Lecture plan

1. Basal ganglia circuitry

2. Nigrostriatal degeneration and symptomatic treatments
   - Motor symptoms → dopamine replacement
   - Deep brain stimulation

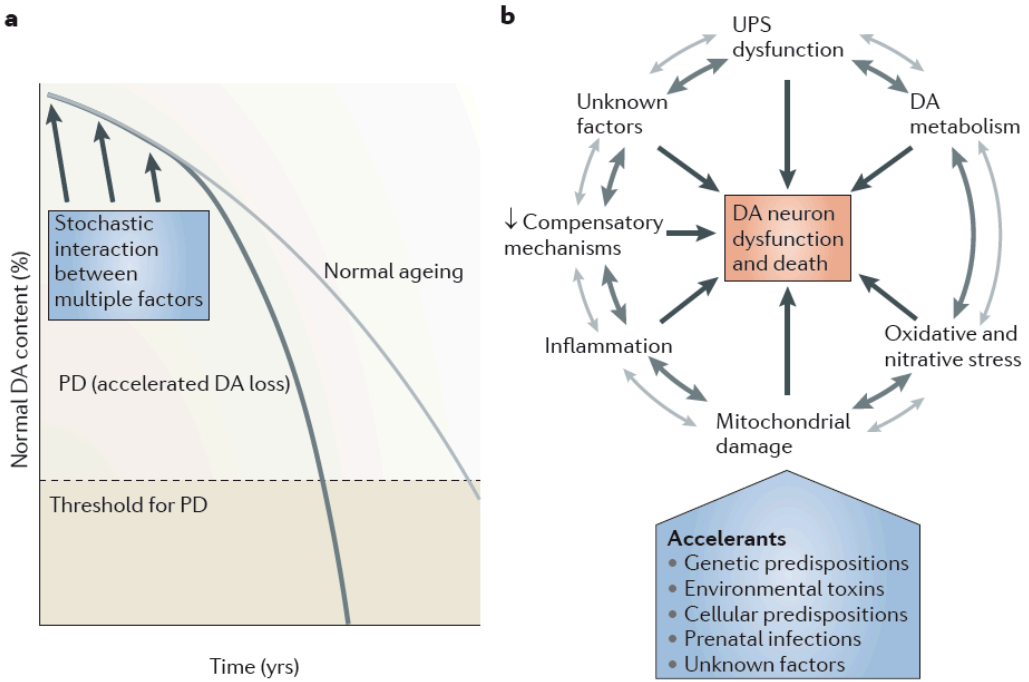
3. Neuronal degeneration / Lewy body pathology
   - Selective vulnerability of neuronal subtypes
   - α-synuclein (physiology, pathology, spreading)

4. PD etiology: organelle quality control
   - Aging, environmental factors, PD risk genes
   - Recessive forms: parkin, PINK1 and mitochondrial turnover

Risk factors: Parkinson's and Gaucher disease

Risk factors for Parkinson's disease

- In most cases, α-synuclein is not the only factor implicated in Parkinson's disease
- Environmental factors may trigger α-synuclein pathology
- Interaction with other genetic predisposition factors is important (e.g. GBA1)



Parkinson's disease : genetic and environmental causes

Parkinson's disease etiology

Genetic factors

- **α-synuclein**
- LRRK2
- Parkin
- PINK1
- DJ-1
- ATP13A2
- …

Environmental factors

Standardized Odds ratio:

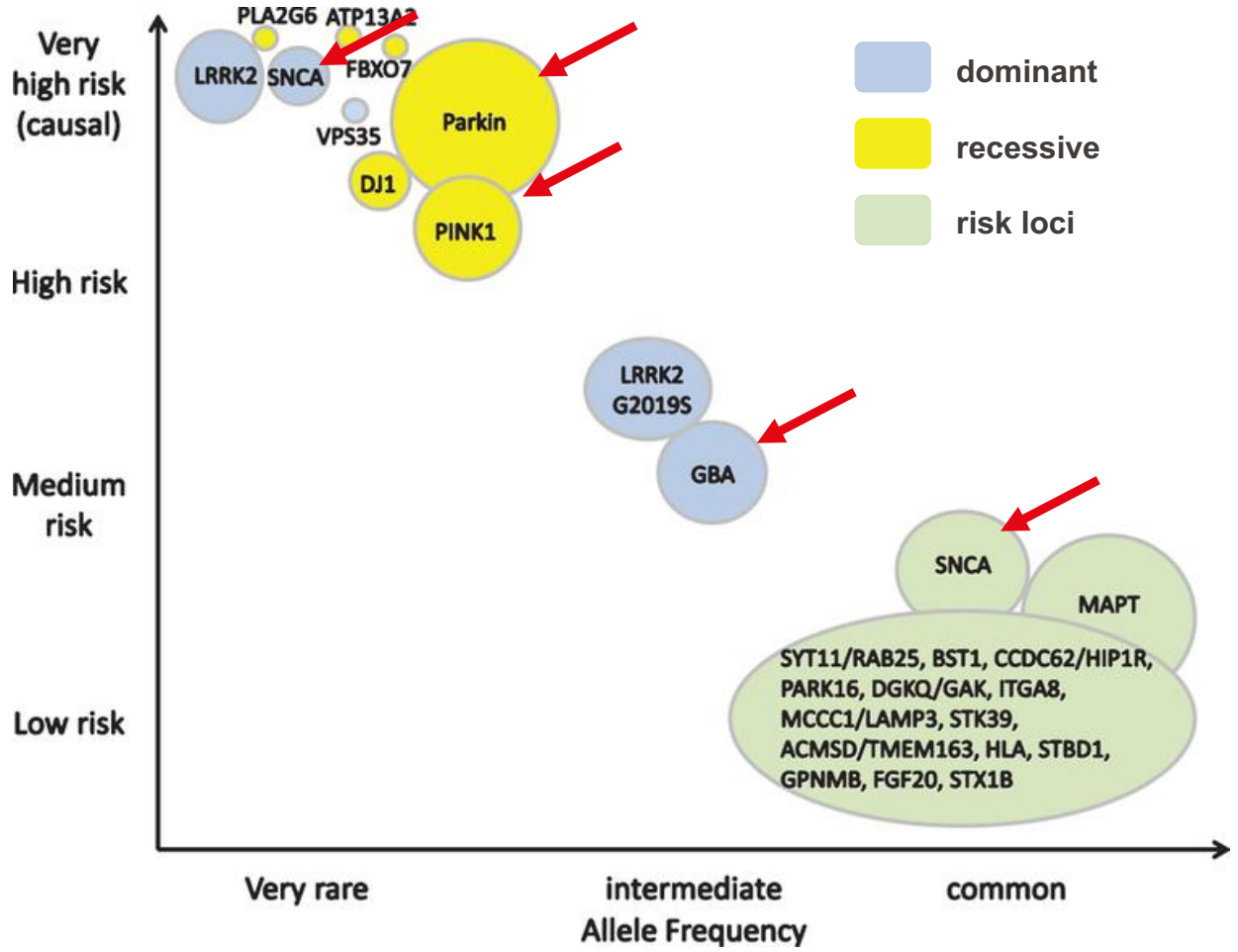
- Pesticides: 1.76
- Herbicides: 1.33 (paraquat: 2.2)
- Insecticides: 1.53
- MPP+

Aging

Gender

Age-standardized M:F ratio = 1.57

Classification of the genes linked to Parkinson's disease



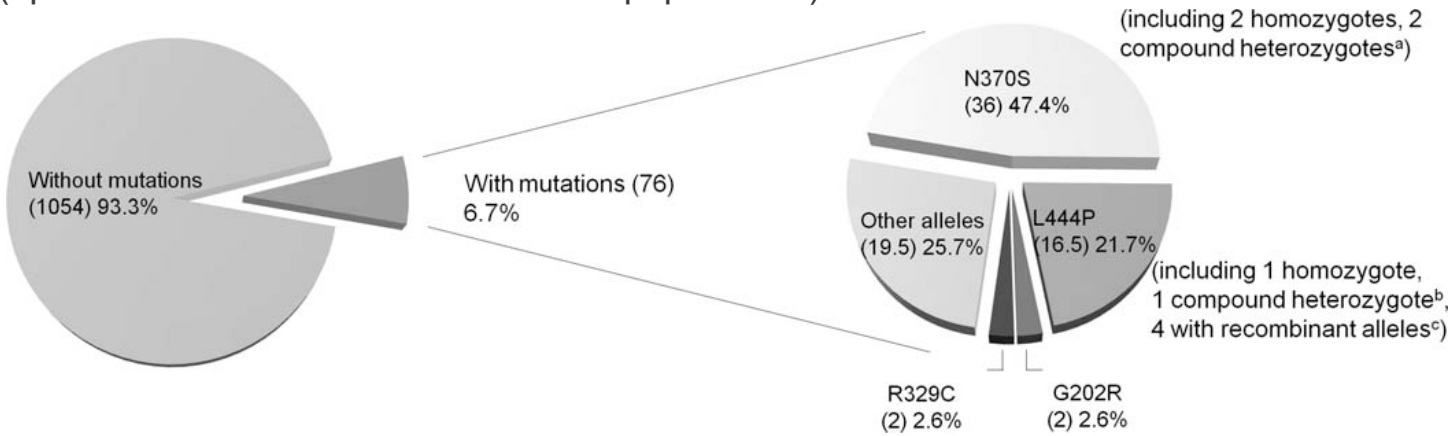
- Gasser T, Journal of Parkinson's Disease, vol. 5, no. 2, pp. 209-215, 2015

Risk factors: Parkinson's and Gaucher disease

Glucocerebrosidase mutations as a risk factor for Parkinson's disease

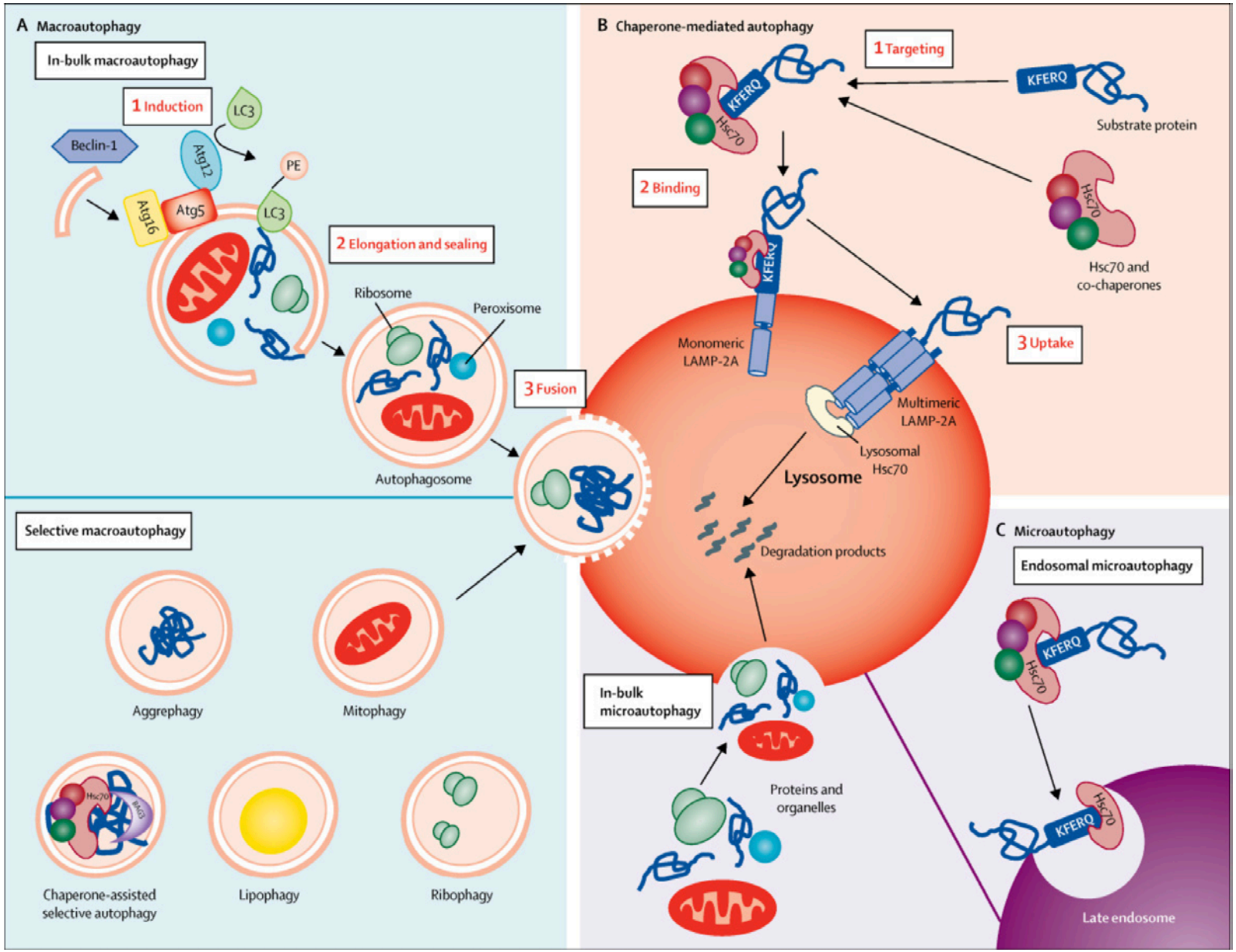
- Patients with GD/parkinsonism: relatives heterozygous for GBA1 mutations developed parkinsonism
- Patients with parkinsonism have an increased incidence of GBA1 mutations
- GBA1 is the most common known genetic risk factor for PD to date (GBA mutations increase the risk of PD by >20-fold)

GBA mutations in Parkinson's disease patients
(up to 20% in Ashkenazi Jewish ethnic populations)



- *Lesage S et al., Hum Mol Genet, 2011, Vol. 20, No. 1 (French Parkinson's Disease Genetics Study Group)*

Autophagic pathways in mammalian cells

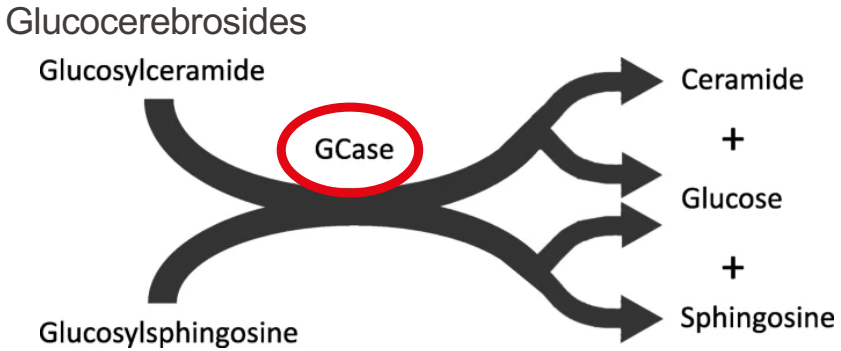


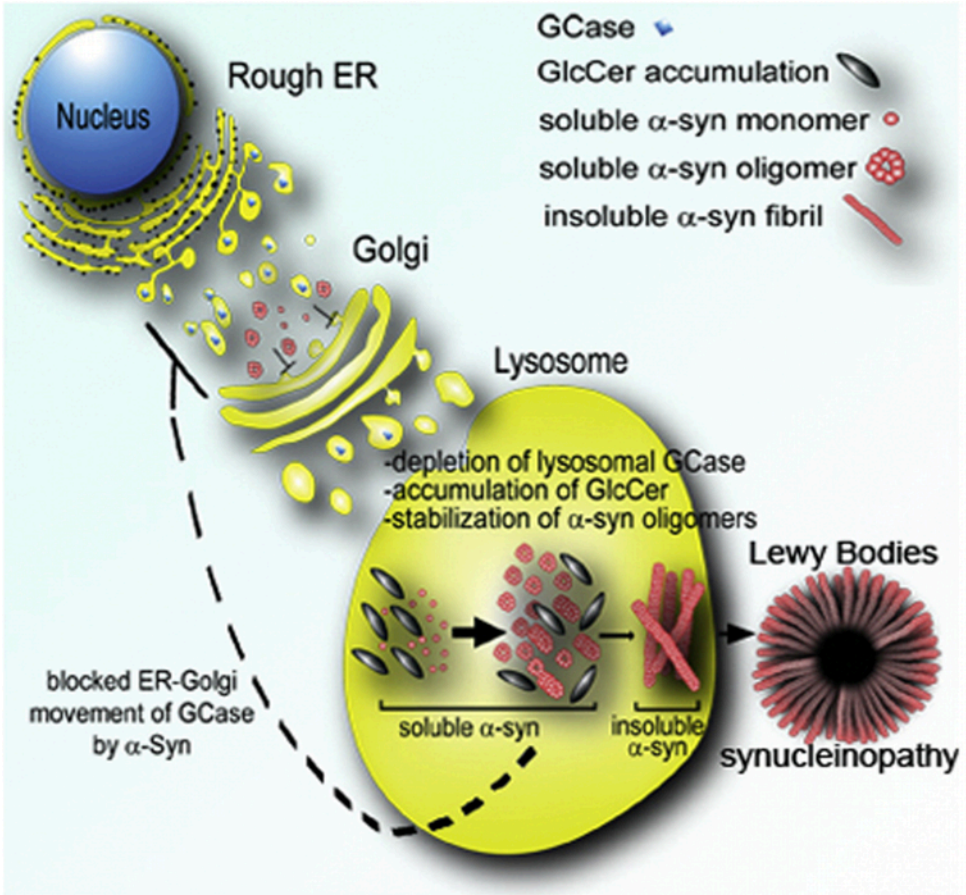
The Lancet
https://doi.org/10.1016/S1474-4422(18)30238-2

Risk factors: glucocerebrosidase and α-synuclein

- Gaucher disease is an autosomal recessive disorder
- **Lysosomal storage disorder**
  = accumulation of glucocerebrosides (lipid metabolism)
- Due to mutations in the GBA gene, which encodes the enzyme **glucocerebrosidase** (GCase).

GCase — Lysosomal degradation ⊣ **α-synuclein accumulation**





GlcSer = Glucosylceramide (GCase substrate)

- Mazzulli JR, et al. Cell. 2011 Jul 8;146(1):37-52, https://doi.org/10.1016/j.cell.2011.06.001

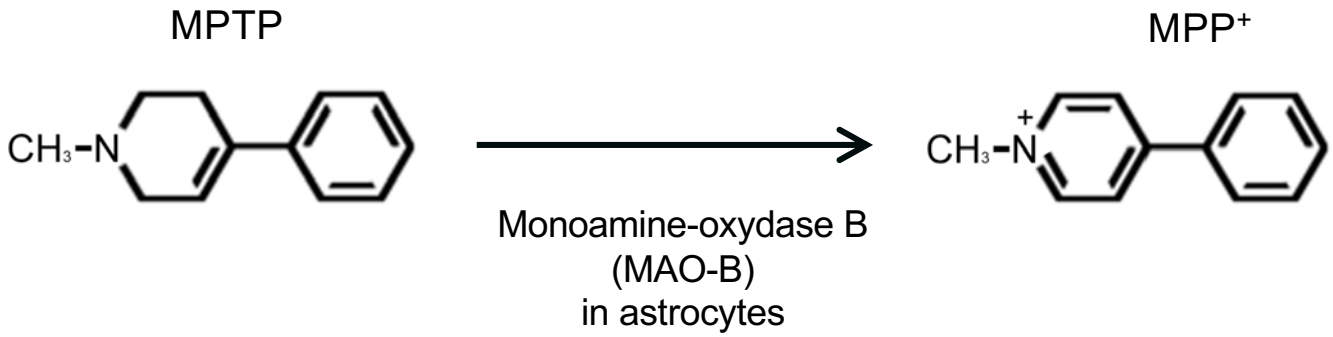
Parkinson's disease etiology : mitochondrial toxins

« Frozen addicts » (early 1980s) :
intoxication with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)

Parkinson's disease etiology : mitochondrial toxins

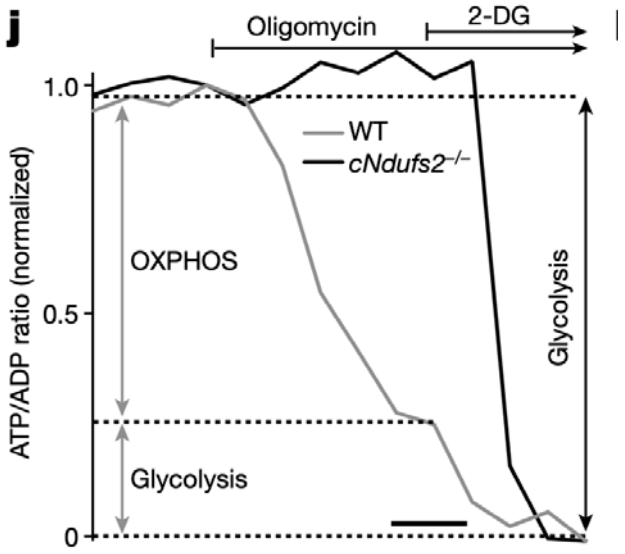
MPTP (1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine)

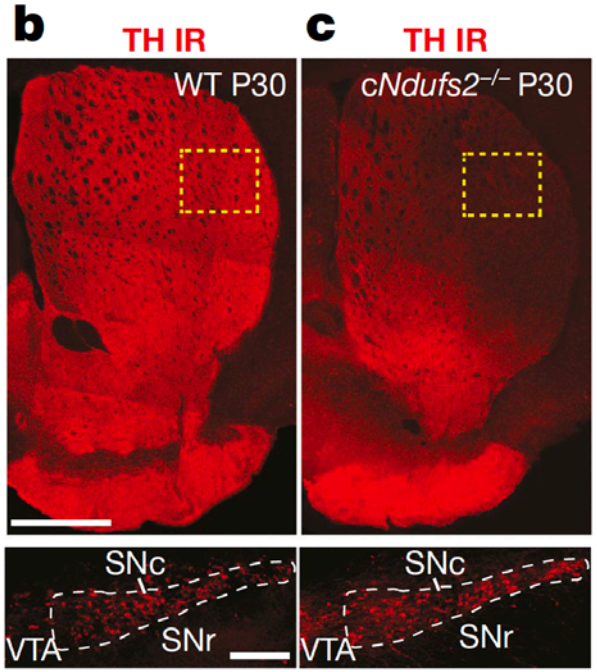
- Produced accidentally instead of MPPP, a synthetic opioid (effects similar to heroin)
- Induces Parkinsonism in mice and primates (not in rats)
- Crosses the blood-brain barrier
- MPP+ is preferentially uptaken by the DAT transporter
- Inhibits NADH--CoQ1 (Complex I) of mitochondrial respiratory chain
- ATP production falls
- MPP+ toxicity is reduced in alpha-synuclein null mice

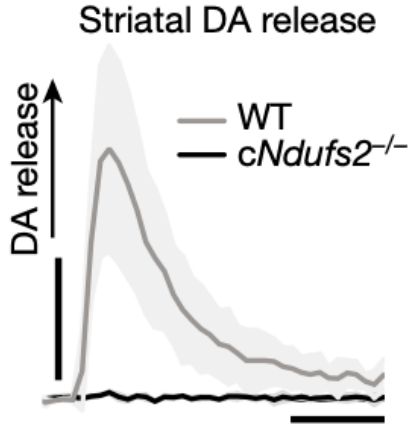


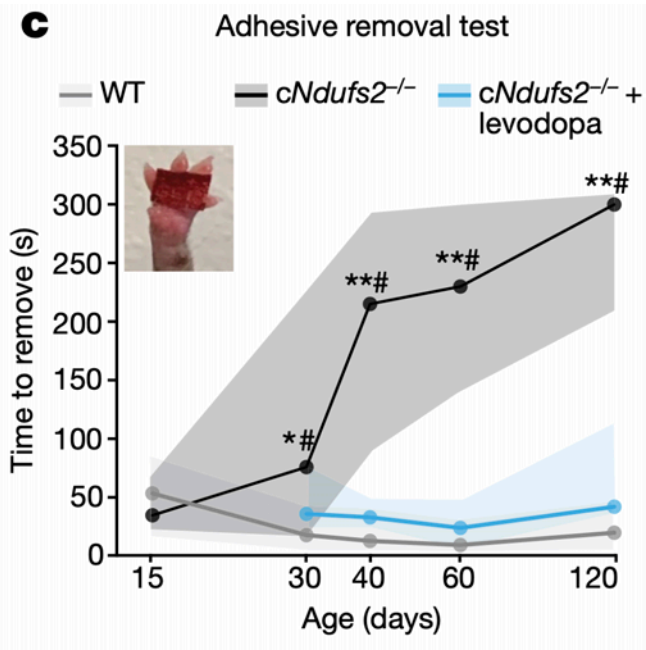
Complex I dysfunction induces Parkinsonism

- Ndufs2 is a core unit essential for the catalytic activity of **mitochondrial complex I**.
- Selective Ndufs2 KO in dopaminergic neurons disrupts mitochondrial complex I and induces progressive Parkinsonism.





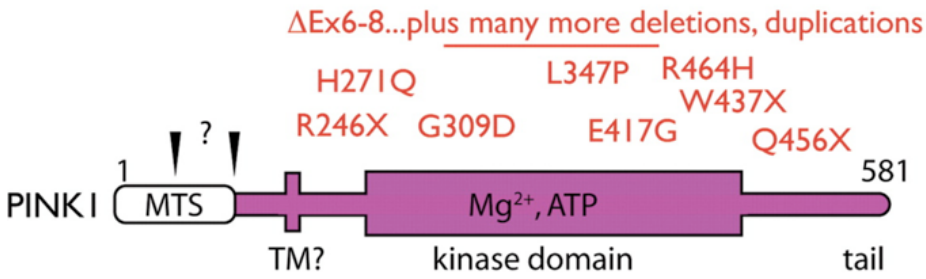




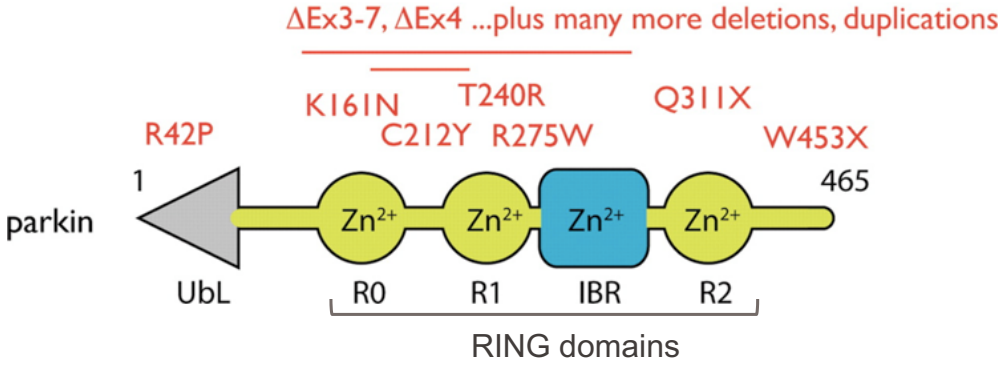
- *Nature 2021, https://doi.org/10.1038/s41586-021-04059-0*

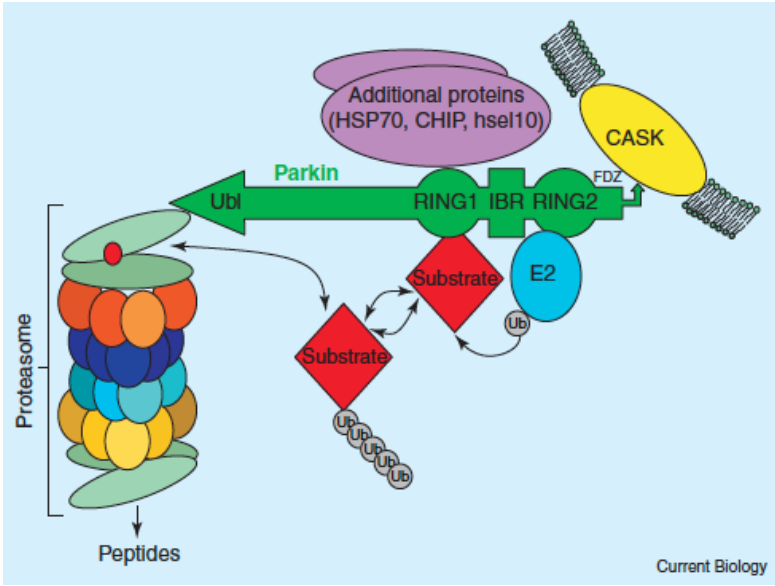
Genetic factors: Parkin and PINK1

PINK1: serine/threonin kinase



Parkin: E3 ubiquitin ligase





Parkinson's disease: question 12

Parkinson's patients with recessive mutations in the Parkin gene have in most cases no Lewy bodies.

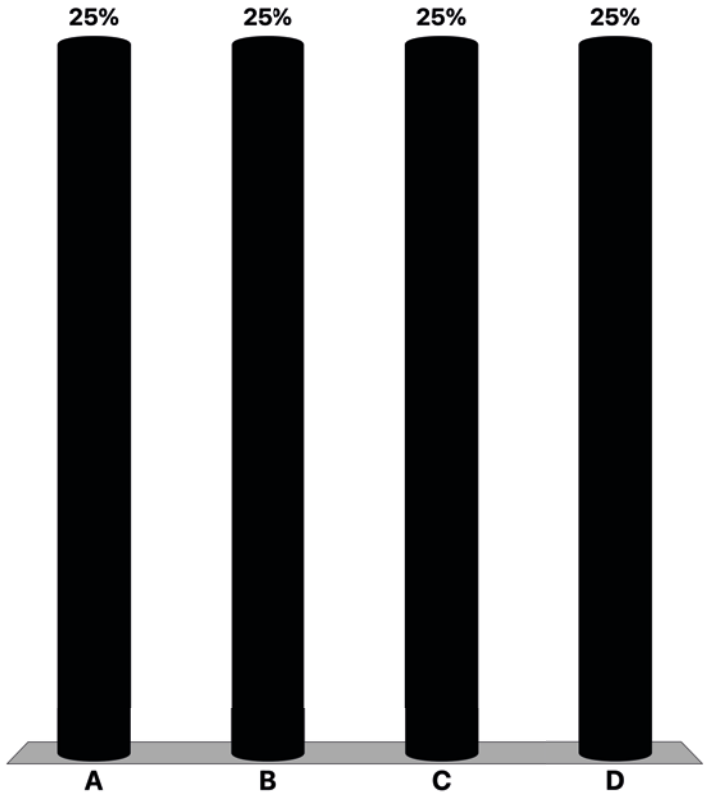
What would you conclude from this observation?

A. This is a different form of Parkinson's disease, with mechanisms different from the typical disease.

B. α-synuclein deposition may require Parkin activity.

C. Parkin-mediated ubiquitination of α-synuclein is required for Lewy body formation.

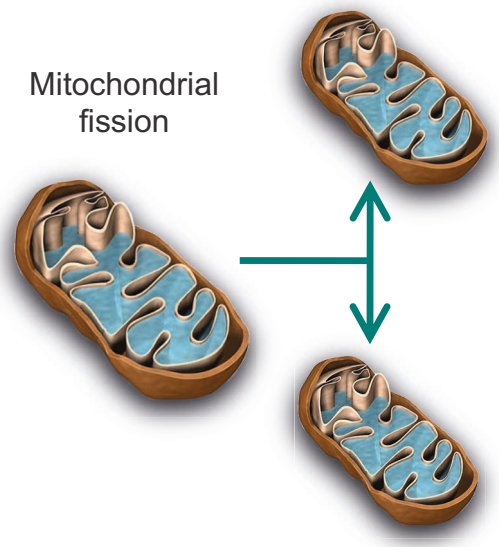
D. As Parkin mutations lead to early-onset juvenile Parkinsonism, Lewy bodies do not have time to develop.

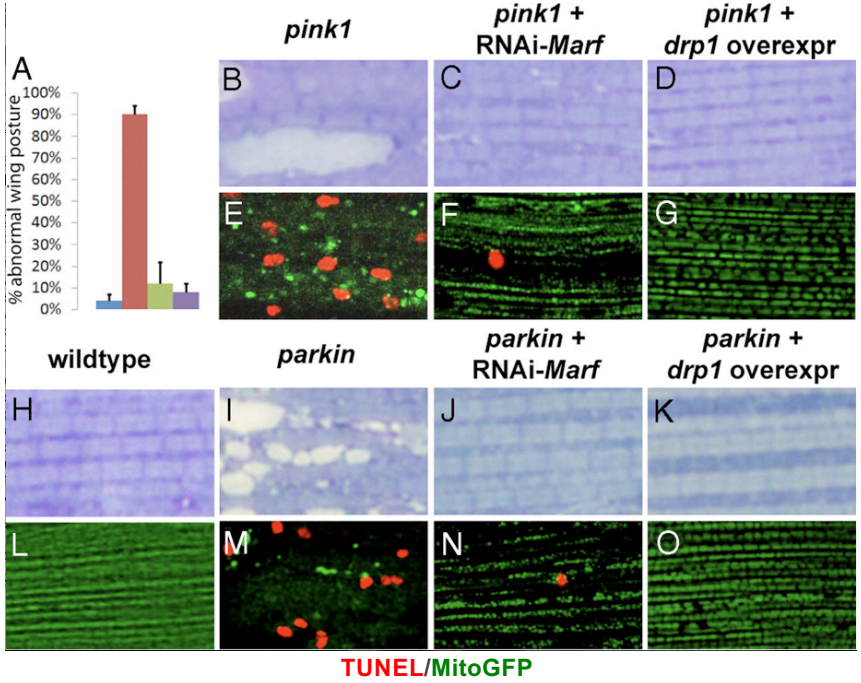


Genetic factors: Parkin and PINK1

Parkin/PINK1:
pathway regulating mitochondrial morphology
(*Drosophila*)

PINK1 → Parkin →



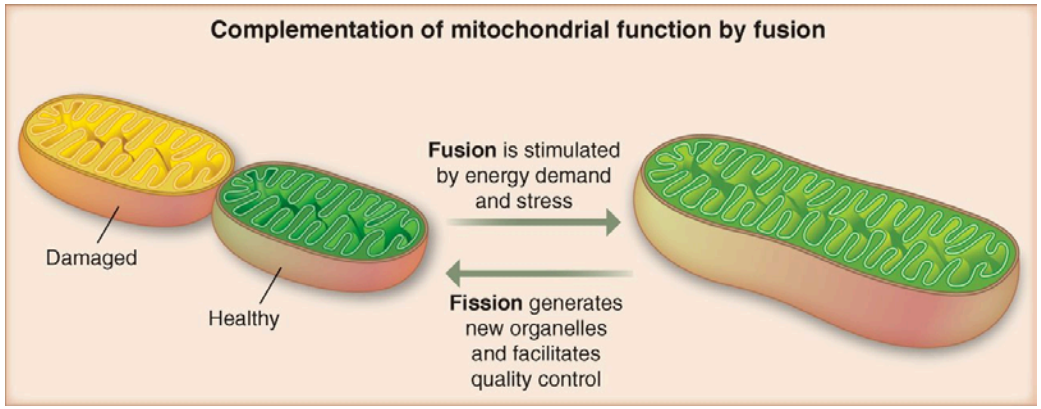


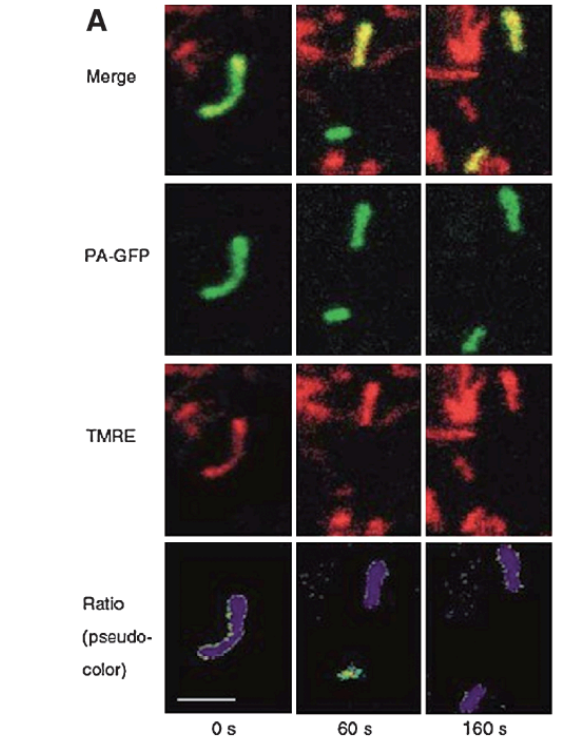
Drosophila melanogaster
Muscle

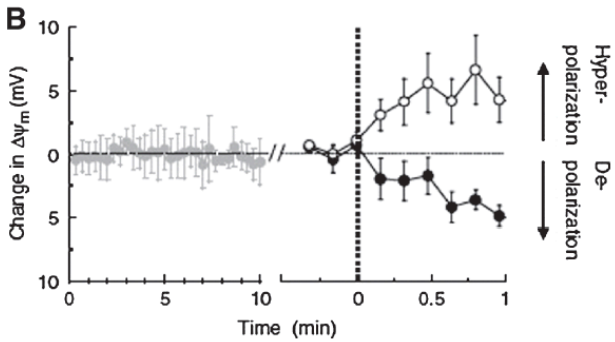
Deng H et al., PNAS 105(38) 2008
Poole AC et al., PNAS 105(5) 2008
Clark IE et al, Nature 441(7097) 2006
Park J et al., Nature 441(7097) 2006
Clark IE et al., Nature 441 2006

Genetic factors: Parkin and PINK1

Parkin/PINK1 in mammalian cells:
Fission as part of quality control of mitochondria



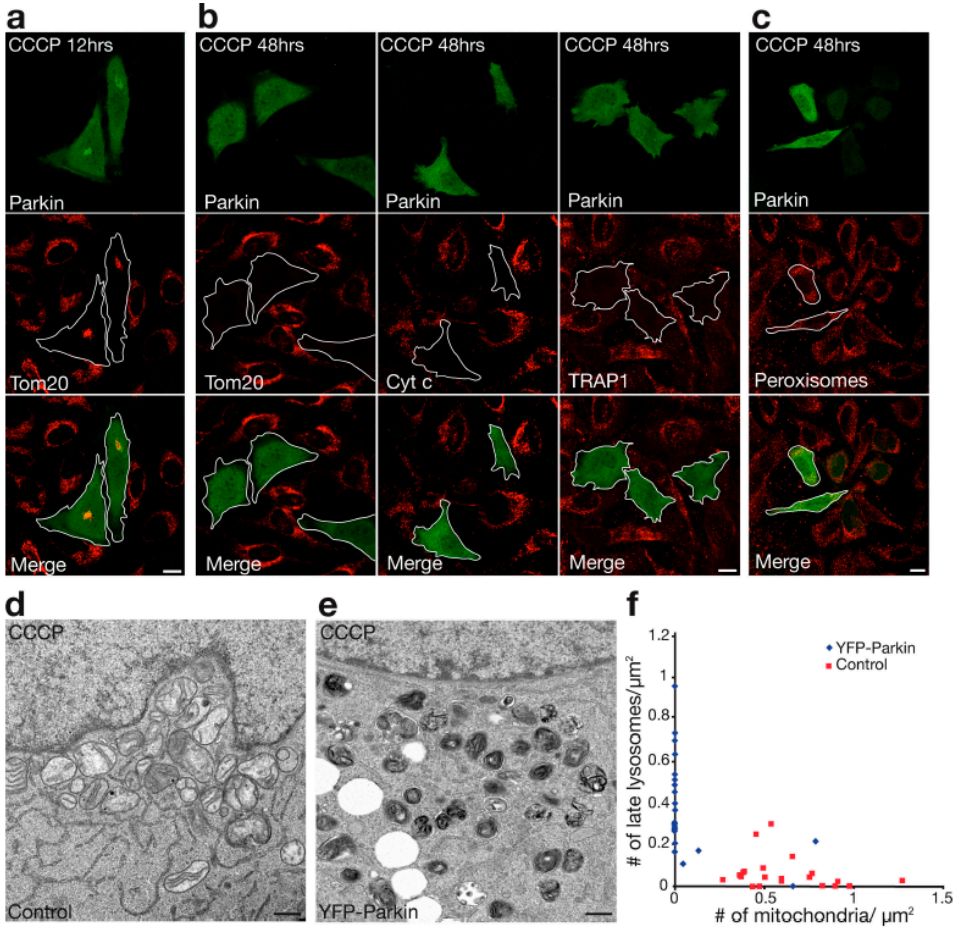




Genetic factors: Parkin and PINK1

Parkin in mammalian cells: a role in the autophagy of depolarized mitochondria

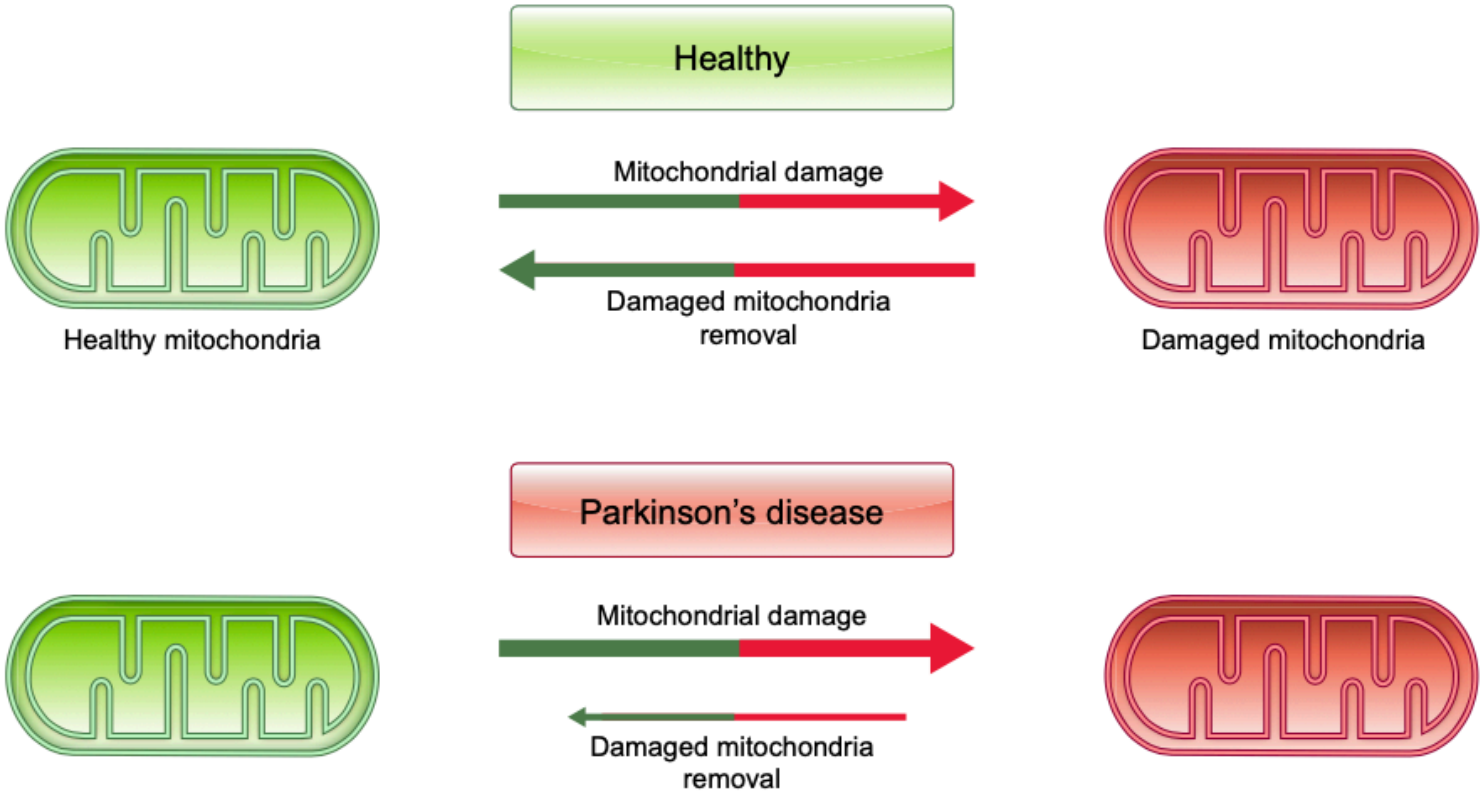
- Parkin promotes the selective elimination of depolarized mitochondria in CCCP-treated HeLa cells [CCCP induces mitochondrial depolarization].
- In cells overexpressing Parkin, there is an accumulation of lysosomes (autophagic degradation of mitochondria) following CCCP exposure.



- Narendra D et al., JCB 2008

Genetic factors: Parkin and PINK1

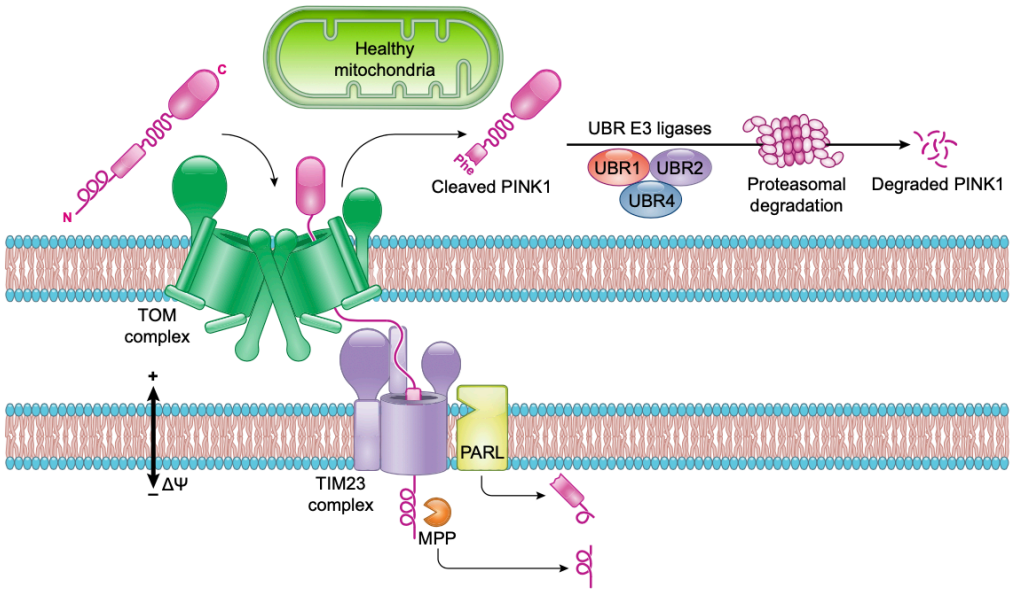
Mitochondria quality control



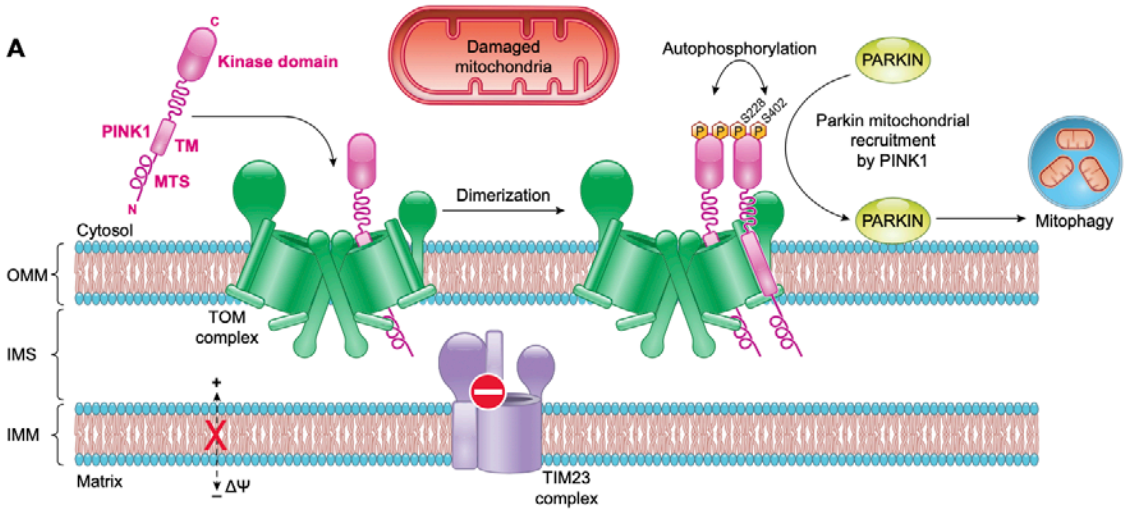
ELDEEB ET AL., 2022, Physiol Rev102: 1721–1755
https://doi.org/10.1152/physrev.00041.2021

Genetic factors: Parkin and PINK1

Mitochondria quality control: PINK1-mediated recruitment of Parkin



Rapid turnover of PINK1

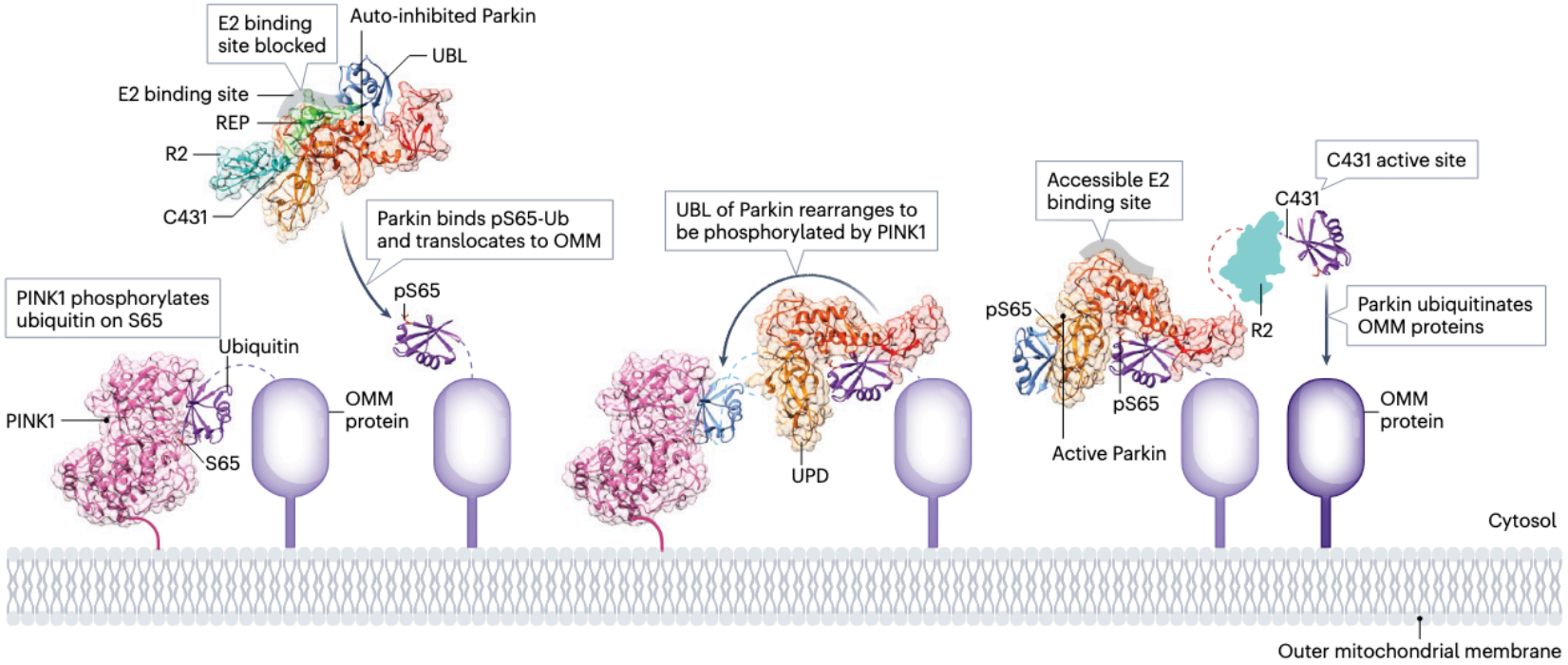


PINK1 ⇒ Parkin activation

- ELDEEB ET AL., 2022, Physiol Rev102: 1721–1755
  https://doi.org/10.1152/physrev.00041.2021

Genetic factors: Parkin and PINK1

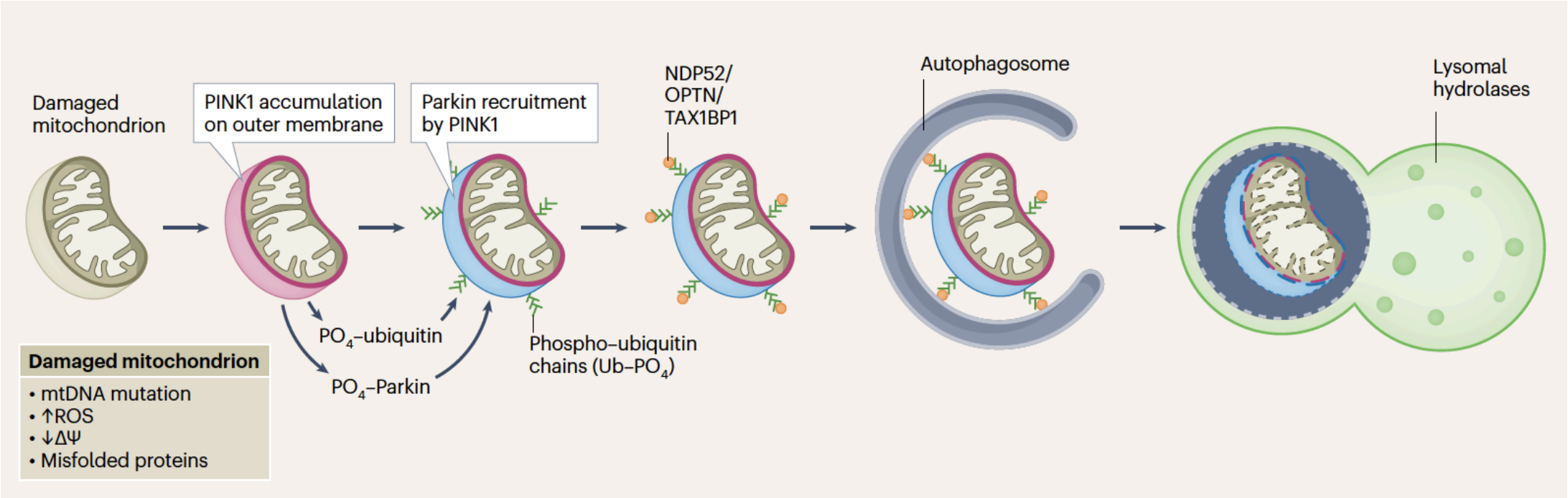
Parkin ubiquitinates proteins on the mitochondrial outer membrane (OMM)



- *https://doi.org/10.1038/s41556-024-01513-9*

Genetic factors: Parkin and PINK1

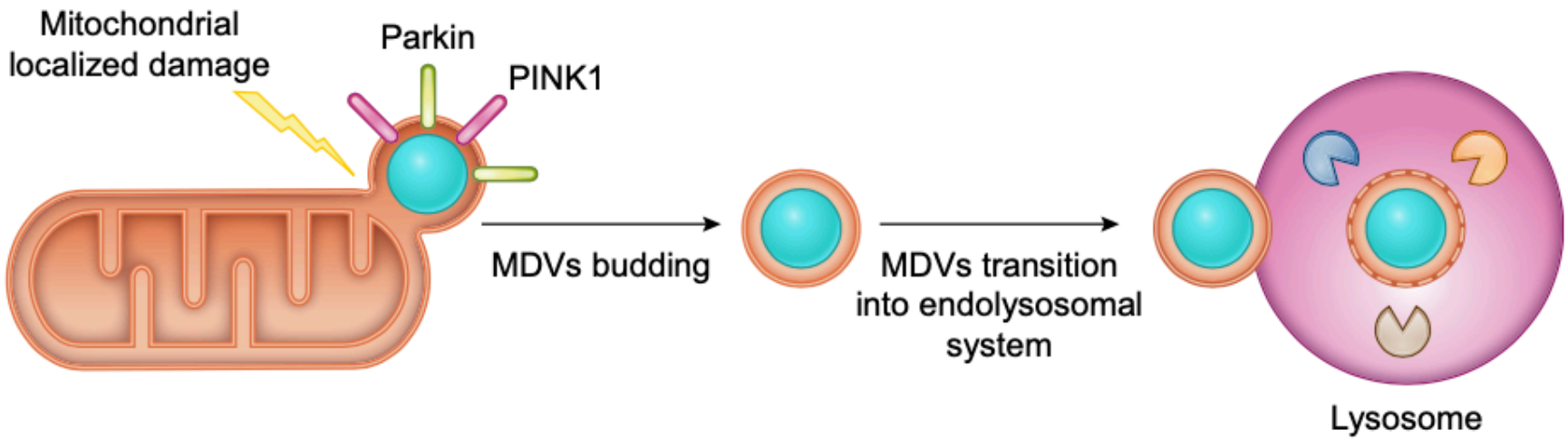
Molecular pathway leading to mitophagy



- *https://doi.org/10.1038/s41556-024-01513-9*

Genetic factors: Parkin and PINK1

Mitochondrial quality control: mitochondrion-derived vesicles

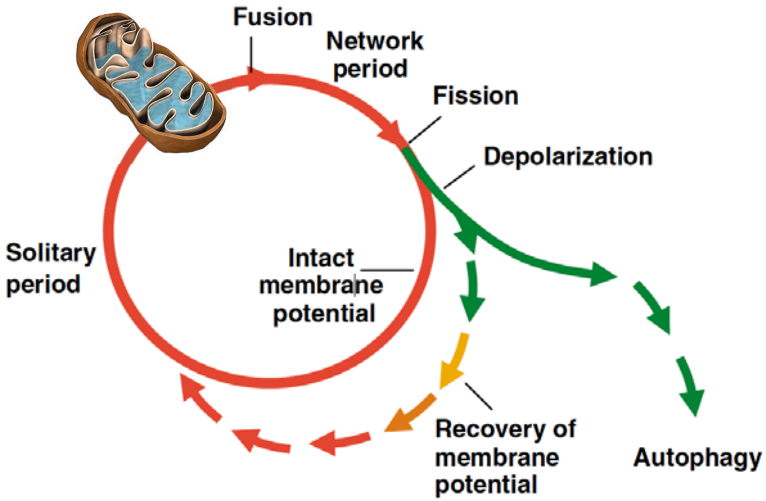


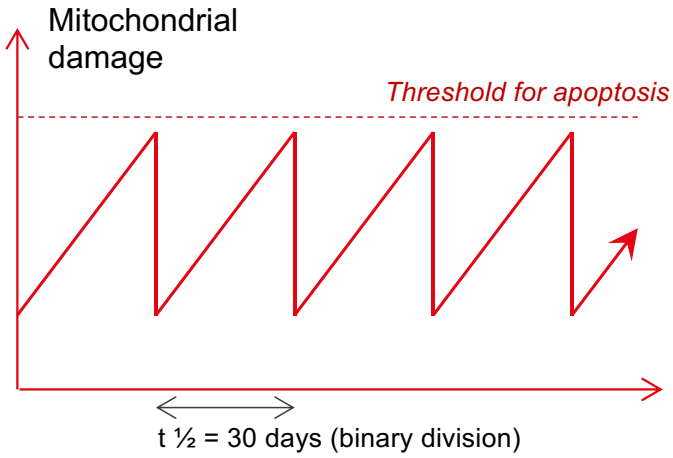
- ELDEEB ET AL., 2022, Physiol Rev102: 1721–1755
  https://doi.org/10.1152/physrev.00041.2021

Parkinson's disease: mitochondria turnover

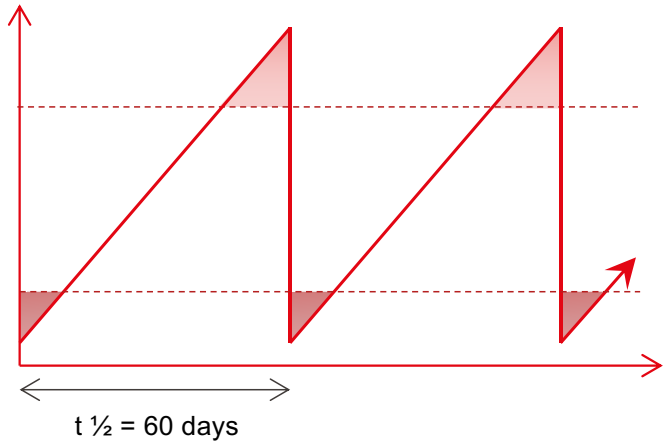
Mitochondrial turnover: an essential component of PD ?

- PD is associated with a reduction of **ETC complex I activity**
- PD toxins affect ETC complex I
- Parkin/PINK1 implicated in **mitophagy**
- Other genetic factors directly involved in **mitochondria/lysosomal function** (incl. α-synuclein)





Aging/neurodegeneration



- *Twig G et al, EMBO J, 27 (2008)*
  Navarro A, Boveris A, Front Aging Neurosci 2010

Parkinson's disease: question 13

There is ample evidence that **mitochondrial impairment** has a critical role in Parkinson's disease. Why are all neurons not equally affected by the disease? Among these statements, which ones are correct?

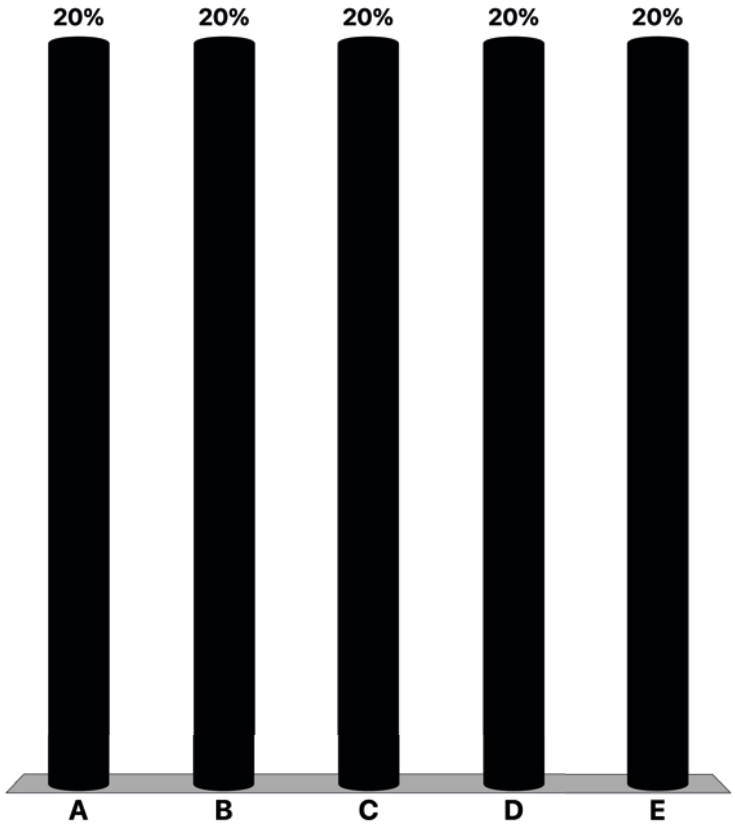
A. Mitochondrial activity is important to the survival and function of neurons producing dopamine.

B. Only the neurons that express α-synuclein are sensitive.

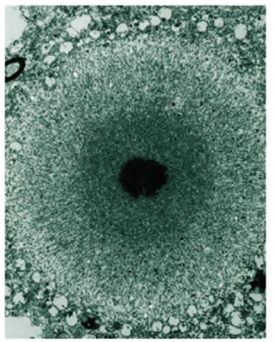
C. Different types of neurons have various mitochondrial content.

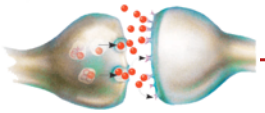
D. Mitochondrial function is critical in neurons with long axons.

E. Mitochondrial pathology depends on calcium signals.



Overview of Parkinson's disease





Dopamine

Mitochondrial activity

Alpha-synuclein aggregation and spreading

Parkin, PINK1 deficiency

Mitochondria quality control and turnover

Autophagic activity

Low GBA1 activity

Selective vulnerability

Neuro-degeneration