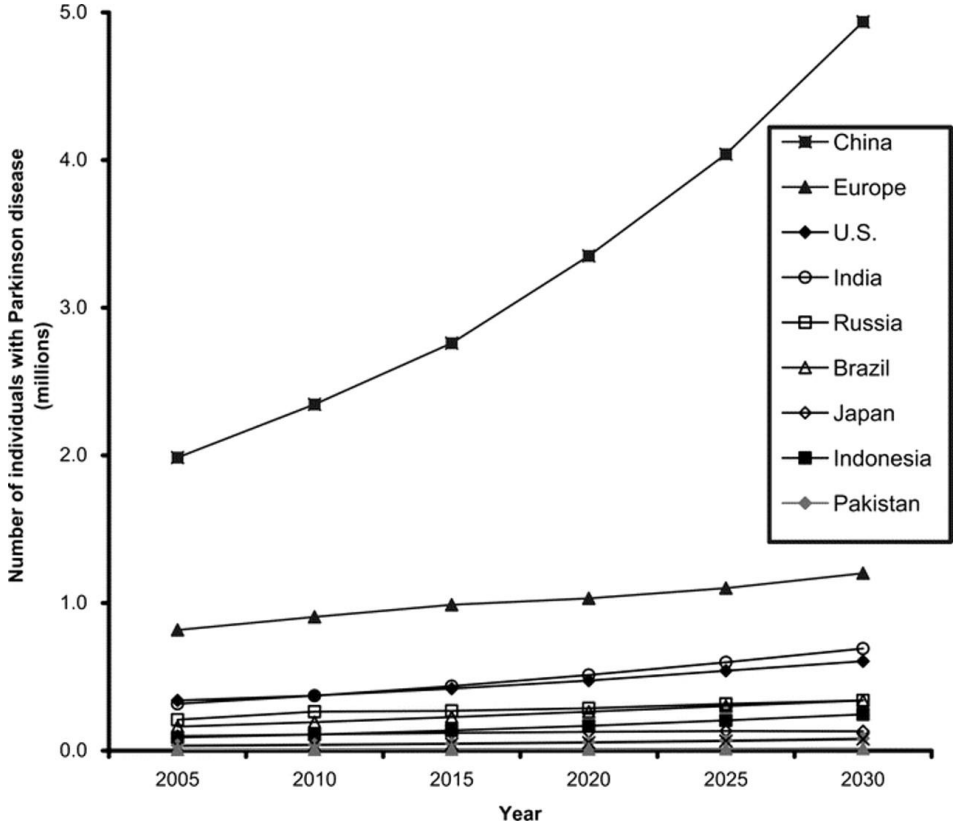
Burden of Parkinson's disease

- ~ 500.000 patients in US
- 1 % of > 50 yo.
- 3% of >65 yo.

- 2nd most common ND

- Lifetime risk
  - 2 % for men, 1.3 % for women

- Projected increase
  - Patient numbers will double to 8-9 million worldwide in 2030



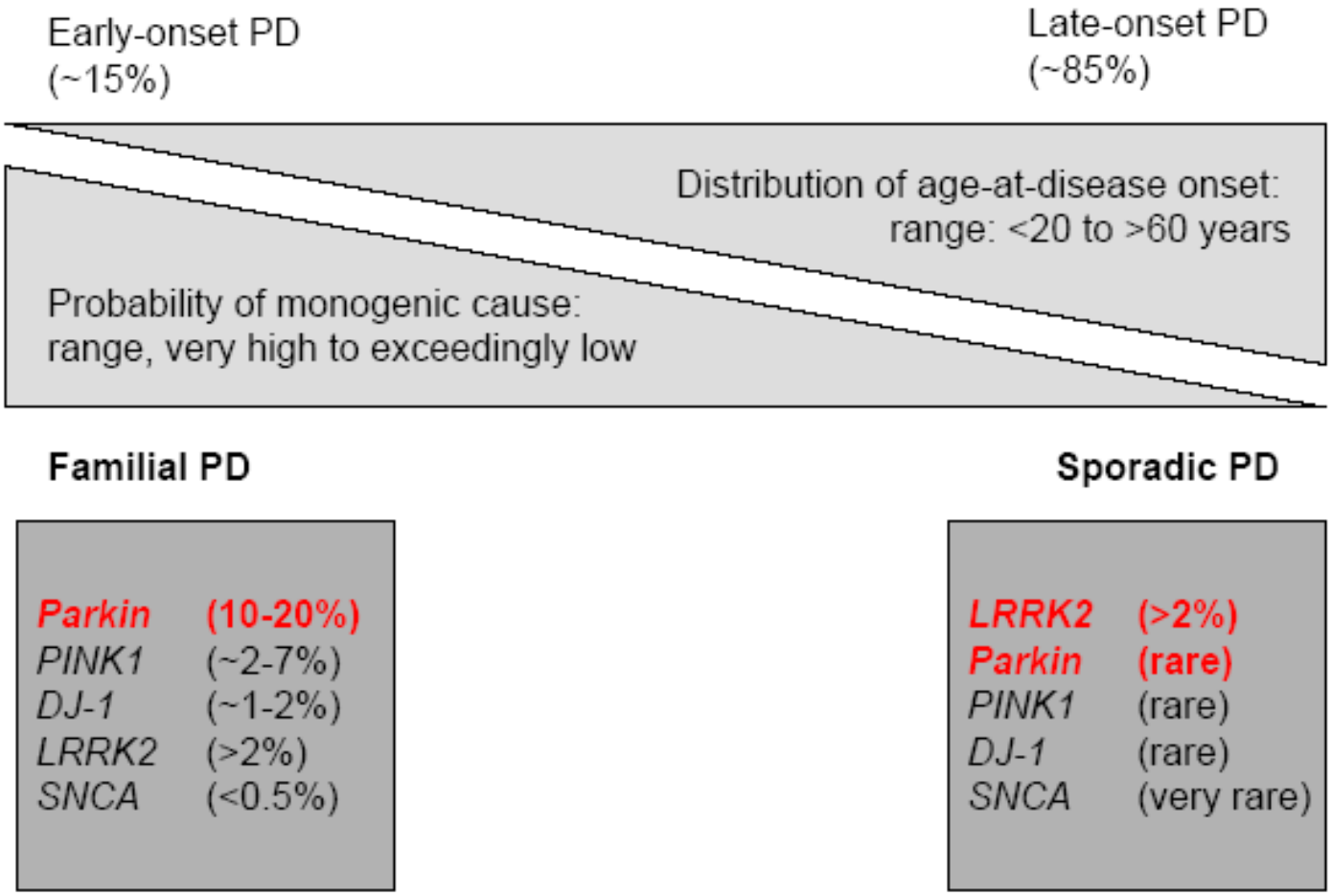
Dorsey et al., NEUROLOGY 2007;68:384-386 Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030

Genetics of Parkinson's disease

Familial Parkinson's disease provides: <10% of patients

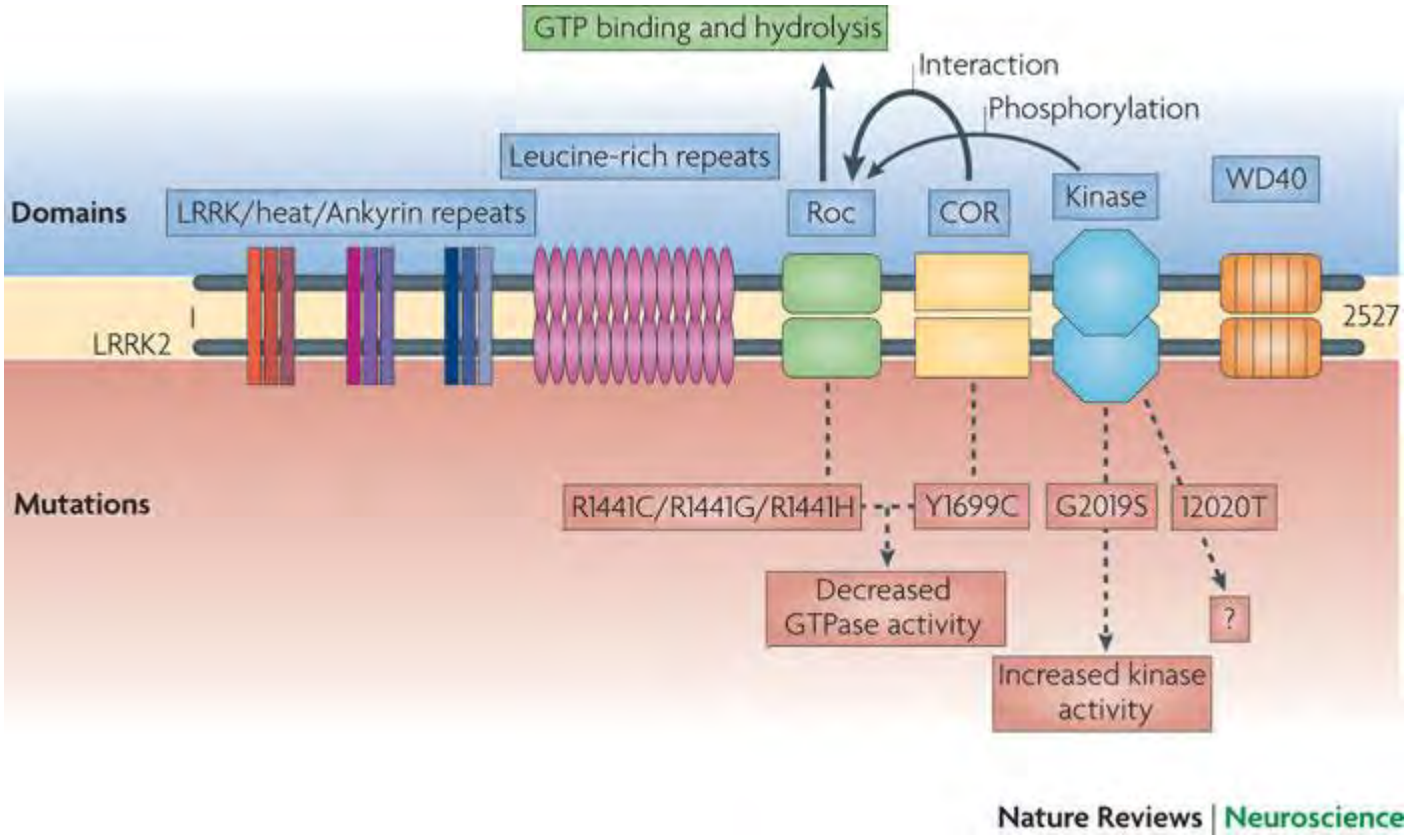
Locus	Inheri-tance	Chromosome	Gene	Name of protein	Protein function	Pathology	Comments
PARK1	AD	4q21-23	*SNCA*	α-synuclein	Synaptic protein	LB+	Protein is major component of LB
PARK2	AR	6q25.2-q27	*PRKN*	Parkin	Ubiquitin-protein ligase	Pleomorphic (most LB-)	Most common cause of AR-JP
PARK3	AD	2q13	*SPR?*	Aldo-keto reductase?	Unknown	Unknown	Gene not known with certainty
PARK4	AD	4q21-23	*SNCA*	α-synuclein	Excess of α-synuclein protein		Multiplication of *SNCA* gene
PARK5	AD	4p14	*UCHL1*	UCHL-1	Hydrolyze small C-terminal adducts of ubiquitin	Unknown	Role uncertain
PARK6	AR	1p36-p35	*PINK1*	PINK1	Mitochondrial kinase	Unknown	Second most common cause of AR-JP
PARK7	AR	1p36	*DJ-1*	DJ-1	Oxidative stress protection	Unknown	Rare
PARK8	AD	12p11-q13	*LRRK2*	LRRK2	Muliple functions by several domains	Pleomorphic (LB+, tau+, ub+)	Most common cause of dominant Parkinson disease
PARK9	AR	1p36	*ATP13A2*	ATPase type 13A2	Lysosomal protein	Unknown	Complex phenotype (Parkinsonism, spasticity, and dementia)
PARK11	AD	2q37.1	*GIGYF2?*	GRB10 interacting GYF protein 2	Unknown	Unknown	Role uncertain
PARK13	AD?	2p12	*OMI/ HTRA2*	HtrA serine peptidase 2	Serine protease+	Unknown	No cosegregation shown to support pathogenicity
PARK14	AR	22q13.1	*PLA2G6*	A2 phospholipase	Phospholipid remodelling+	Unknown	Allelic to neuroaxonal dystrophy: adult-onset dystonia-parkinsonism in two patients
PARK15	AR	22q12-q13	*FBXO7*	F-box protein 7	Phosphorylation-dependent ubiquitination	Unknown	Early-onset, severe phenotype with spasticity and dementia

AD, autosomal dominant; AR, autosomal recessive



Klein and Schlossmacher, Nat Clin Pract Neurol, 2006

LRRK2

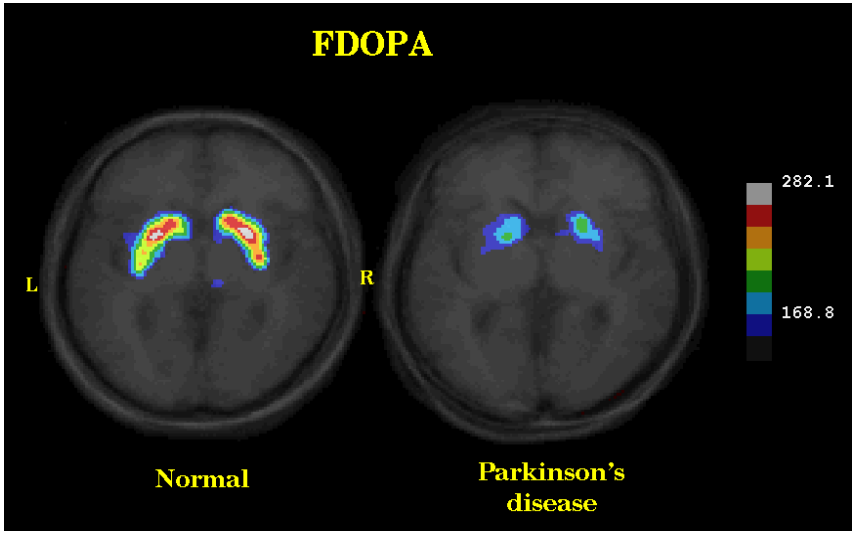

GTP binding and hydrolysis
Interaction
Phosphorylation
Leucine-rich repeats
Domains
LRRK/heat/Ankyrin repeats
Roc
COR
Kinase
WD40
LRRK2
1
2527
Mutations
R1441C/R1441G/R1441H
Y1699C
G2019S
I2020T
Decreased GTPase activity
?
Increased kinase activity
Nature Reviews | Neuroscience

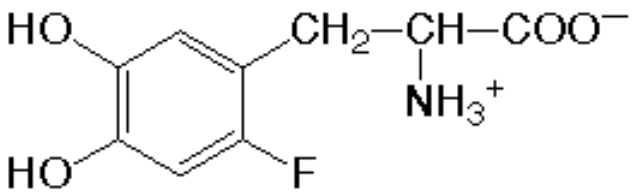
Diagnosis

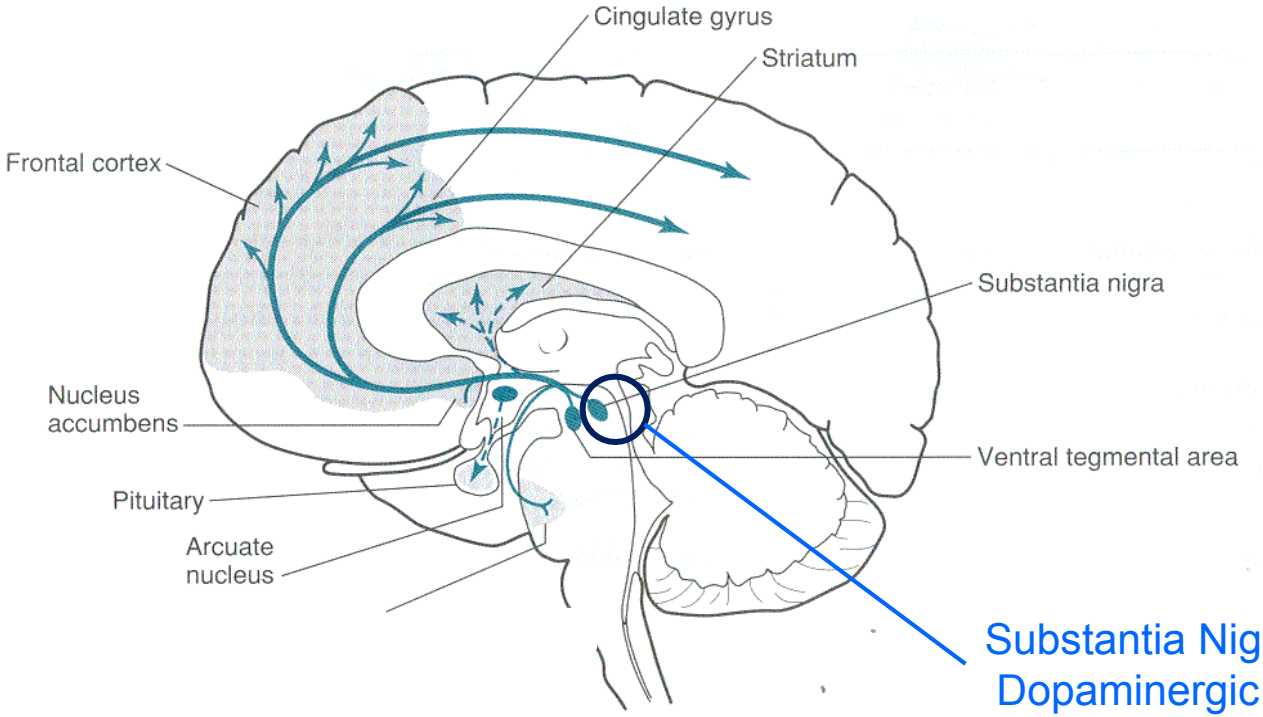
- PET Scan—decreased dopaminergic activity in the substantia nigra
- Unified Parkinsons Disease Rating Scale—cognitive interview
- Normal CT
- Normal MRI

PET Scan Reveals Loss of Dopamine Receptors in the Brain

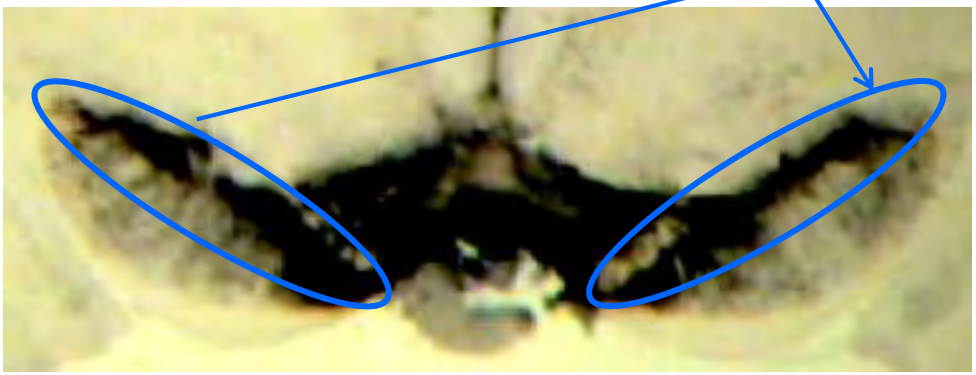
- Injecting patients with ^{18}F-dopamine allows quantification of dopaminergic receptors in the brain.
- PD patients have a great diminishment of receptors in the brain (as a results of DA neuron death).







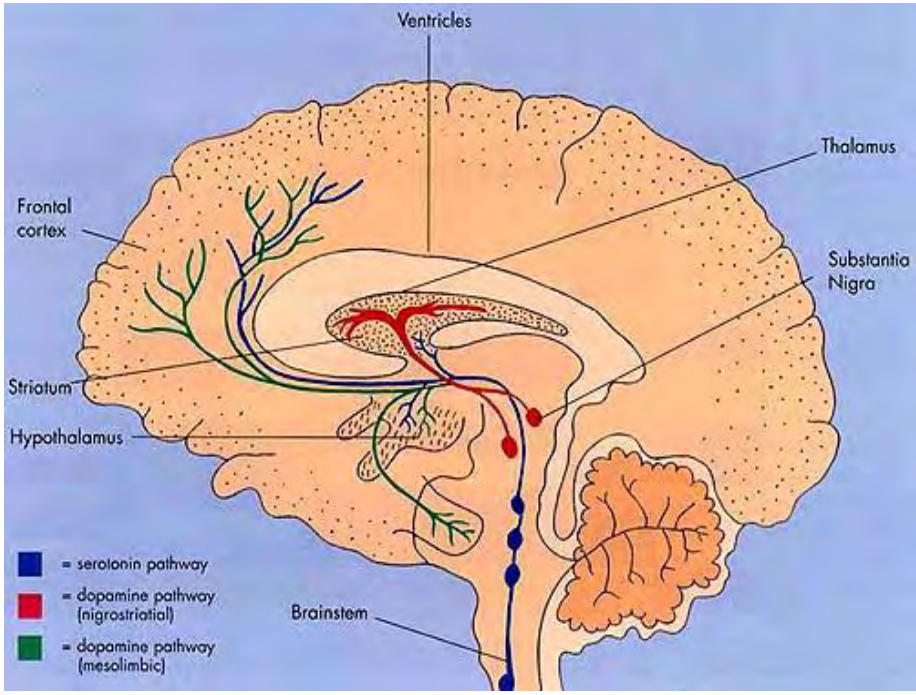
Substantia Nigra:
Dopaminergic neurons die in PD



Rodent brain section, stained for tyrosine hydroxylase: coronal view

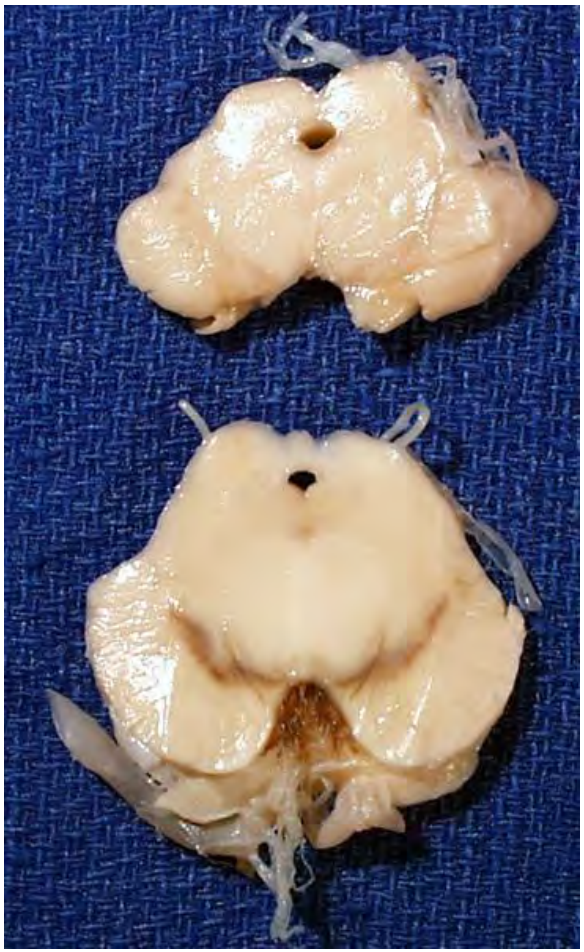
Dopaminergic Circuits

- **<u>Mesolimbic pathway</u>:** project from the ventral tegmental area (VTA) to the cerebral cortex, nucleus accumbens, and the hippocampus.
    - This system appears to be involved in the dopaminergic arm of addiction.
    - Overactivation of dopamine in this circuit is associated with schizophrenia.
- **<u>Nigrostriatal pathway:</u>** project from the substantia nigra to the striatum
    - This is the zone where most loss of neurons occurs in PD



Parkinson's Disease Pathology

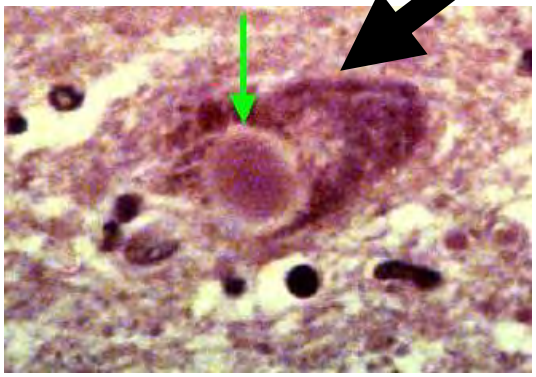
- Disease becomes manifest when ~80% of dopamine lost and 60% of substantia nigra dopaminergic neurons are lost.
- Dopaminergic dropout can be seen in the destaining of neuromelanin in the substantia nigra
- Some loss of neurons is also observed in noradrenergic (locus coeruleus), serotonergic (raphe), and cholinergic, olfactory bulb and autonomic nervous system.



PD

Normal

http://www.path.sunysb.edu/neuropath/images/neuro_degen/neoro_degen_parkinsons_1.JPG

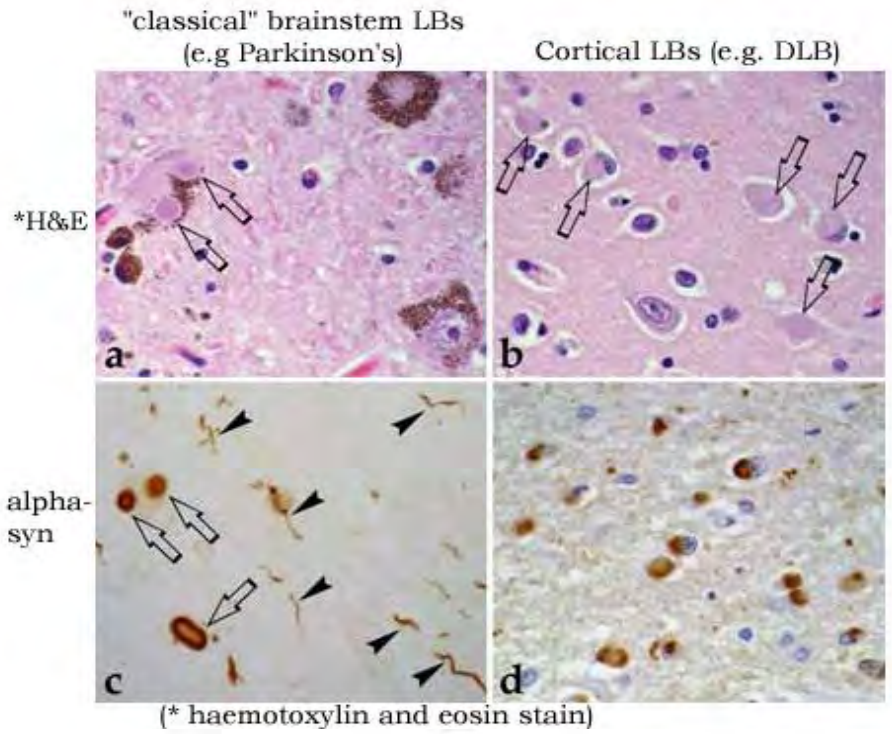


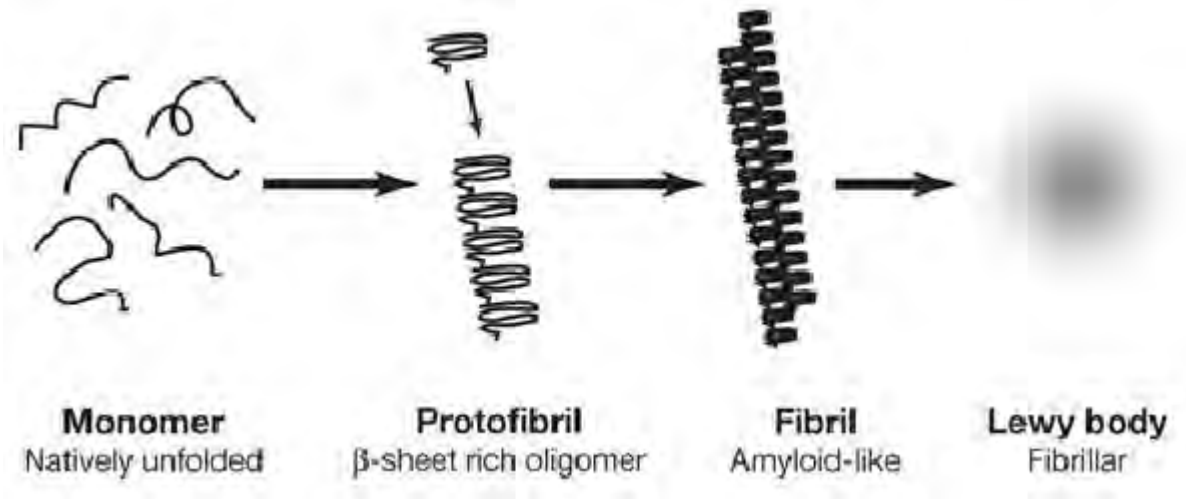
Lewy Bodies: α- Synuclein inclusions

Spillantini, M., et al. (1998).

Lewy Bodies

- Histological analysis of PD brains reveals inclusion bodies in dopaminergic neurons, known as Lewy bodies.
- These appear to be primarily constituted of alpha-synuclein, parkin, ubiquitin, and neurofilaments.





What is α-Synuclein?

- 140 amino acid protein

  Jakes, R., et al. (1994).

- Associated with
  1. Synaptic membranes

     Davidson, W. S., et al. (1998).

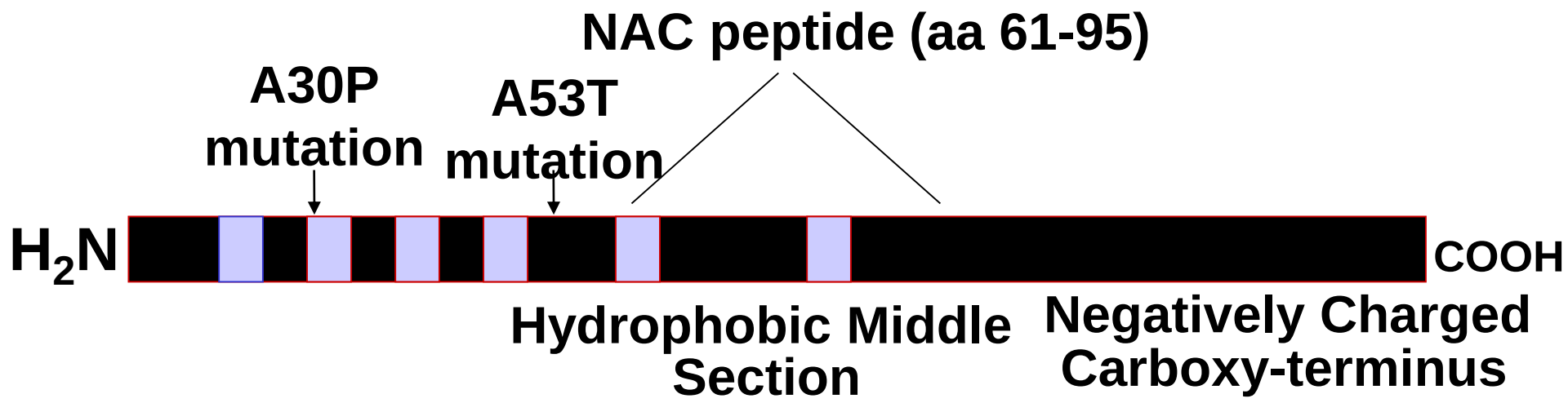
  2. Secretory pathway

     Dixon, C., et al. (2005).

N	NAC	C

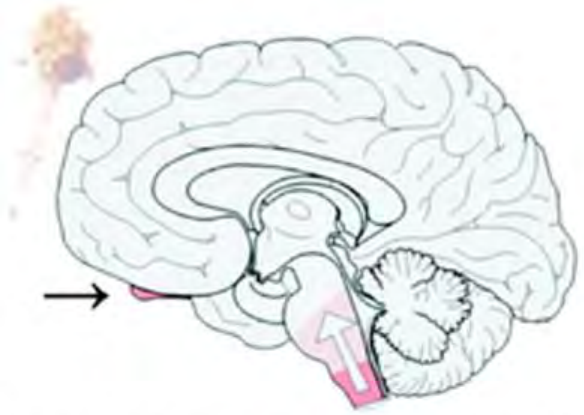
Alpha-Synuclein Mutations Cause Familial Parkinson's Disease

= 6 imperfect repeats of 11 amino acids with the conserved core KTKEGV

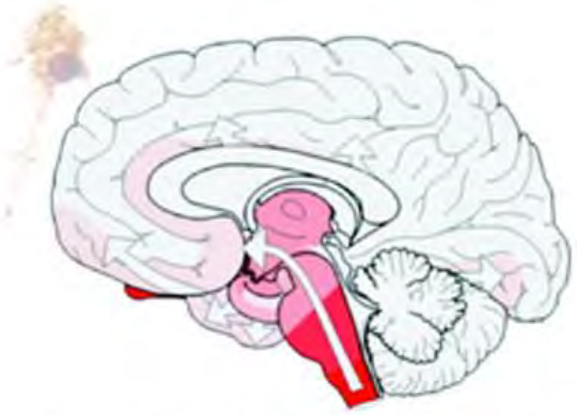


Mutations promote protein aggregation and filament formation

Braak Staging of PD



Braak Parkinson's disease stages 1 & 2
PRECLINICAL

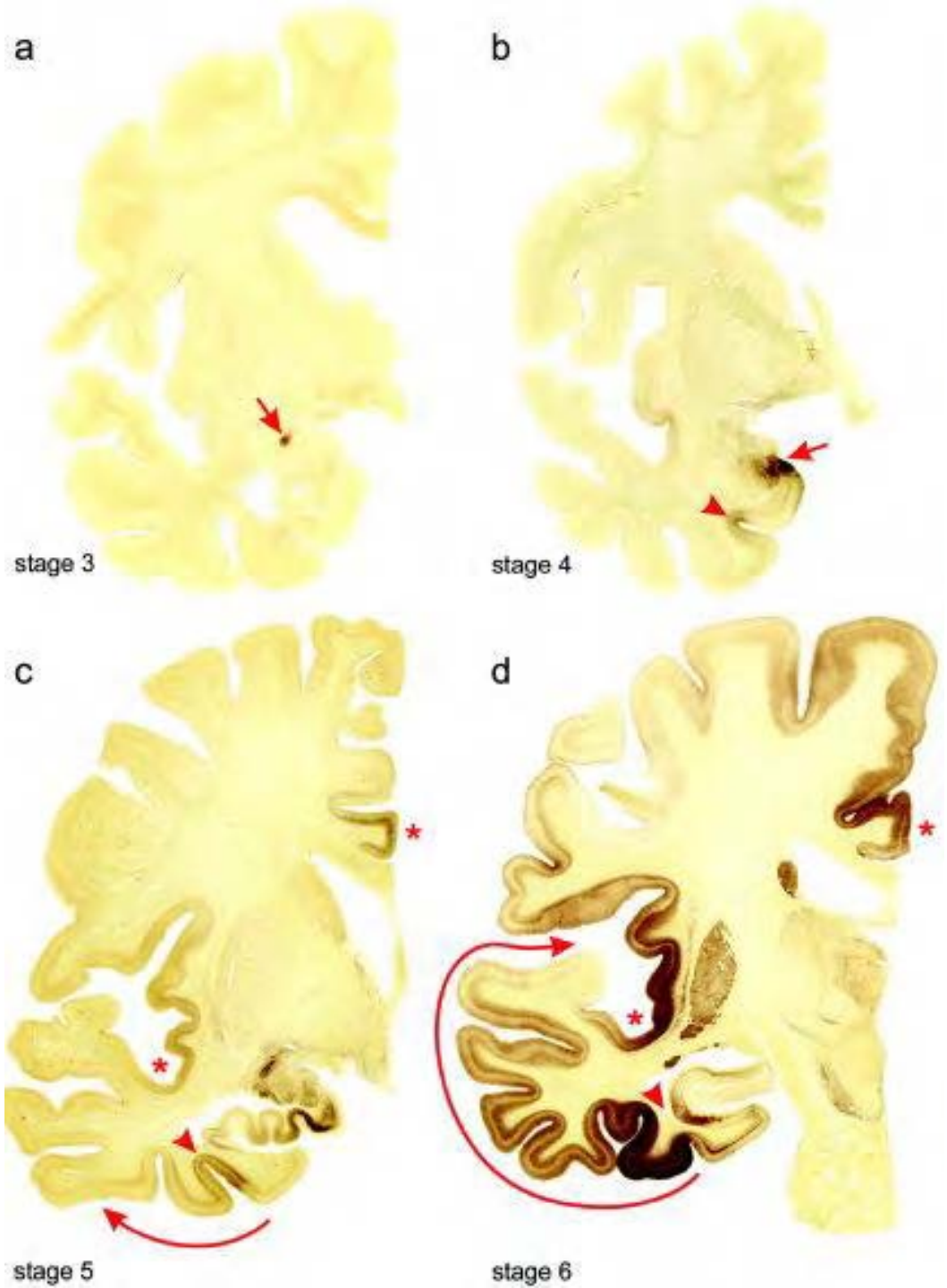


Braak Parkinson's disease stages 3 & 4
CLINICAL PARKINSON'S DISEASE

Braak Parkinson's disease stages 5 & 6
COGNITIVE IMPAIRMENT

Olanow, C. W. et al. Neurology 2009;72:S1-S136

AMERICAN ACADEMY OF NEUROLOGY



Progression of a-synuclein immunopositive labelling from stages 3 to 6, Braak 2006

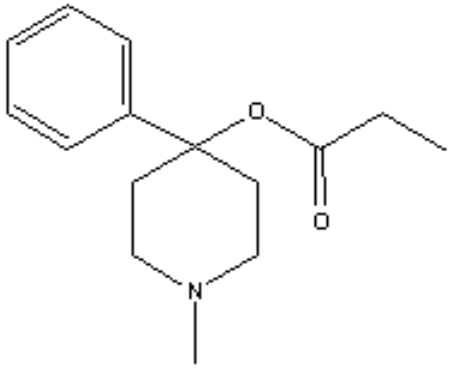
Common Problem

Disease	Culprit Protein
Parkinson's Disease	α -Synuclein
Alzheimer's Disease	Amyloid-β peptide
Huntington's Disease	Huntingtin
Prion Disease	Prion protein
ALS	SOD1

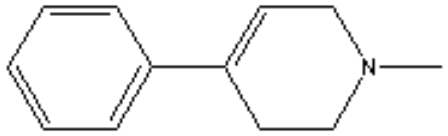
Misfolding & Aggregation

MPTP

- 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
- Metabolized into MPP+, which kills dopaminergic neurons in the substantia nigra by oxidative damage
- Discovered in 1972 when a graduate student, Barry Kidston, incorrectly synthesized the opioid MPPP and injected the product. He began displaying classic parkinsonian symptoms within 3 days. Two years later, he committed suicide and autopsy showed characteristic loss of DA neurons in the substantia nigra.
- In 1982, MPPP was manufactured illicitly in Santa Clara County, CA and distributed as a synthetic heroin. Soon after, a surge of clinical cases began to appear, some as young as 19 years old, displaying idiopathic, end-stage parkinsonian symptoms. These cases were ultimately linked to use of MPPP batches tainted with a byproduct of MPTP.
- Taken up by dopamine transporters and inhibits complex-1 of the mitochondrial transport chain.

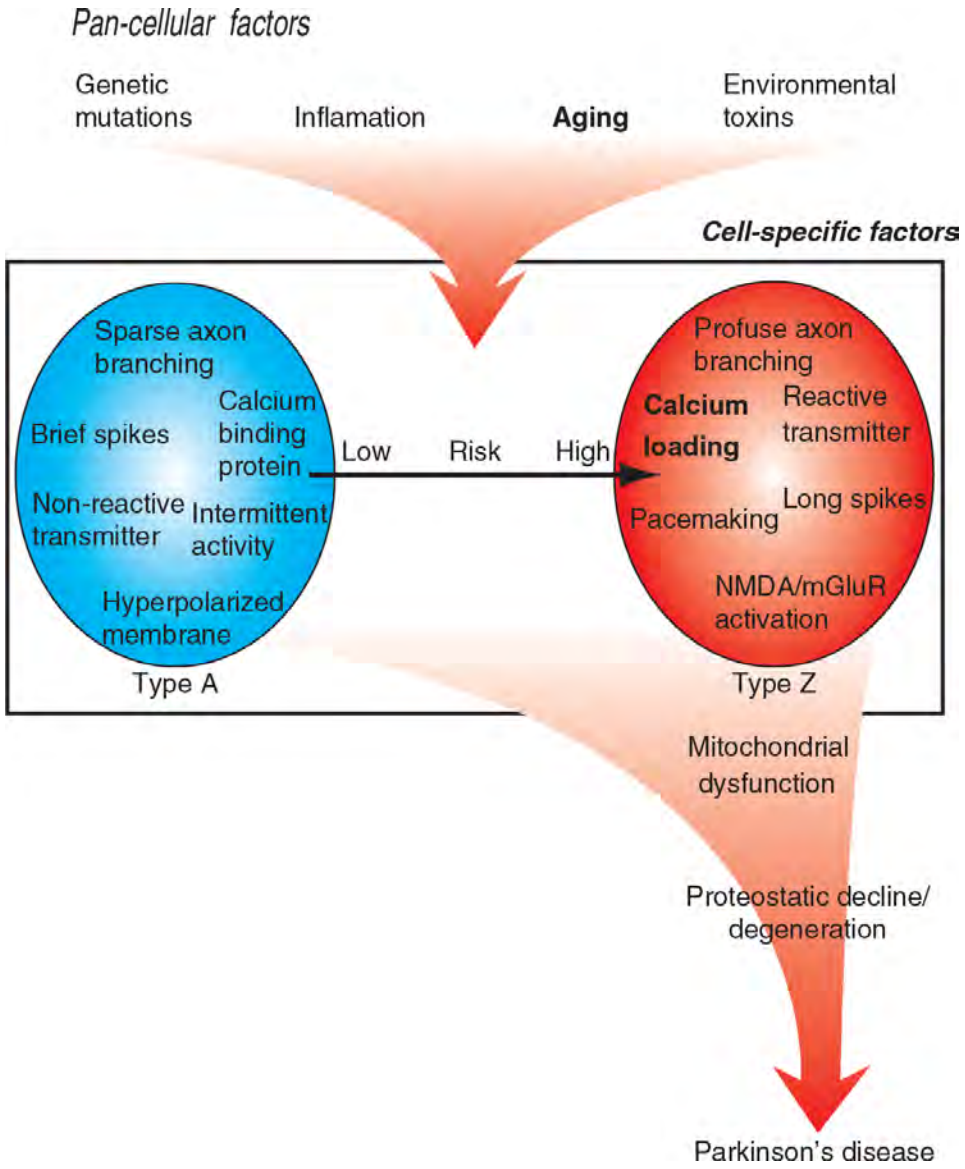


MPPP

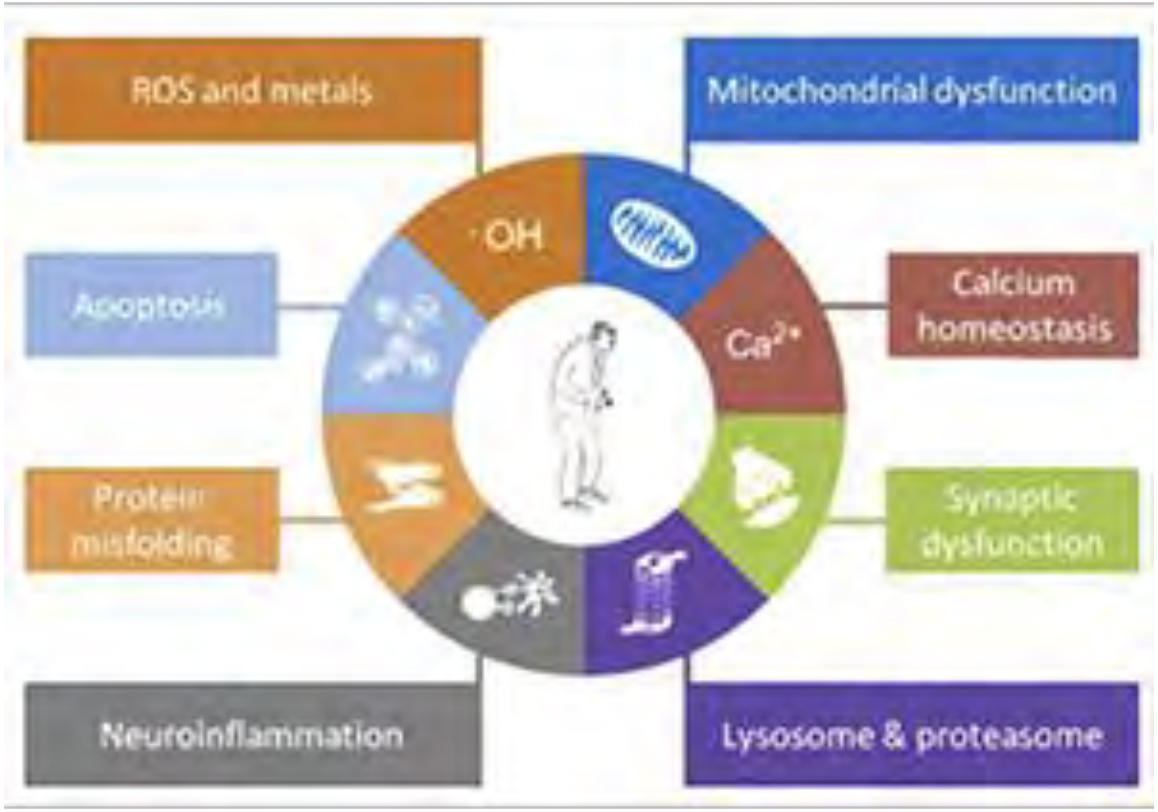


MPTP

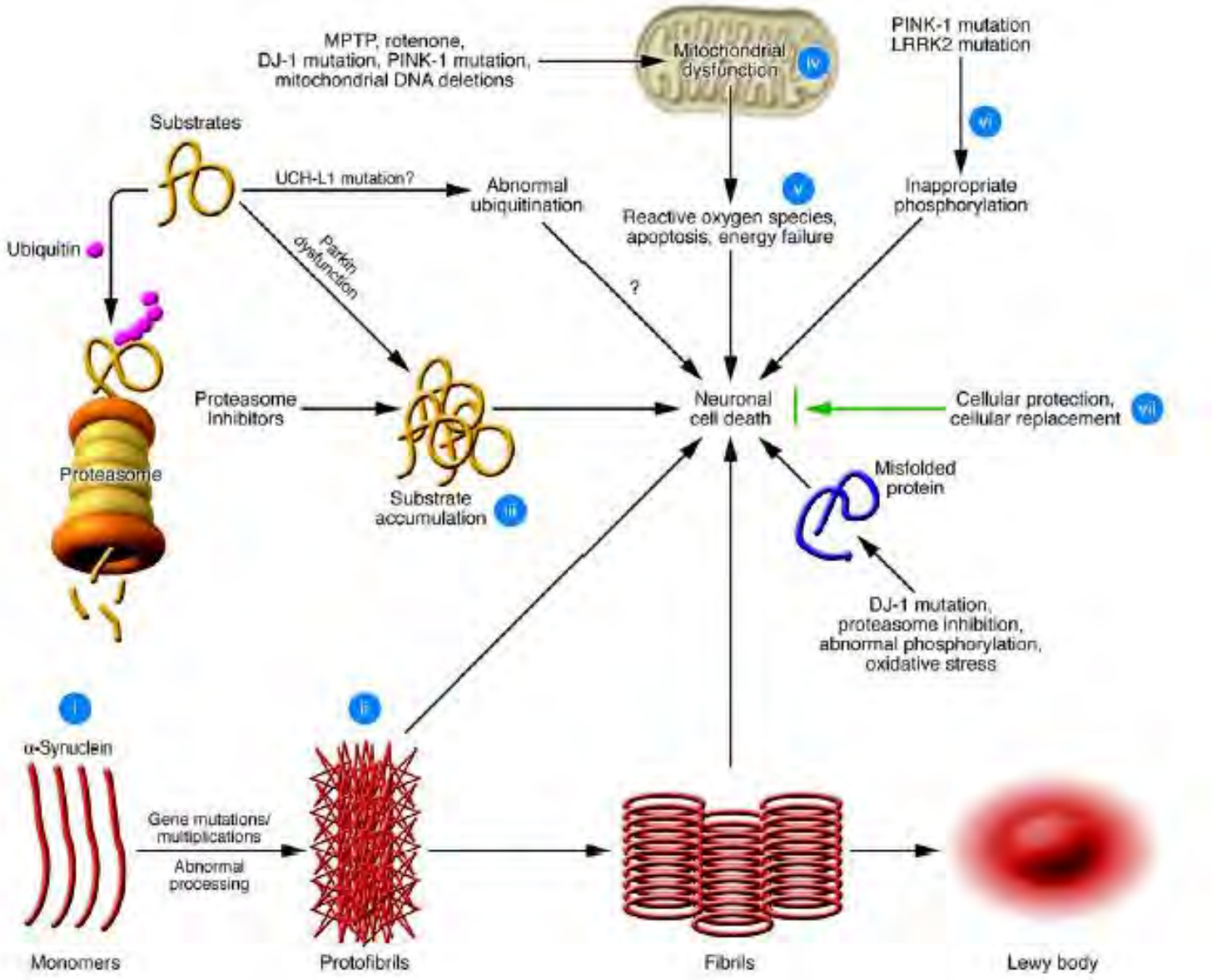
Why do dopaminergic neurons die?



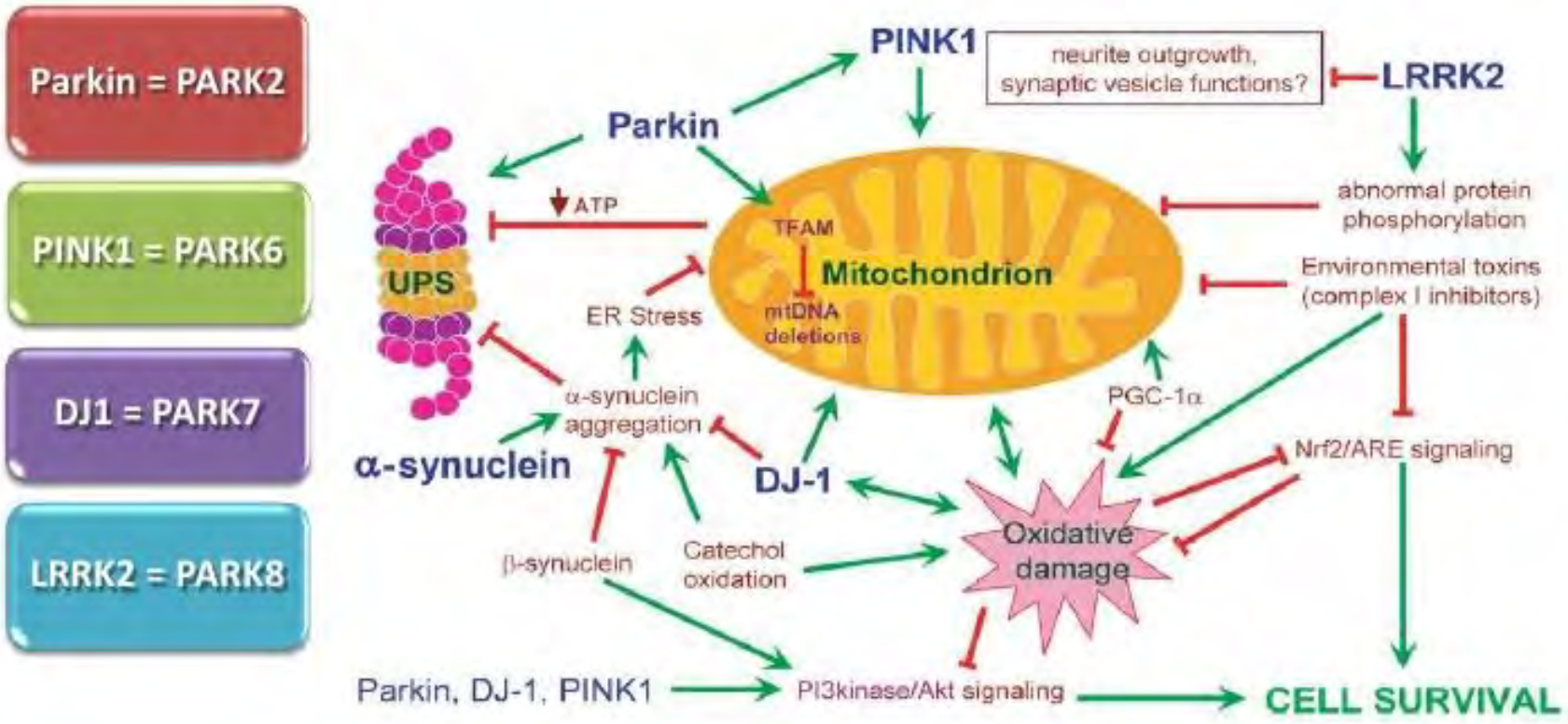
Why do dopaminergic neurons die?



Loss of proteostasis causes loss of cellular homeostasis in PD



Common intersecting pathway in PD



Thomas B, Beal MF. Parkinson's disease. Hum Mol Genet. 2007 Oct 15;16 Spec No. 2:R183-94. Review.

The PINK1/parkin signaling pathway: a role in mitophagy

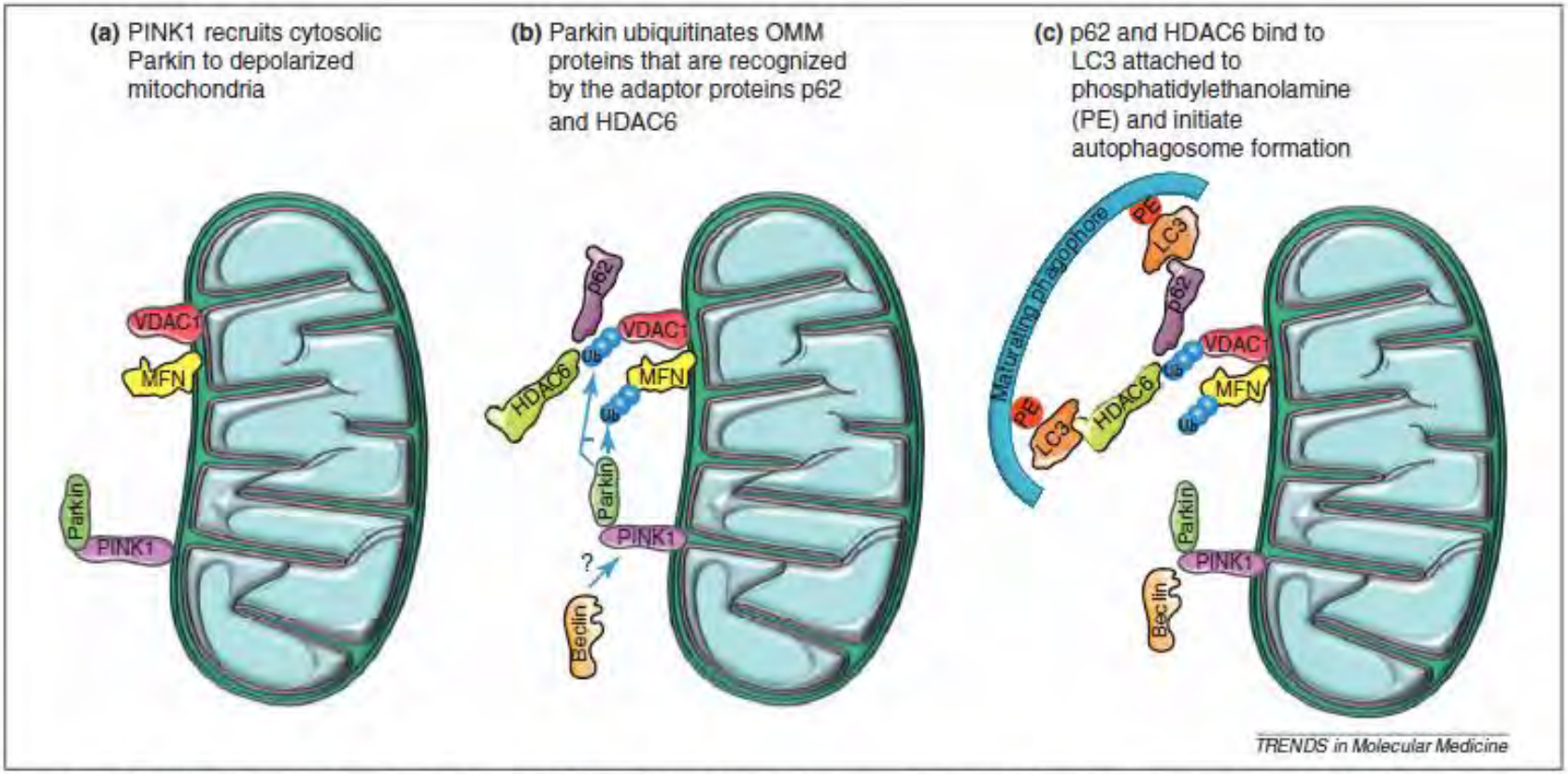
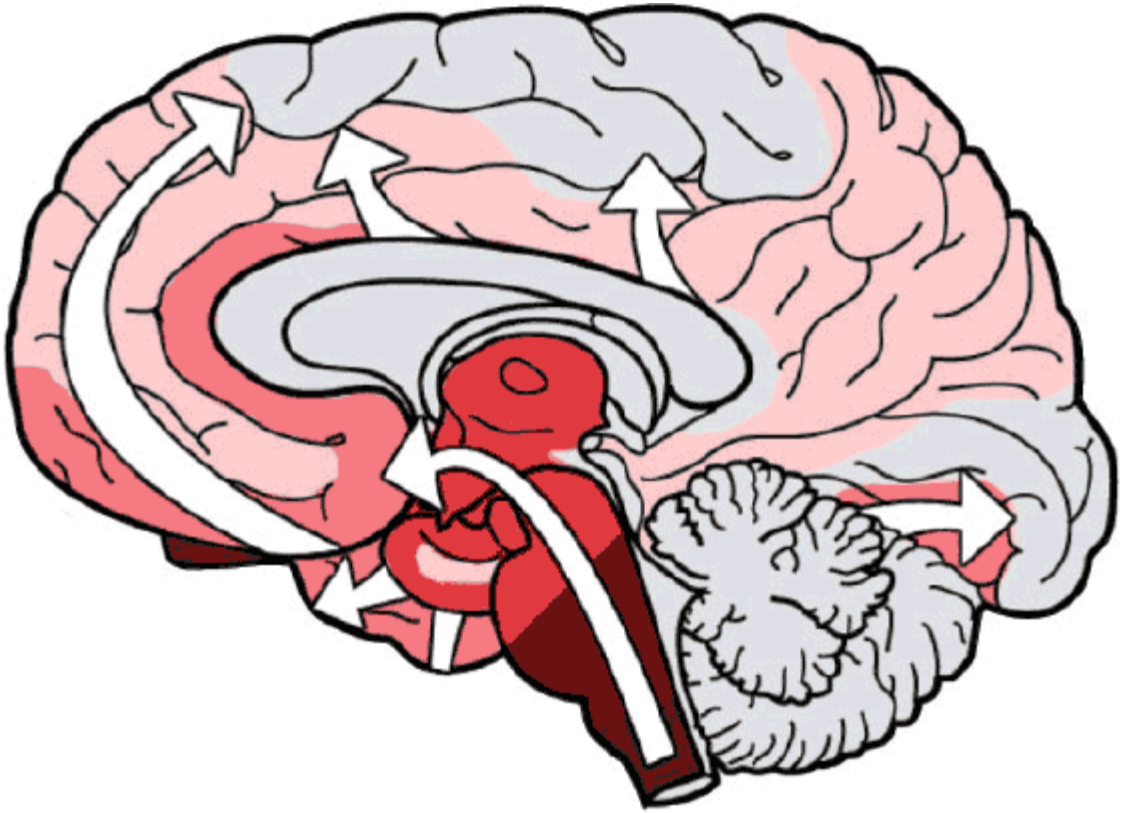


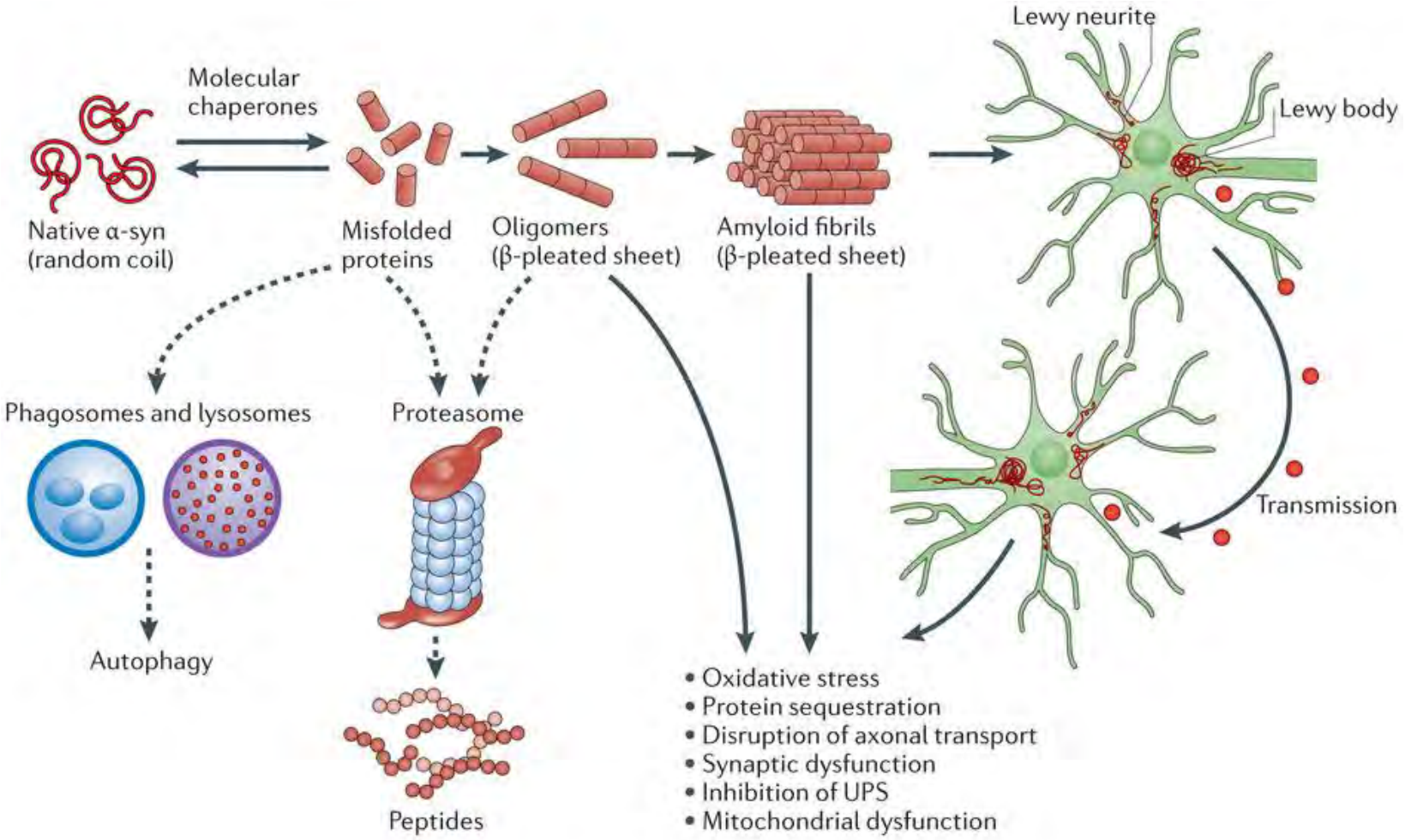
Figure 1. The PINK1/Parkin signaling pathway. Damaged mitochondria lose their membrane potential, which inhibits PINK1 cleavage. The mitochondrial content of full-length PINK1 thereby increases, which enhances PINK1 signaling. By an unknown mechanism, this triggers either directly or indirectly **(a)** Parkin recruitment to mitochondria. **(b)** VDAC1 and/or MFN are ubiquitinated in a Parkin-dependent manner. Then, mitochondrial aggregation occurs because of the Parkin-mediated ubiquitination of mitochondrial outer membrane proteins. **(c)** Both p62 and HDAC6 link polyubiquitinated mitochondria with LC3, initiating mitophagy.

Trends in Molecular Medicine, March 2011, Vol. 17, No. 3 pag 158

Parkinson's disease is a spreading disorder

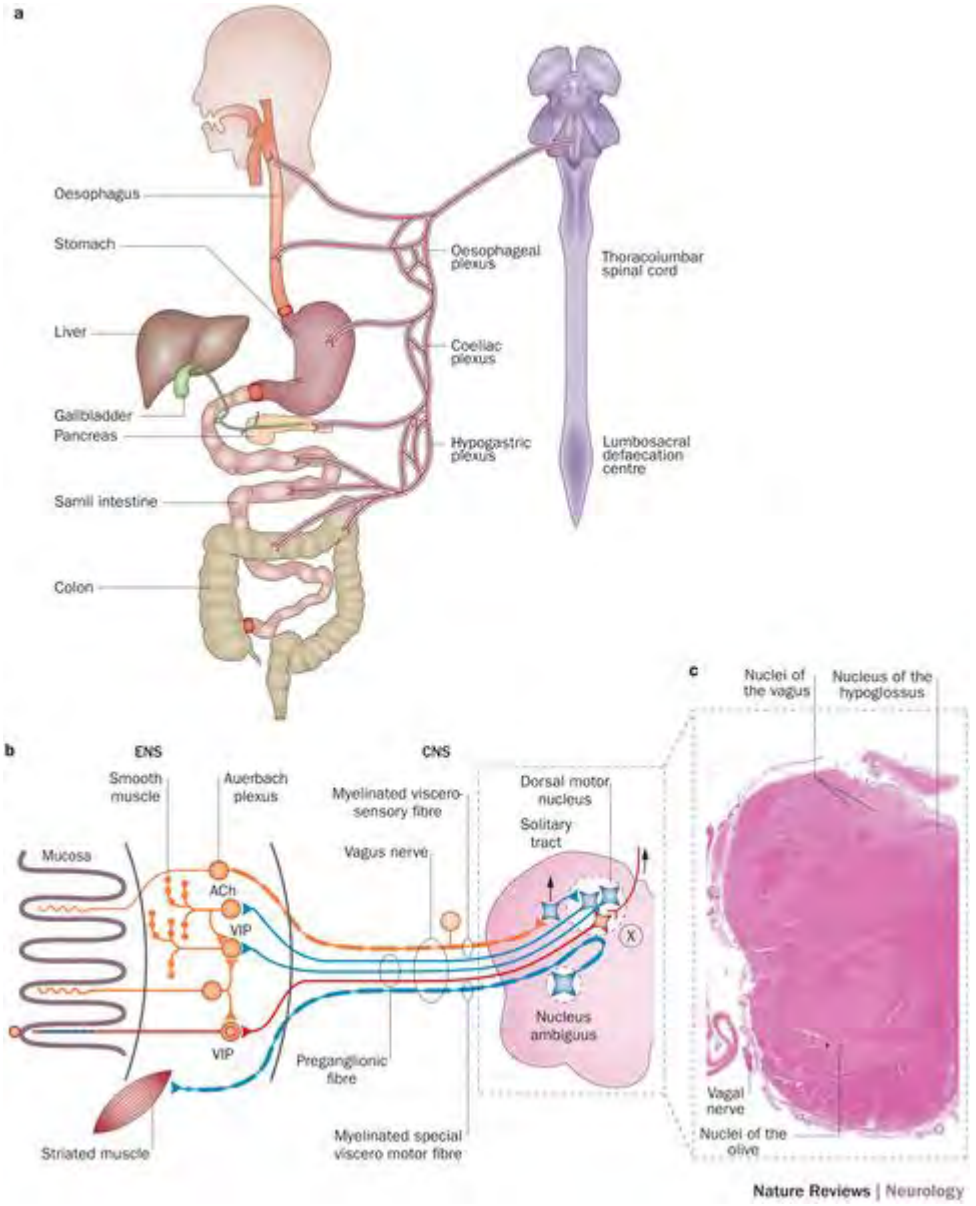


Parkinson's disease is a spreading disorder

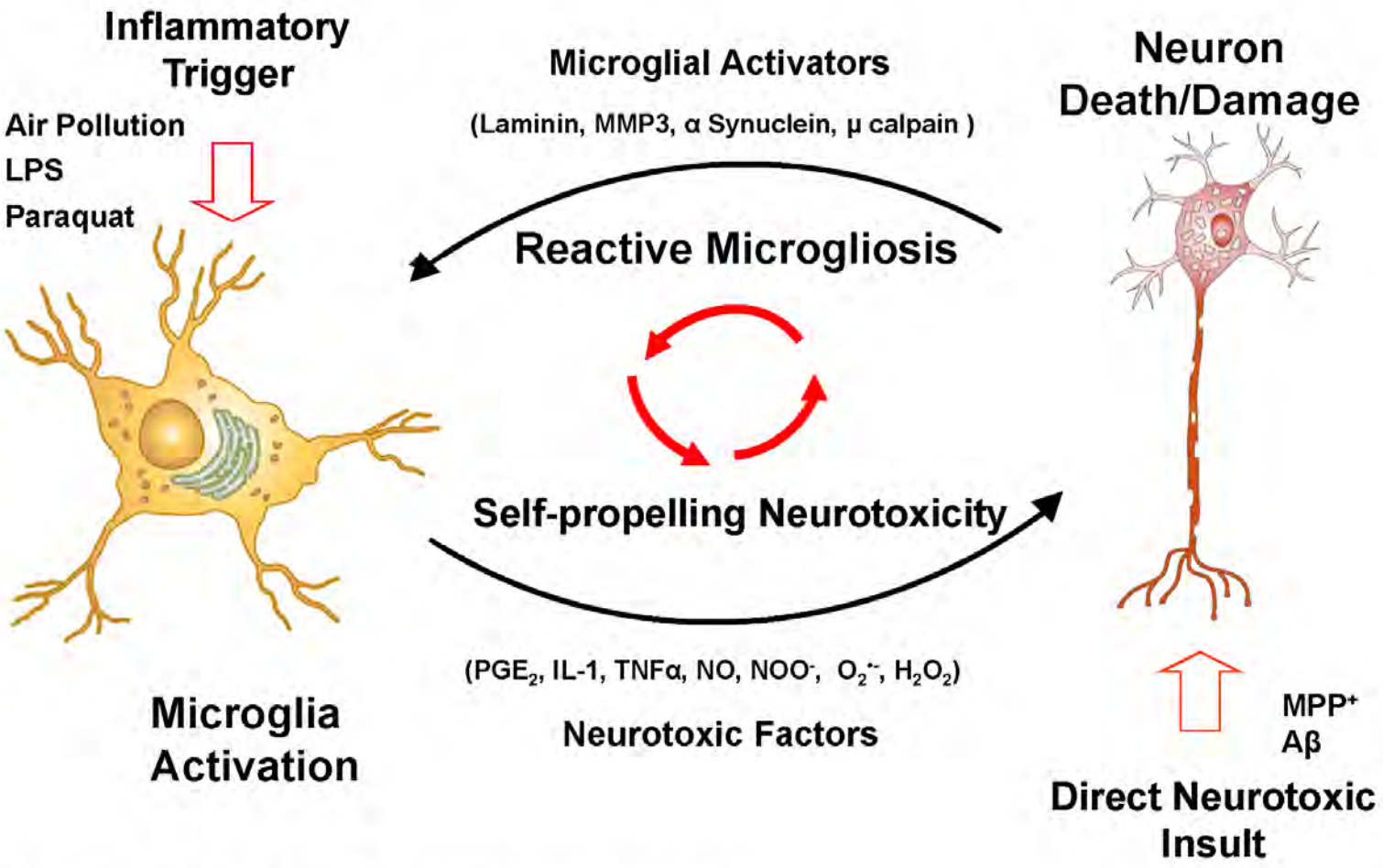


Nature Reviews | Neuroscience

Spreading from the intestine?



Microglia Can Become a Chronic Source of Cytokines & ROS

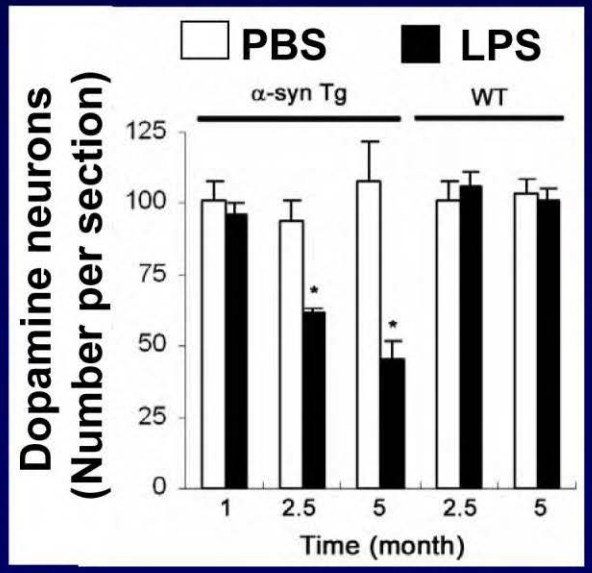


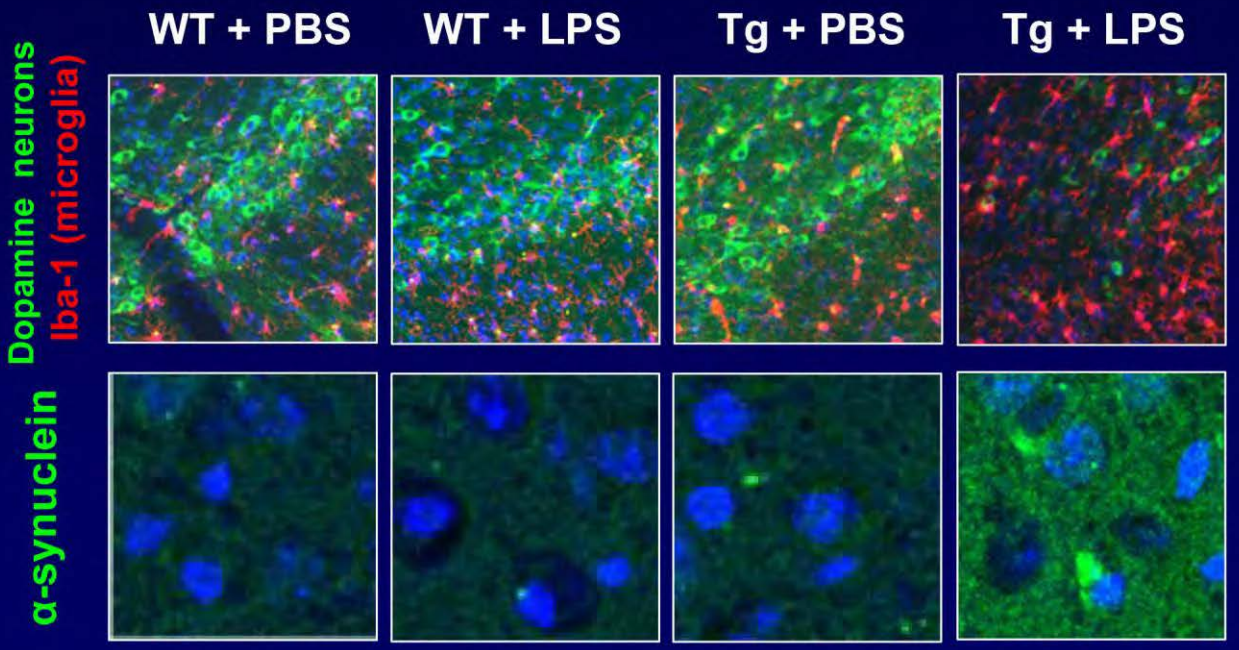
(Revised from Block, et al., 2007, *Nature Reviews Neuroscience*)

The two hit model

genetic lesion: A53T mutant human α-synuclein

environmental trigger: neuroinflammation (LPS, 3 X 10^6 EU/kg)





Iba-1: ionized calcium binding adapter molecule 1

Gao *et al*. 2008. J Neurosci. 28:7687-98; Gao *et al*. 2011. Environ. Health Perspect. 119: 807-814

Is PD a developmental disorder?

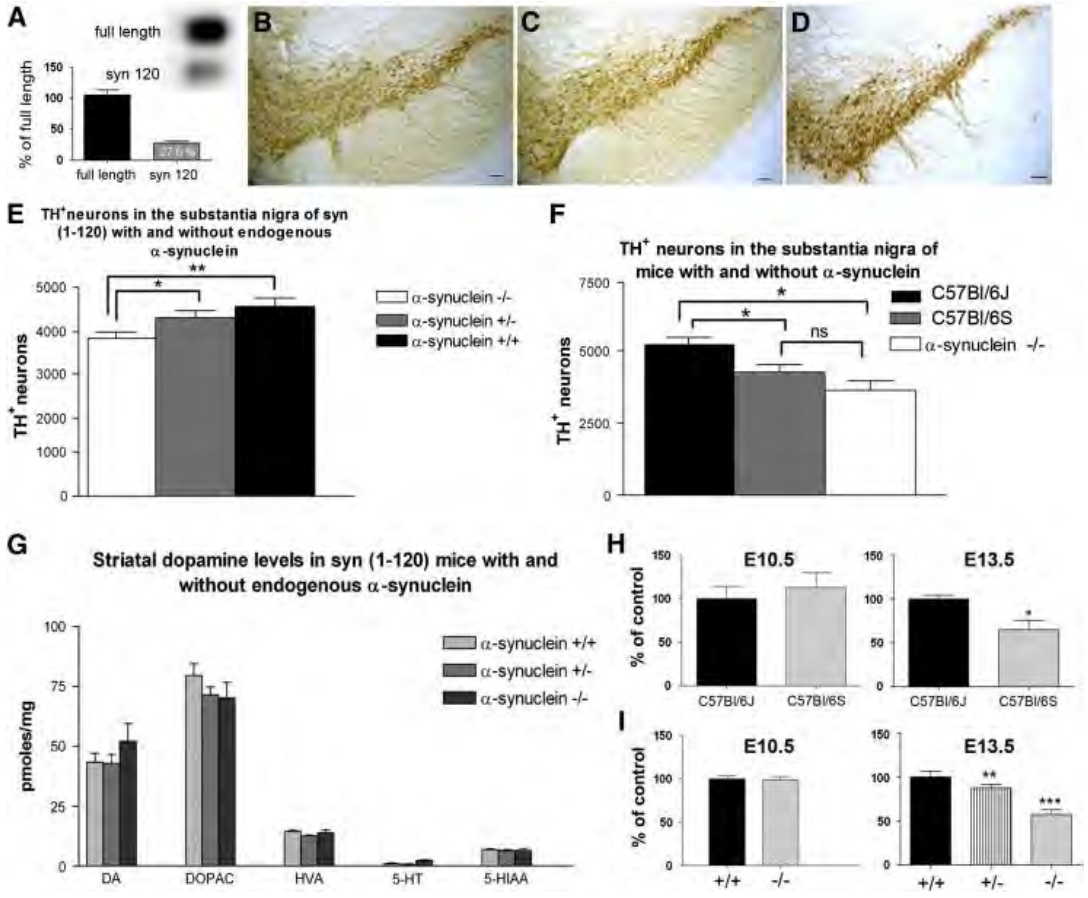


Fig. 1. Western blot analysis of olfactory bulb (OB) extract demonstrates the expression of truncated human 1-120 α-synuclein in the presence of endogenous α-synuclein in α-syn (1-120)E mice. Quantification was performed by analyzing the relative optic density...

Pablo Garcia-Reitboeck, Oleg Anichtchik, Jeffrey W. Dalley, Natalia Ninkina, George K. Tofaris, Vladimir L. Buchman, Maria Grazia Spillantini

Endogenous alpha-synuclein influences the number of dopaminergic neurons in mouse substantia nigra

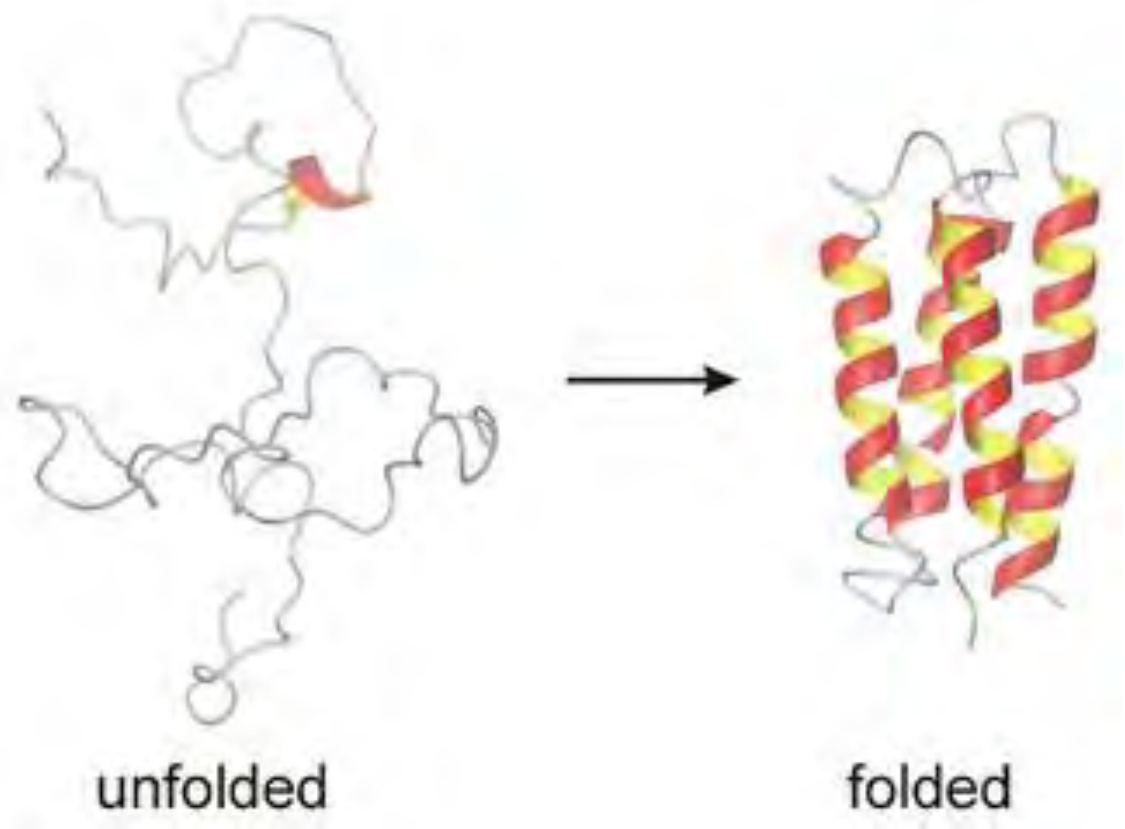
Experimental Neurology, Volume 248, 2013, 541–545

Summary

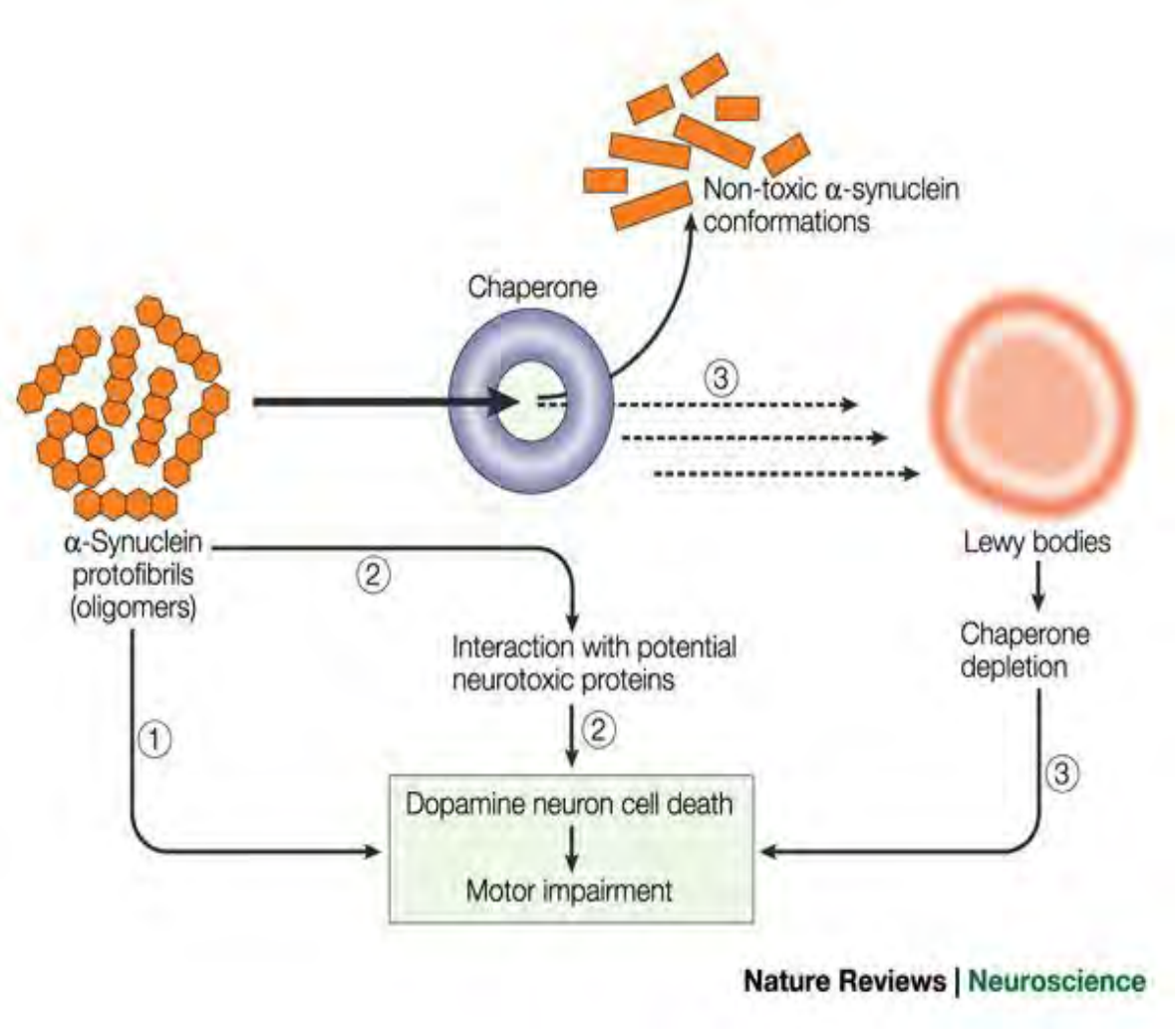
- PD is a complex age associate neurodegenerative disorder.
- Hallmarks are the degeneration of dopaminergic neurons in the SN and the occurrence of protein aggregates (Lewy bodies).
- Interaction of genes and environment.
- PD is multifactorial (stratification needed).
- Only symptomatic therapies are available.

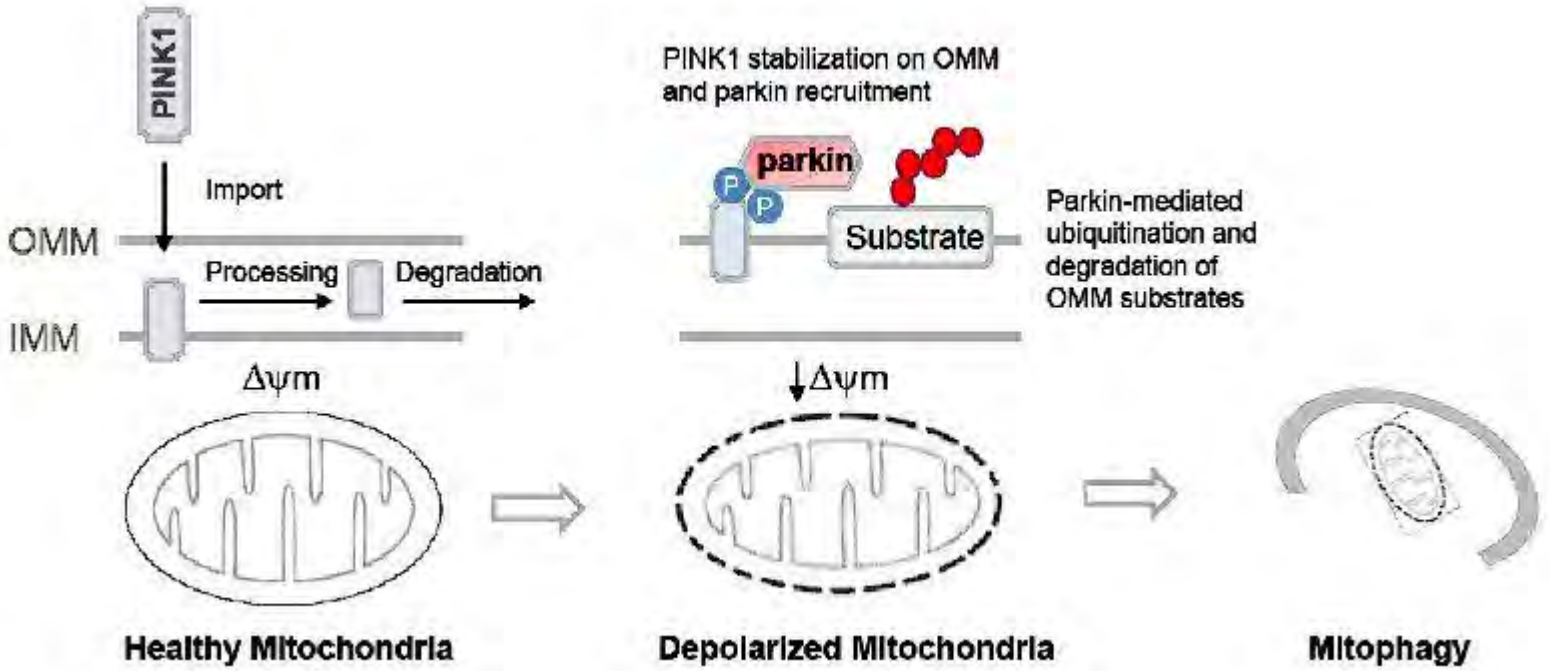
Break

Alpha Synuclein



Toxic Alpha-synuclein




PINK1
Import
OMM
Processing
Degradation
IMM
Δψm
Healthy Mitochondria
PINK1 stabilization on OMM
and parkin recruitment
parkin
P
P
Substrate
Parkin-mediated
ubiquitination and
degradation of
OMM substrates
↓Δψm
Depolarized Mitochondria
Mitophagy

PINK1 and Parkin also to regulate mitochondrial trafficking and fission

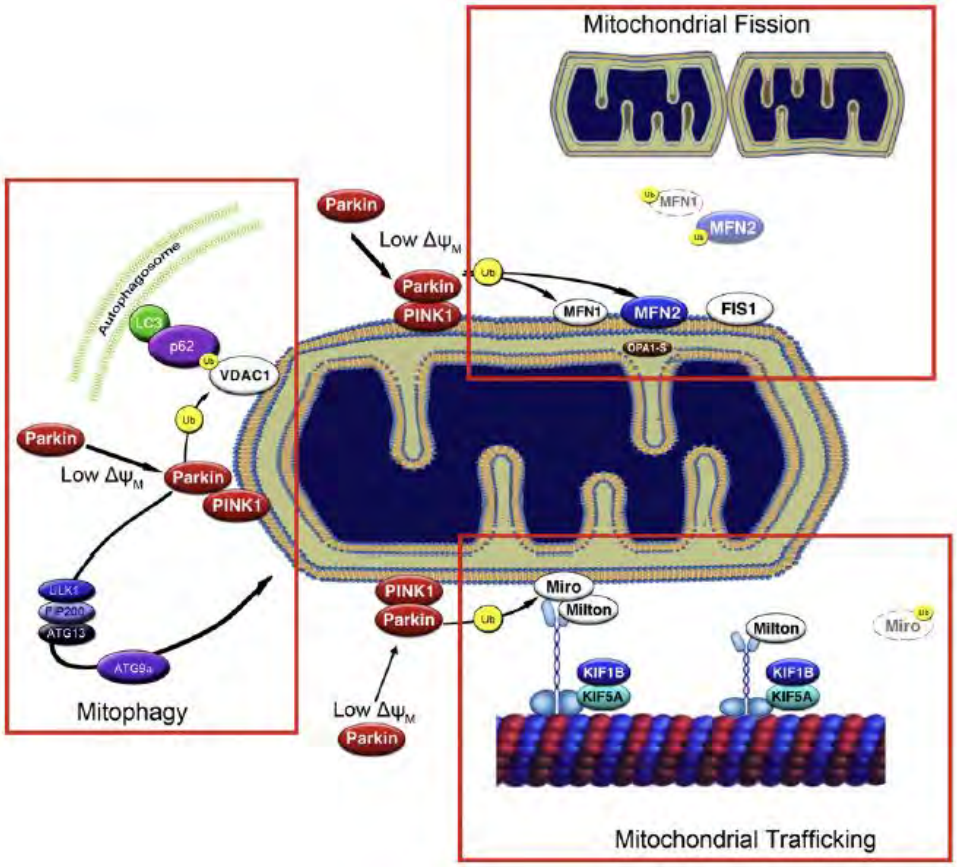


Fig. 2. The figure depicts three potential scenarios for the role of PINK1/Parkin in mitophagy. Each begins with the recruitment of Parkin to the mitochondria in a PINK1 dependent manner after membrane depolarization. This then leads to 1) a shift towards fission. MFN1/2 is ubiquitinated and degraded, allowing fission to take place over fusion. 2) A decrease in anterograde mitochondrial trafficking. Miro is ubiquitinated and consequently degraded, resulting in the detachment of mitochondria from the microtubules. 3) Recruitment of the autophagic machinery. Mitochondrial outer membrane proteins like VDAC1 are ubiquitinated and as such recognized by p62. LC3 on the autophagic vesicles directly interacts with p62 that has accumulated on the mitochondria. Alternatively, the ULK1/FIP200/Atg13 complex and Atg9A, accumulate at the mitochondria and initiate the formation of mitophagosomes.
Figure adapted from Schon and Przedborski (2011).

Please cite this article as: de Vries, R.L.A., Przedborski, S., Mitophagy and Parkinson's disease: Be eaten to stay healthy, Mol. Cell. Neurosci. (2012), http://dx.doi.org/10.1016/j.mcn.2012.07.008

Parkin Mutation Linked to PD

- The gene Parkin, originally identified in a consanguineous Pakinstani family known to have congenital early onset PD.
- A mutation in parkin has been found in 50% of the cases of early onset PD.
- Parkin, containing a RING finger domain, is a E3 ubiquitin ligase involved in the ligation of ubiquitin to proteins for proteosomal degradation targeting.
- Dysfunction of this gene is thought to allow abnormally folded and old proteins to inappropriately linger and accumulate in the cell, perhaps leading to aggregation.

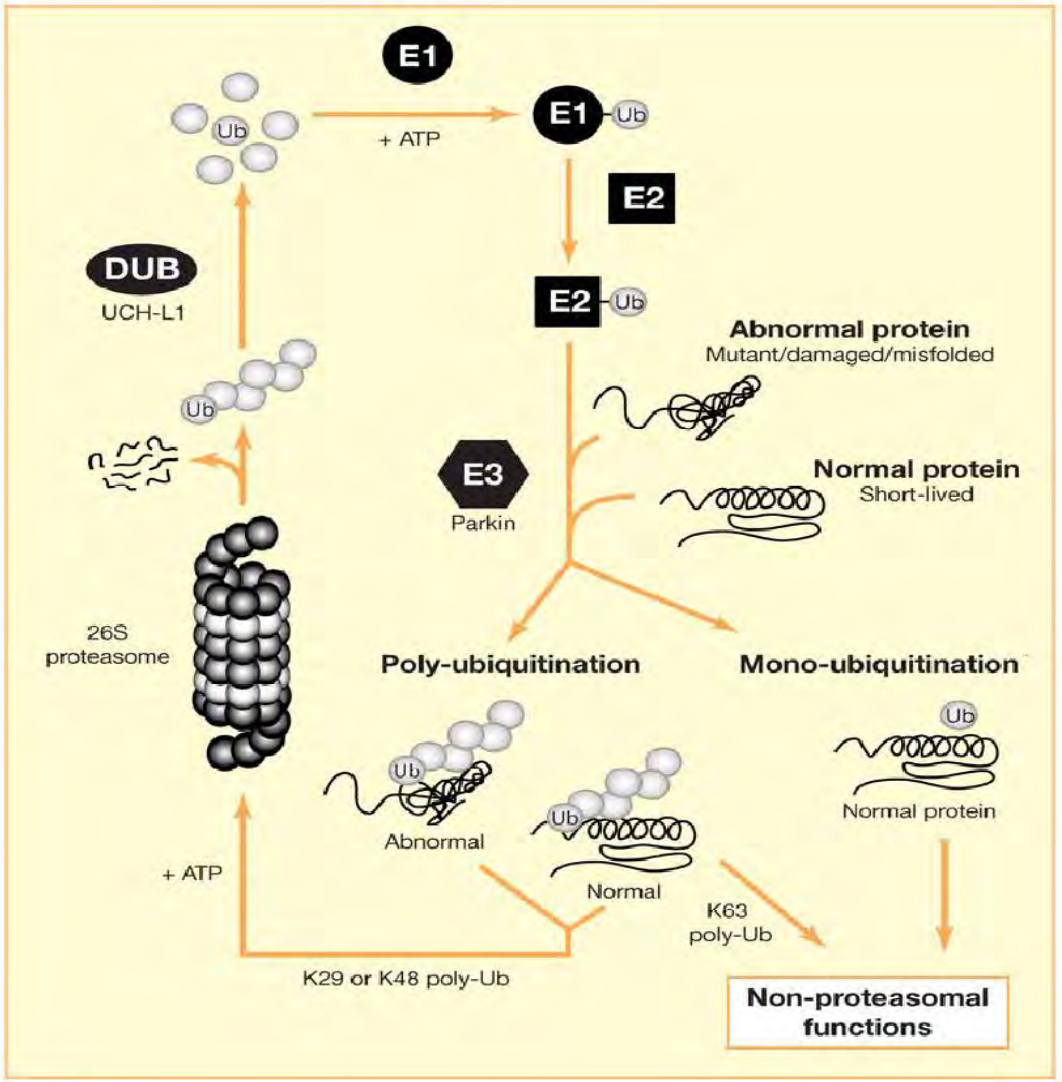


Figure 3