Lecture plan

1. Basal ganglia circuitry

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

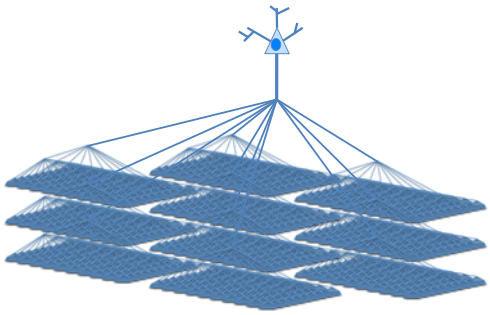
3. Neuronal degeneration / Lewy body pathology
   - Selective vulnerability of neuronal subtypes
   - Spreading of the α-synuclein pathology

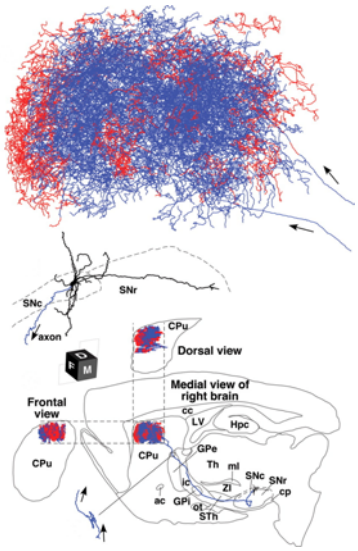
4. PD etiology: organelle quality control
   - Recessive forms: parkin, PINK1 and mitochondrial turnover

Parkinson's disease pathology: selective neuronal vulnerability

Ventral midbrain dopamine neurons

- Long, unmyelinated axons, high energy demand
- Accumulation of DA degradation products in **neuromelanin**
- >1'000'000 presynaptic terminals/neuron in humans
  Massive dendrites, cell body <<1% total cell volume
- Depend largely on axonal transport
- Presence of **DOPAMINE** is a stress factor
- DA metabolism produces ROS sequestration into vesicles is crucial
- **Autonomously active**, slow pacemaking firing activity (2-4Hz)
- Ca_V 1.3 channels

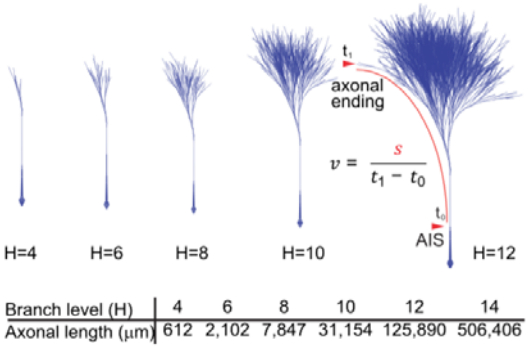




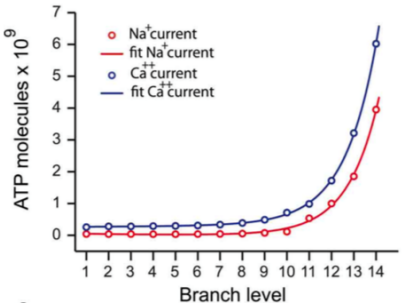
Chan CS et al., TINS 32(5), 2009
Matsuda W et al., J. Neurosci 29(2), 2009

Parkinson's disease pathology: selective neuronal vulnerability

ATP demand increases exponentially with increasing levels of axonal branching



Branch level (H)	4	6	8	10	12	14
Axonal length (μm)	612	2,102	7,847	31,154	125,890	506,406



- Pissadaki E.K. & Bolam P, Front Comput Neurosci. 2013; 7: 13

Parkinson's disease : genetic and environmental causes

Parkinson's disease: complex etiology !

Extreme cases: purely genetic

Genetic factors ➡ susceptibility

Polygenic

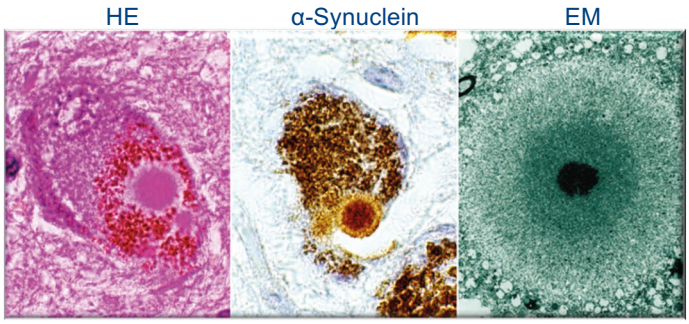
Environmental risk factor

Extreme cases:
environmental intoxication

Parkinson's disease pathology: Lewy bodies

Lewy body

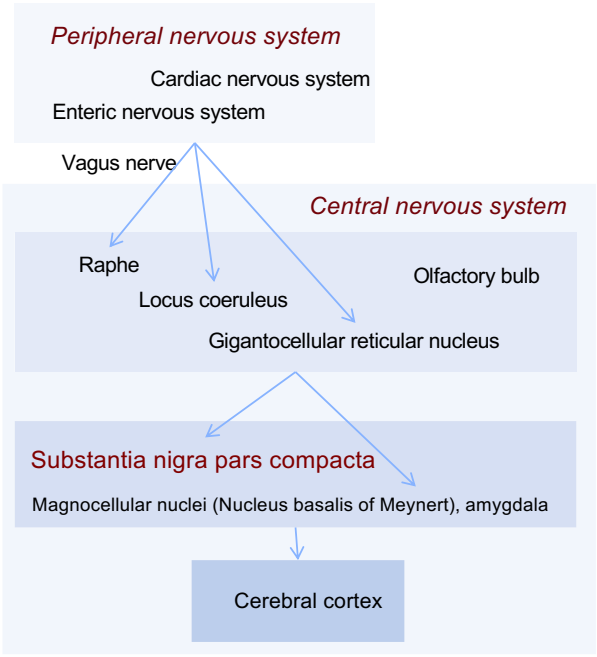
- First described in 1912 by Friedrich Lewy
- Hallmark of synucleinopathies
- Aggregates, composed mainly of proteins, and some lipids
- The protein **alpha-synuclein** is the main constituent
- Cytoplasmic
- Mostly neuronal
- In the cell soma (Lewy bodies)
- In the neurites (Lewy neurites)

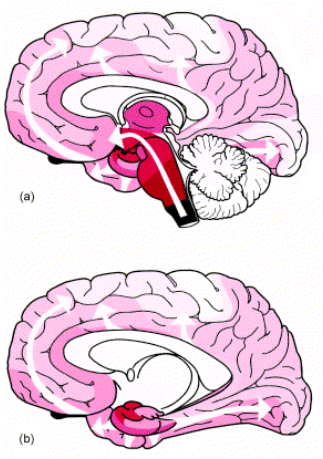


Parkinson's disease etiology : familial forms

Locus	Protein	Mode of inheritance	Atypical PD features	Lewy bodies	Frequency
PARK1/4	**α-synuclein (SNCA)**	**AD**	**Early onset, rapid progression**	**+**	**<1%**
PARK8	LRRK2	AD	-	+	1-7% of PD patients
PARK5	UCH-L1	AD	?	?	rare
PARK17	VPS35	AD	?	?	0.13% of PD patients
PARK2	Parkin	AR	Early onset, dyskinesias, slow progression	(-)	10-25% of early-onset PD
PARK6	PINK1	AR	Early onset, slow progression	(+)	1-8% of early-onset PD
PARK9	ATP13A2	AR	Juvenile onset, dementia	?	rare
PARK7	DJ-1	AR	Early onset, slow progression, psychiatric symptoms	?	1-2% of early-onset PD
PARK14	PLA2G6	AR	Early onset, dystonia	?	rare

Widespread and progressive Lewy body pathology in Parkinson's disease

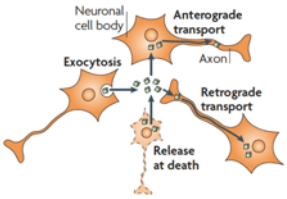




Braak H. et al.,
Neurobiology of Aging 2003, 24: 197-211

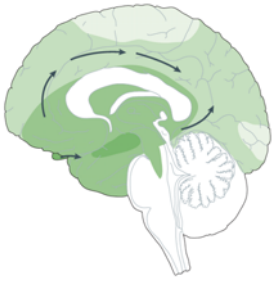
Neurodegeneration: spreading pathologies

Propagation patterns of neurodegenerative proteopathies

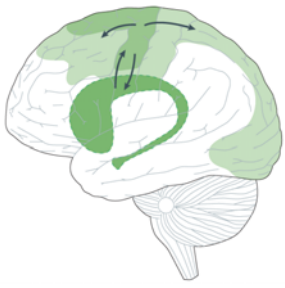


Parkinson's disease (α-synuclein)

Alzheimer's disease (tau)



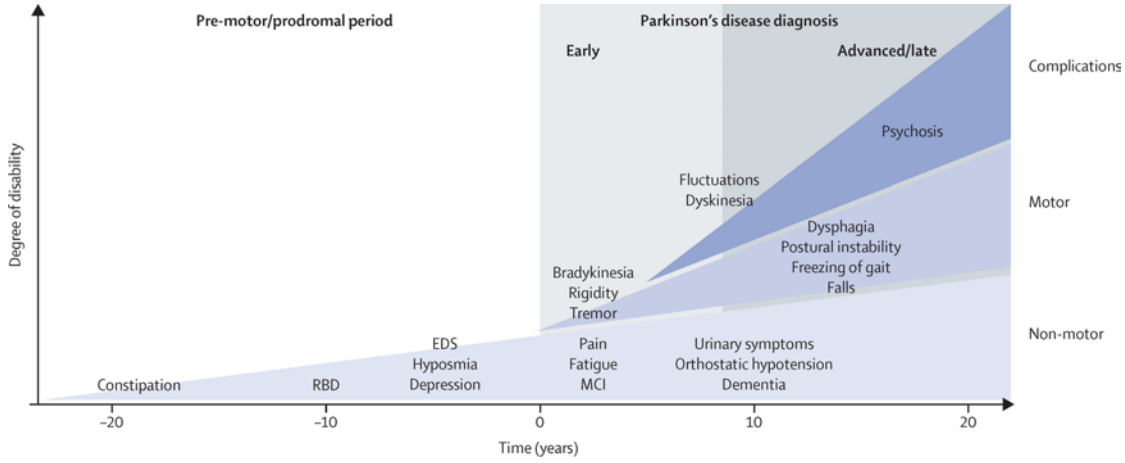
Huntington's disease (huntingtin)



Lewy body pathology in Parkinson's disease: correlation with early symptoms

Evolution of Parkinson's disease

(many symptoms poorly respond to dopamine treatment)

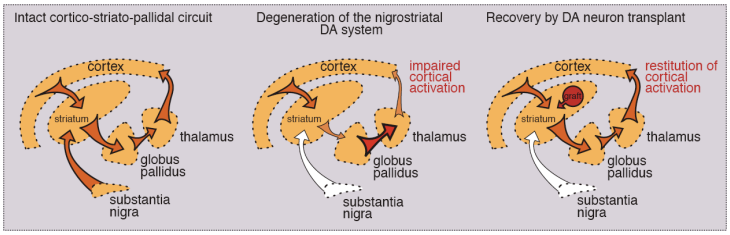


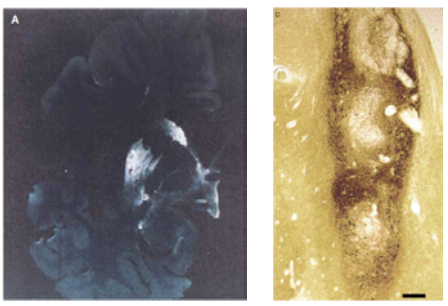
- Kalia LV et al, the Lancet 2015

RBD: REM (rapid eye movement) Sleep Behavior Disorder
EDS: Excessive daytime sleepiness

PD pathology: evidence for spreading

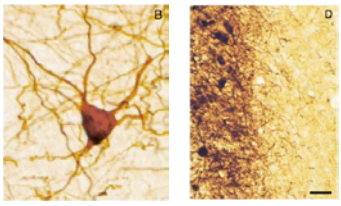
Cell replacement: fetal grafts of dopamine neurons





Survival / engraftment

Fetal graft (7 embryos, 6½-9 wks)
18 months post transplantation
Tyrosine hydroxylase staining



Connectivity with host striatum

- *Kordower et al., NEJM 332 (1995), Björklund & Lindvall, Nature Neuroscience 3 (2000)*

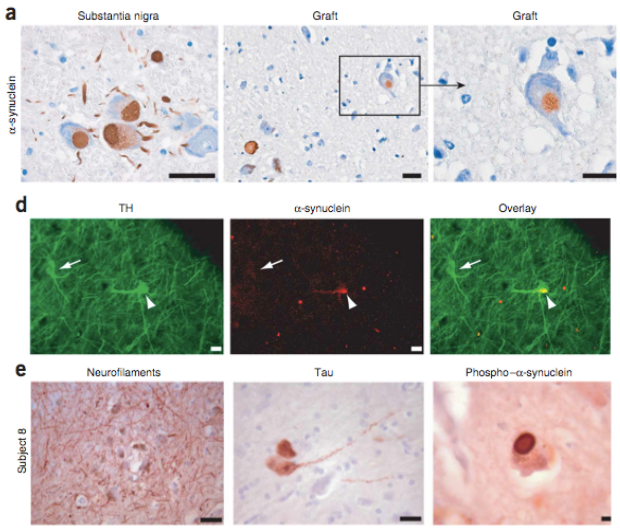
PD pathology: evidence for spreading

Post-mortem analysis of long-term grafted patients: 11-16 yrs post surgery

Lewy-body pathology in some grafted neurons !

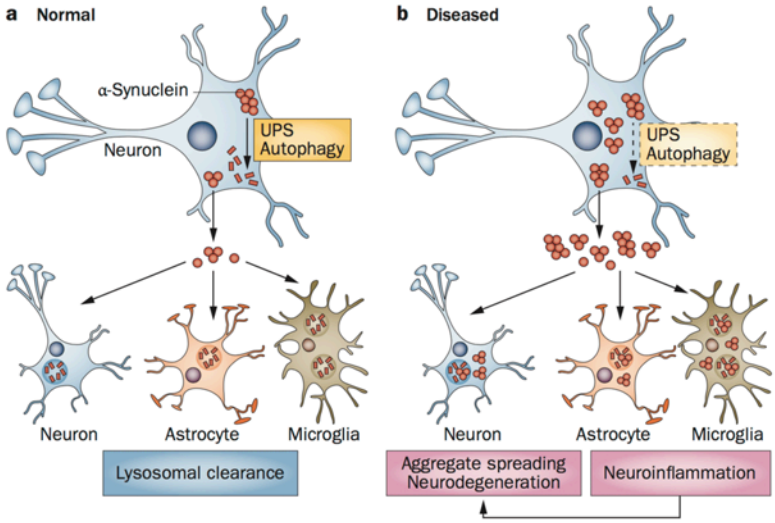
« Prion-like » disease transmission ?

Graft exposed to a noxious microenvironment (microglia, lack of trophic support) ??



- *Li et al., Nature Medicine 2008*
  Kordower et al., Nature Medicine 2008
  Mendez et al., Nature Medicine 2008

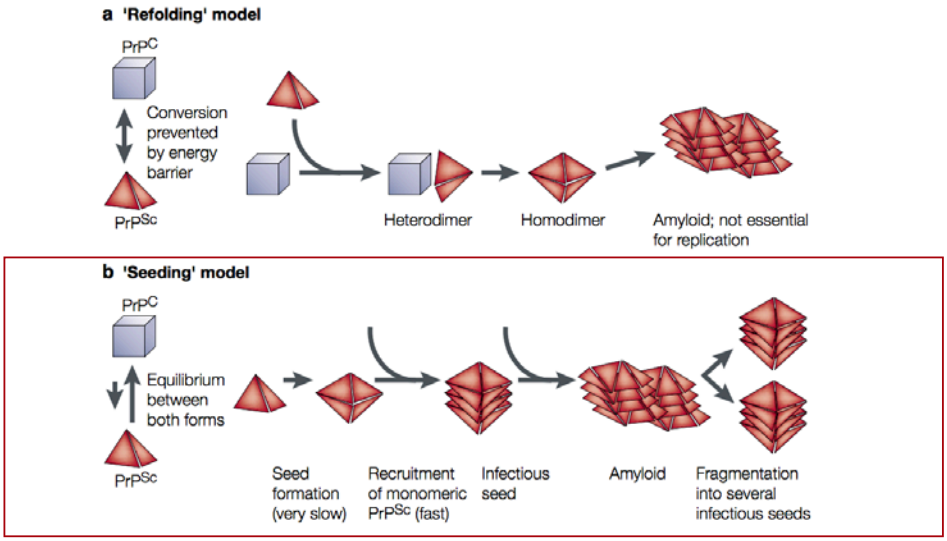
PD pathology: evidence for spreading



- *Lee HJ et al, Nat Rev Neurol 2014*

Spreading of PD pathology: a prion-like mechanism ?

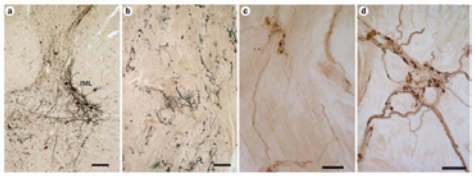
Infectious proteins: proposed models



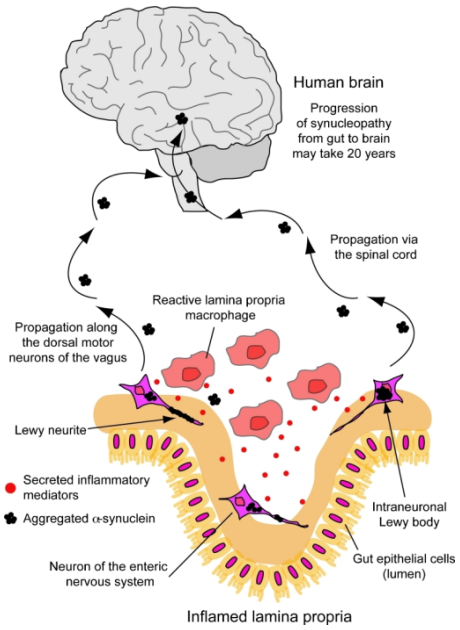
- *Aguzzi A et al, Nat Rev Mol Cell Biol 2, 118-126 (2001) | doi:10.1038/35052063*

PD pathology: evidence for spreading

Is there a propagation of the α-synuclein pathology from the periphery towards the brain ?

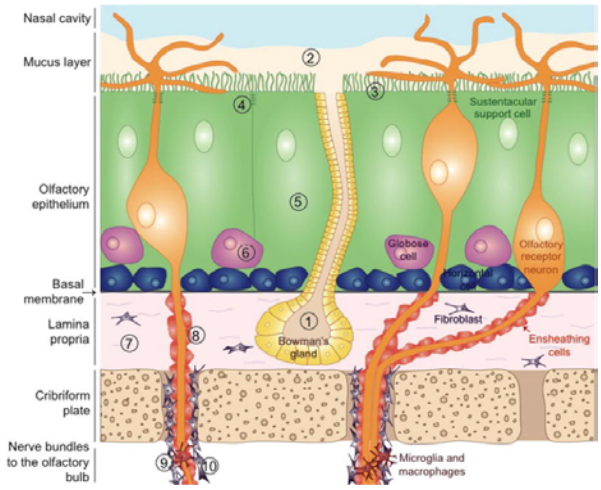


Synuclein-immunoreactive Lewy pathology in the PD spinal cord, coeliac ganglion and gastrointestinal tract

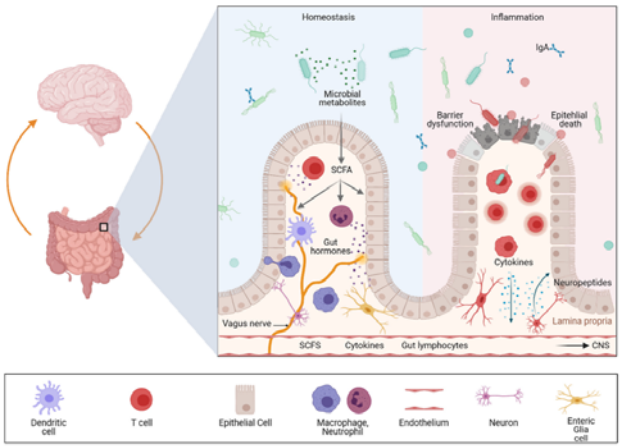


Are the olfactory epithelium and the gut epithelium starting points for spreading of the α-synuclein pathology to the central nervous system ?

Olfactory epithelium



Gut epithelium



Parkinson's disease: question 6

Alpha-synuclein pathology propagates across defined pathways in the CNS. What are the implications of this observation ?

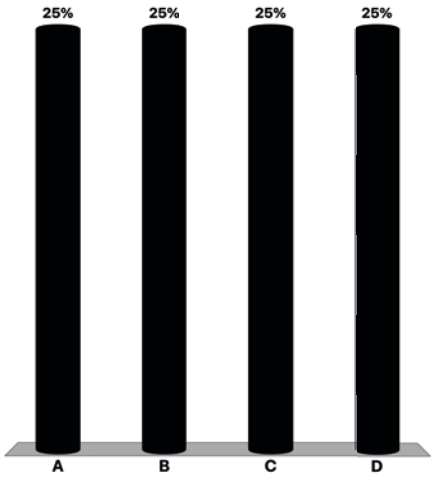
Select all the correct statements:

A. Similar to prion, α-synuclein misfolding is an infectious mechanism

B. This shows that the protein may be accessible to therapeutic intervention outside cells

C. This mechanism may be either pathological or physiological

D. This mechanism has no therapeutic implication



Pathology: α-synuclein

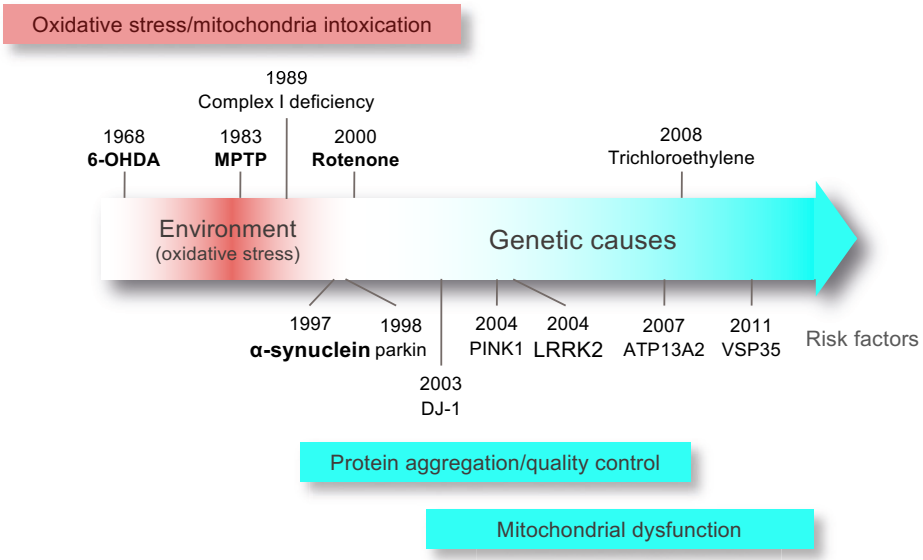
Parkinson's disease: a cerebral proteopathy ?

	Aggregated protein	Pathological lesion	Proteopathy
Alzheimer's disease	Amyloid β	Amyloid β Plaques	Amyloidosis
	Tau	Neurofibrillary tangles	Tauopathy
Pick's disease (FTLD)	Tau	Pick bodies	Tauopathy
Parkinson/Lewy Body Disease	αSynuclein	Lewy bodies/neurites	Synucleinopathy
Creutzfeldt-Jakob Disease	Prion	Prion plaques	Prionopathy

"Prionoids"?

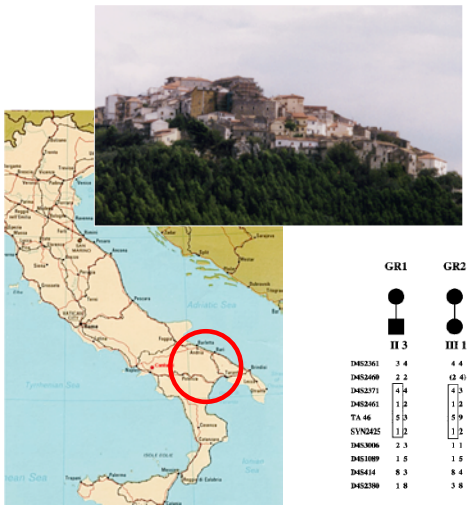
Parkinson's disease etiology : genetic factors

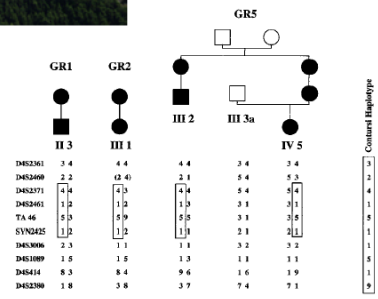
Parkinson's disease: a shift in the paradigm…



Genetic factors: α-synuclein (SNCA)

Contursi kindred (α-synuclein A53T mutation)





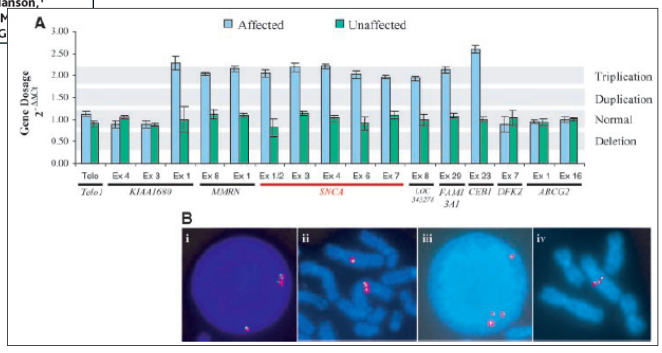
Autosomal dominant inheritance

Genetic factors: α-synuclein (SNCA)

α-Synuclein: importance of gene dosage

α-Synuclein Locus Triplication Causes Parkinson's Disease

A. B. Singleton,[1*†] M. Farrer,[4†] J. Johnson,[1] A. Singleton,[2] S. Hague,[1] J. Kachergus,[4] M. Hulihan,[4] T. Peuralinna,[1] A. Dutra,[3] R. Nussbaum,[2] S. Lincoln,[4] A. Crawley,[2] M. Hanson,[1] D. Maraganore,[5] C. Adler,[6] M. R. Cookson,[1] M. M[illegible] M. Baptista,[1] D. Miller,[1] J. Blancato,[7] J. Hardy,[1] K. G[illegible]



α-synuclein locus duplication as a cause of familial Parkinson's disease

Marie-Christine Chartier-Harlin, Jennifer Kachergus, Christophe Roumier, Lydie Lanvar, Joris Andrieux, Mary Hulihan, Nawal Waucquier, Luc Defeb[illegible]

Causal relation between α-synuclein gene duplication and familial Parkinson's disease

Lancet 2004

P Ibáñez, A-M Bonnet, B Débarges, E Lohmann, F Tison, P Pollak, Y Agid, A Dürr, A Brice, French Parkinson's Disease Genetics Study Group*

Genetic factors: α-synuclein (SNCA)

α-Synuclein: importance of gene dosage

	Fold increase in expression	Syndrom	Age of onset	Mode of inheritance
Promoter polymorphism	?	Risk factor for Parkinson	?	?
Duplication	1.5 X	Parkinsonism	48 yrs (39-65)	Dominant (incomplete penetrance)
Triplication	2 X	Parkinsonism Dementia	34 yrs	Dominant

Parkinson's disease: question 8

You have discovered that a triplication of a genomic locus containing the α-synuclein gene can lead to autosomal dominant Parkinson's disease (PD), which is characterized by the deposition of Lewy bodies.

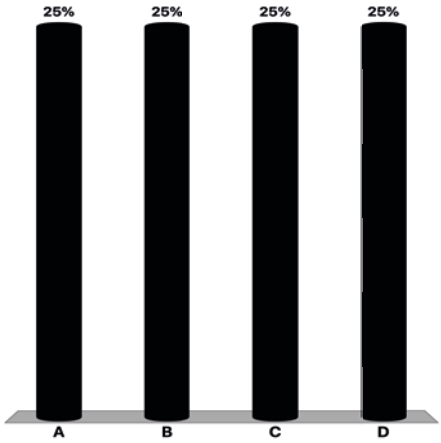
Which one(s) of the following statements can you conclude from this finding?

A. PD can be caused by an overabundance of α-synuclein.

B. PD is not caused by the loss of the α-synuclein physiological function.

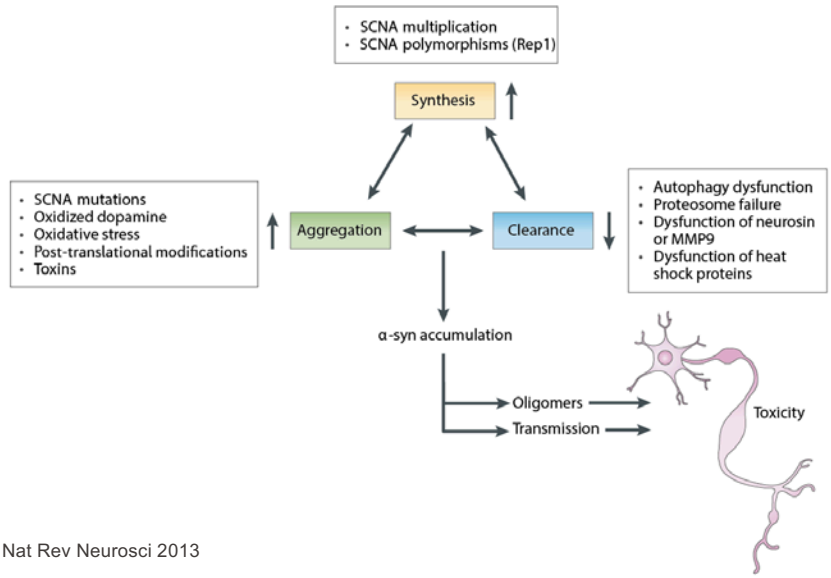
C. The locus does not contain only the α-synuclein gene. There could be another gene involved in this case.

D. When overabundant, α-synuclein leads to the formation of Lewy bodies and these aggregates are toxic to the neurons.



Genetic factors: α-synuclein (SNCA)

Alpha-synuclein – dysregulation



- Lashuel HA et al, Nat Rev Neurosci 2013

Genetic factors: α-synuclein (SNCA)

α-Synuclein

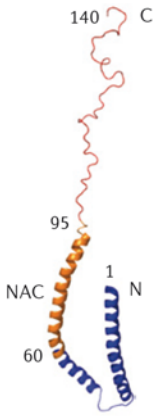
Chromosom 4q
140 a.a., cytoplasmic, MW ≈ 19 kDa
Mainly neuronal

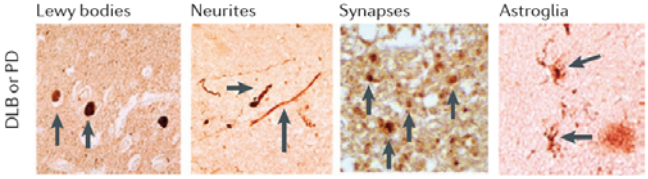
Three regions:

N-terminal (1-60):
Repetitive, associates with membranes

NAC (61-97):
hydrophobic
prone to aggregation

C-terminal (98-140):
acidic

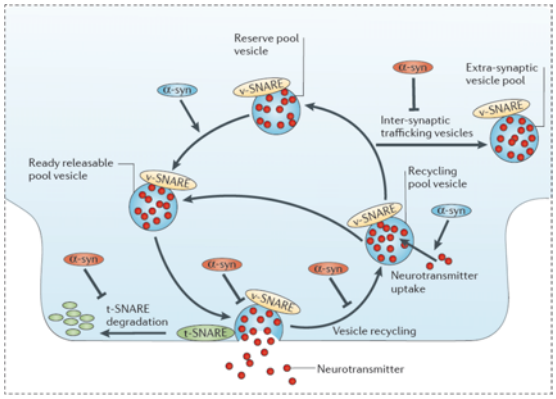




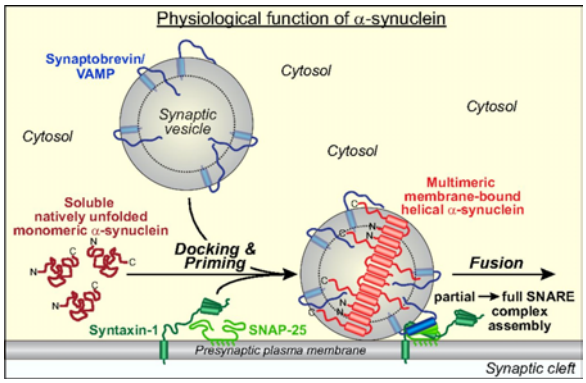
- Lashuel HA et al, Nat Rev Neurosci 2013

Genetic factors: α-synuclein (SNCA)

A physiological function for α-synuclein oligomers:
regulation of presynaptic vesicle fusion

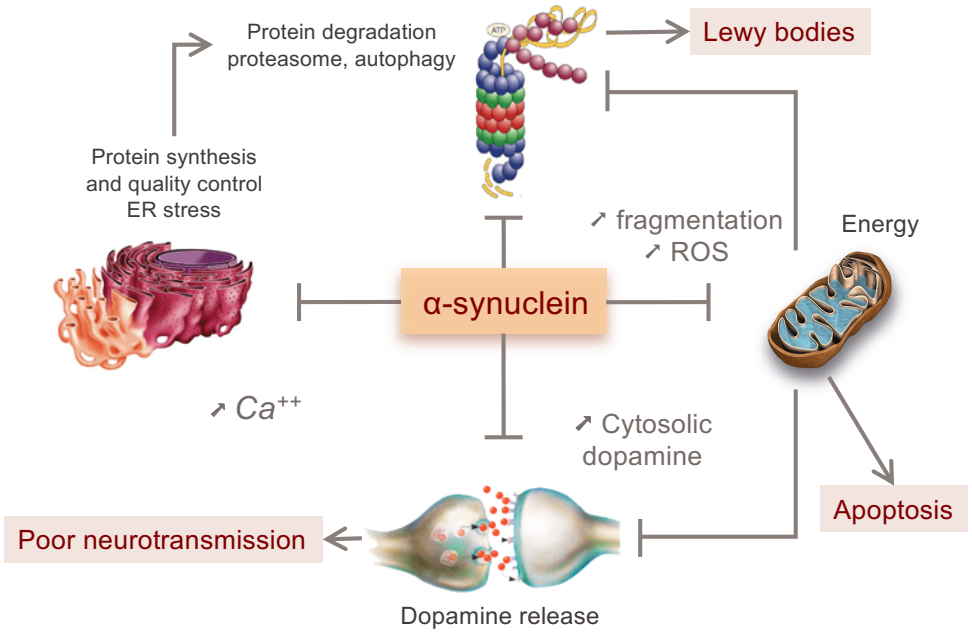


α-Synuclein forms multimers upon membrane binding to promote SNARE complex formation

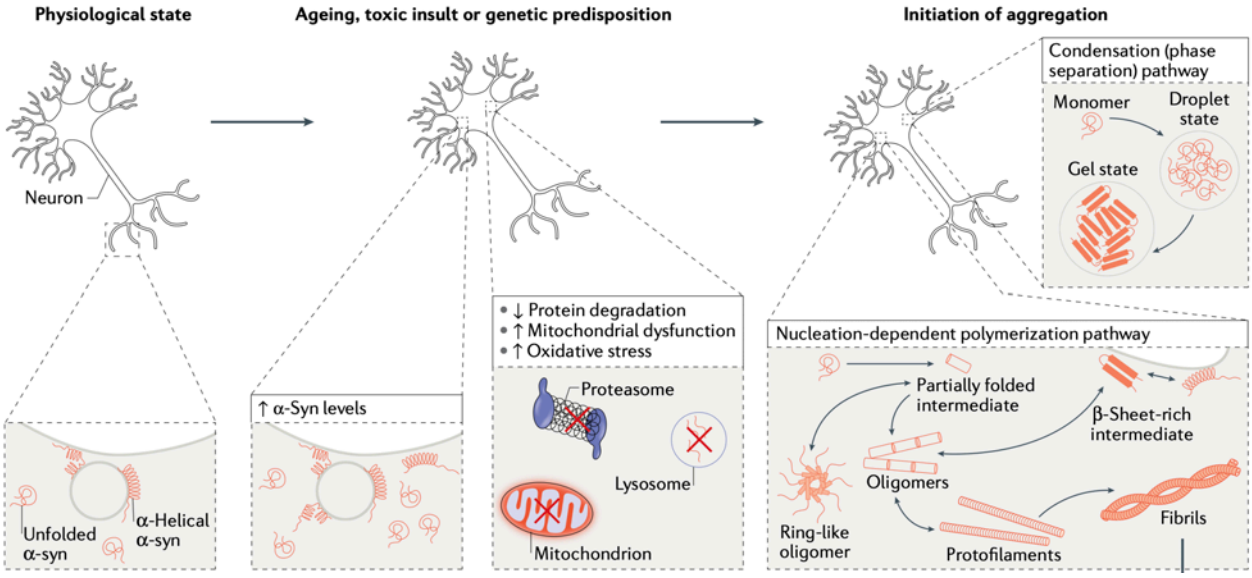


- Lashuel HA et al, Nat Rev Neuroci 2013
- Burré et al, PNAS 2014
- Wang et al, Current Biol 2014

Alpha-synuclein: cellular pathology



Alpha-synuclein: pathology

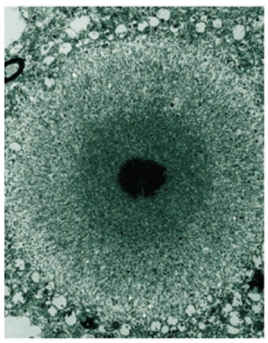


- Fares MB et al, Nat Rev Neurosci 2021

Pathology: α-synuclein

"Synucleinopathies"

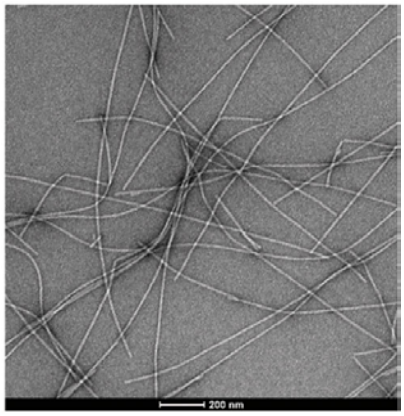
Parkinson's disease	**Sporadic** Familial with aS mutations Familial with mutations other than aS
Dementia with Lewy bodies	**"Pure" Lewy body dementia** Lewy body variant of Alzheimer disease Familial Alzheimer disease with APP mutations Familial Alzheimer disease with PS-1 mutations Familial Alzheimer disease with PS-2 mutations Down syndrome
Multiple system atrophy	Shy-Drager syndrome Striatonigral degeneration Olivopontocerebellar atrophy
Neurodegeneration with brain iron accumulation, type 1	Hallervorden-Spatz syndrome Neuroaxonal dystrophy
Other diseases that may have synuclein-immunoreactive lesions	Traumatic brain injury Pick's disease Amyotrophic lateral sclerosis



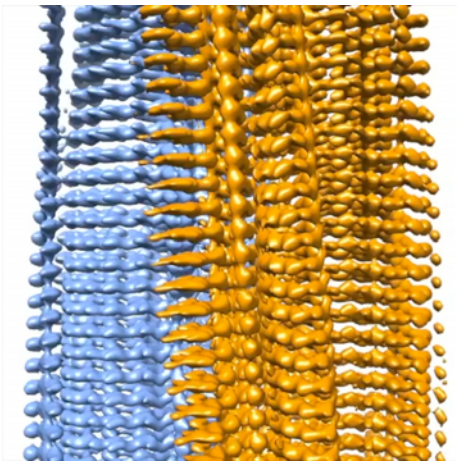
- J.E. Galvin et al., Arch Neurol. 2001;58:186-190

α-synuclein (SNCA): a protein which forms amyloid fibrils

α-synuclein fibrils

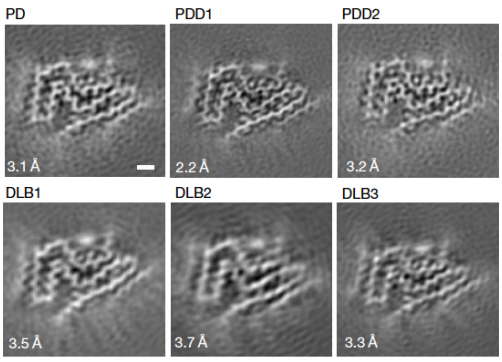


Cryo-EM structure analysis

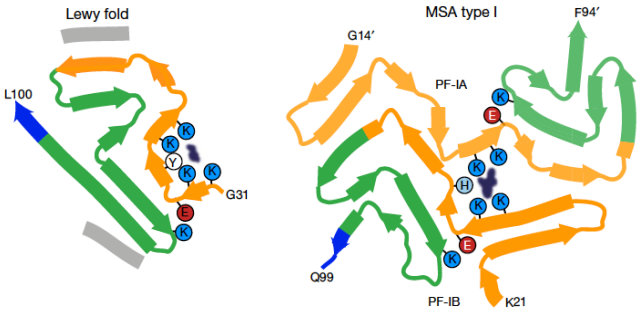


- Li Y et al, Cell Research 2018
  Guerrero-Ferreira G et al, eLife 2018

CryoEM structure of α-synuclein fibrils from PD, DLB and MSA patients

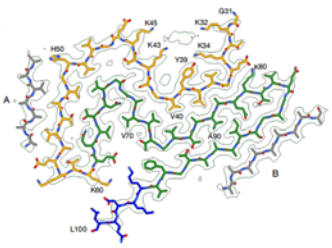


Cryo-EM cross-sections of α-synuclein filaments (Lewy fold) from the cingulate or frontal cortex



Comparison of the Lewy and MSA α-synuclein filament folds.

Amino acid sequence of human α-synuclein



Cryo-EM density map of the Lewy fold

- *Nature 610, 791–795 (2022). https://doi.org/10.1038/s41586-022-05319-3*
  Nature 2020, https://doi.org/10.1038/s41586-020-2317-6

Parkinson's disease: question 9

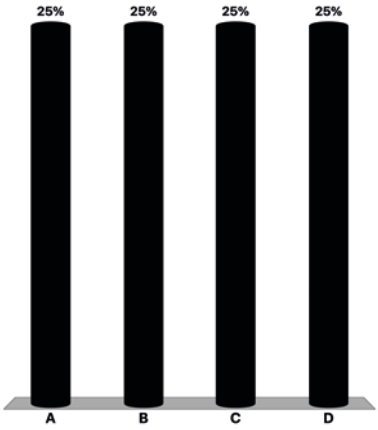
Why is it important to explore the structure of alpha-synuclein fibrils?
Rank the following statements from "correct" to "possible" to "wrong" ?

A. The shape of the fibrils will tell use what is the structure of the α-synuclein protein in normal conditions.

B. It will guide the design of therapeutic antibodies targeting alpha-synuclein pathology.

C. Because different types of fibrils may by associated with different diseases (e.g. PD or DLB).

D. We could try to identify therapeutic molecules to disassemble these fibrils.



From α-synuclein fibrils to Lewy bodies

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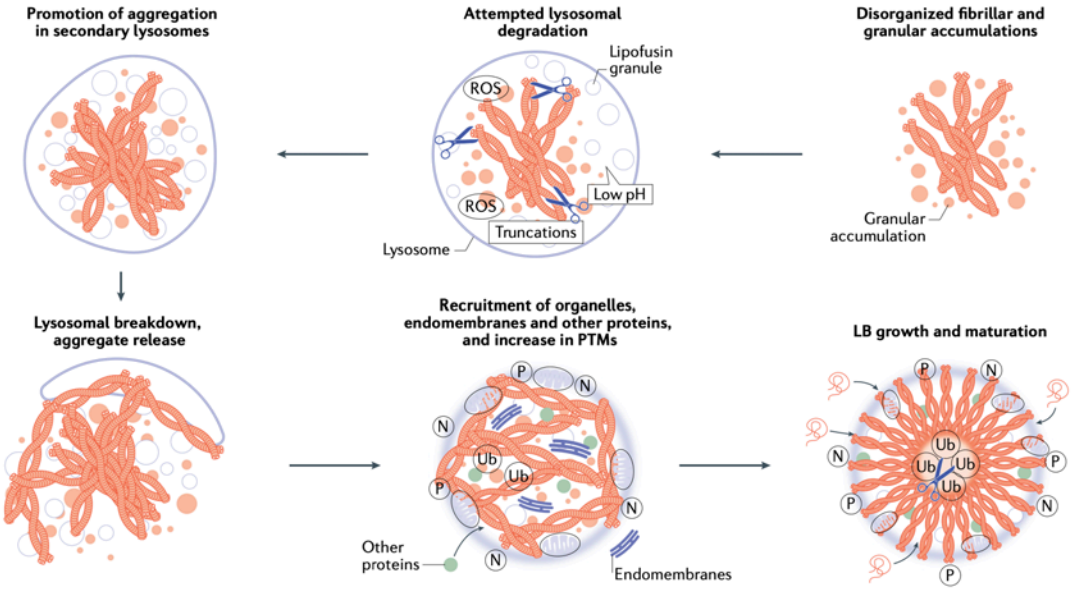
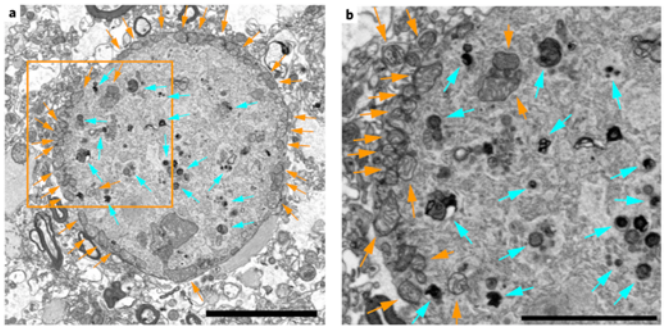


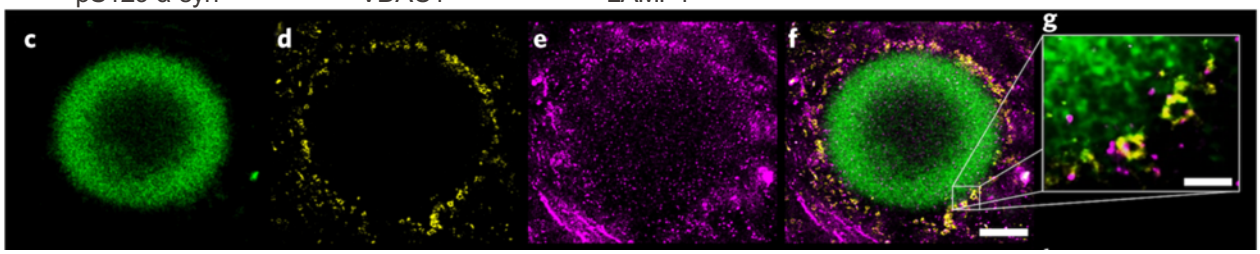
Fares MB et al, Nat Rev Neurosci 2021

Lewy bodies: accumulation of (defective?) organelles

Lewy bodies contain mitochondria and lysosomal structures



pS129 α-syn VDAC1 LAMP1

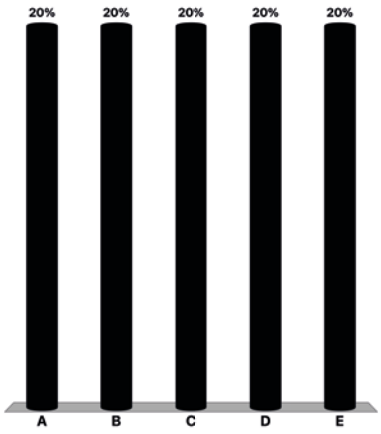


- Shahmoradian, S.H. et al. Nat Neurosci 22, 1099–1109 (2019)

Parkinson's disease: question 10

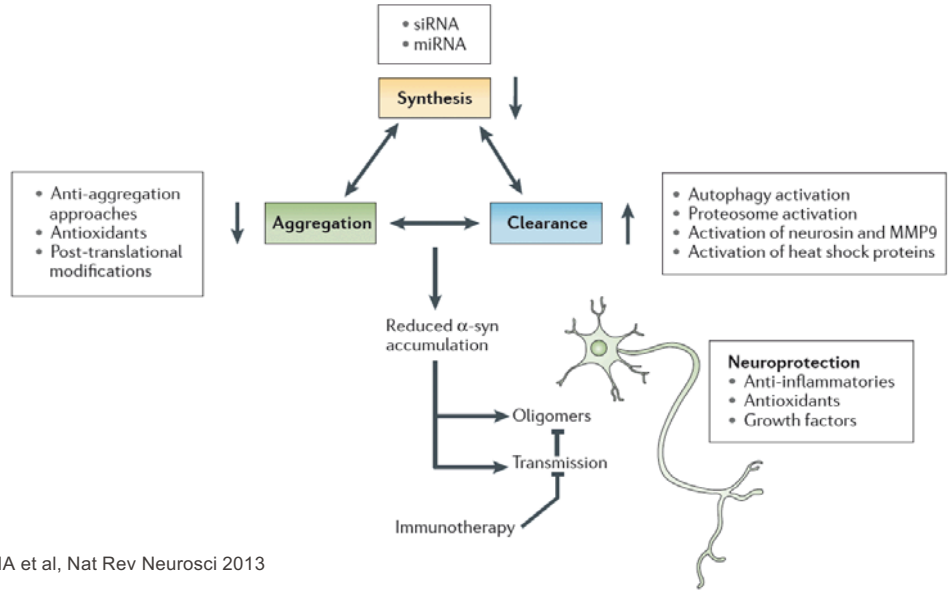
The presence of Lewy bodies (LB) is considered as a pathological signature of Parkinson's disease. Rank the following statements from "correct" to "possible" to "wrong" ?

A. Neurons containing Lewy bodies are usually in the process of dying.
B. The presence of Lewy bodies is an indicator of α-synuclein misfolding.
C. The presence of Lewy bodies is a sign of brain aging and not necessarily of the disease.
D. α-Synuclein accumulation in Lewy bodies is a protective mechanism in neurons.
E. Therapeutic strategies that protect neurons in model systems and enhance the formation of Lewy bodies are unlikely to succeed.



Genetic factors: α-synuclein (SNCA)

Alpha-synuclein – therapeutic approaches



- Lashuel HA et al, Nat Rev Neurosci 2013