European Reference Network
for rare or low prevalence complex diseases

Network Neurological Diseases (ERN-RND)

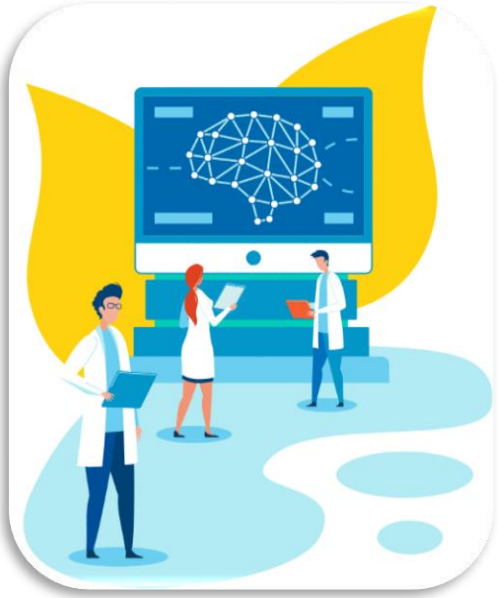
ean european academy of neurology

European Reference Network
for rare or low prevalence complex diseases

Network Neuromuscular Diseases (ERN EURO-NMD)

14.09.2021

Joint webinar series



‘Genetic forms of Parkinson’s diseases’

by Thomas Gasser

University Hospital Tübingen, Germany

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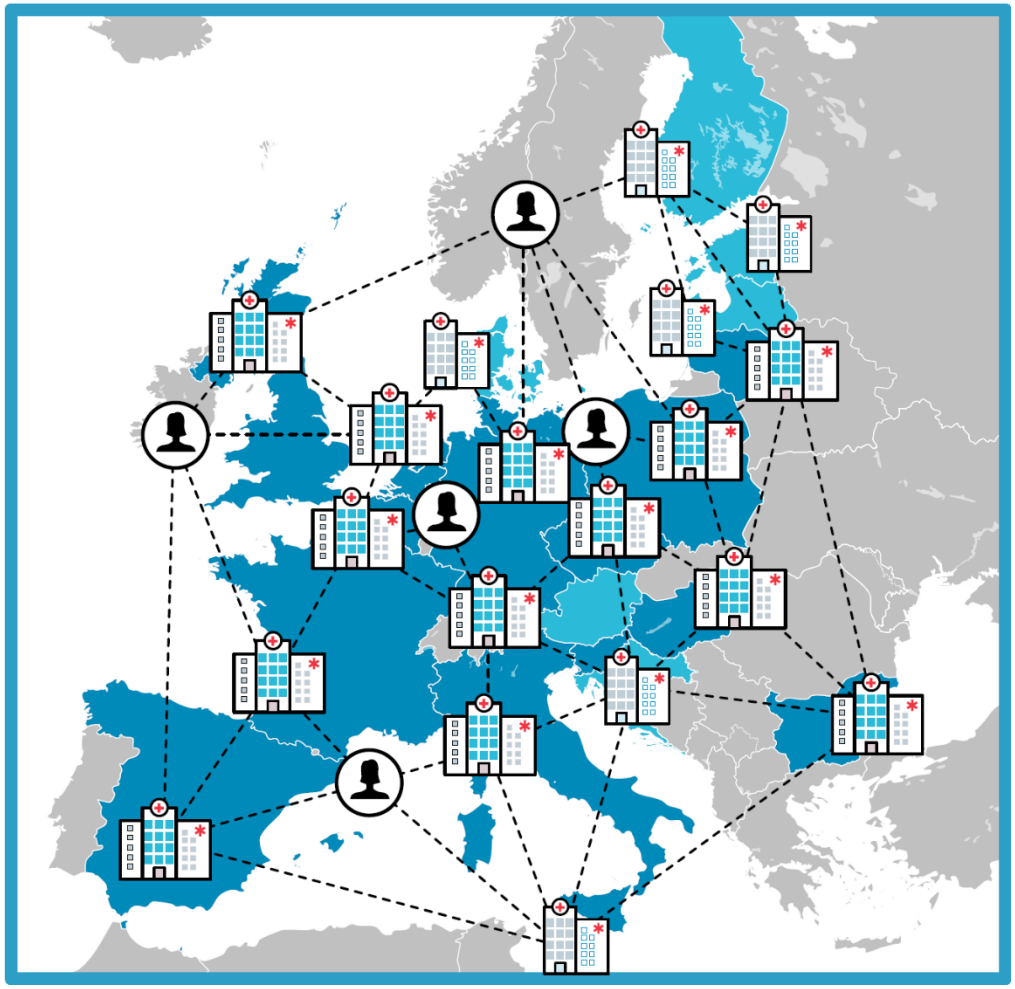
European Reference Network for RARE Neurological Diseases (ERN-RND)

- **Countries with Full Members**
- **Countries with Affiliated Partners**



ERN-RND covers 6 disease groups:

1. Ataxia and HSP
2. Leukodystrophies
3. Dystonias /NBIA/Paroxysmal disorders
4. Chorea and HD
5. FTD
6. Atypical/genetic Parkinsonism

General information about the webinars

- Focus on : RARE neurological, neuromuscular and movement disorders, neurorehabilitation, advanced therapies and DBS
- Alternating adult and paediatric topics
- 40-45min presentation
- 15min Q&A session at the end (please write your questions in the Q&A)
- Post-webinar survey (2-3min): satisfaction, topic/speaker ideas for next webinars

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Speaker: Thomas Gasser

- **Training: MD: Freiburg/Germany and Yale University, USA**
- **Current positions:** **Director, Department of Neurodegenerative diseases, University of Tübingen**
  Group leader: Parkinson‘s Genetics
  German Center of Neurodegenerative diseases, DZNE
- **Other key activities**: Dean of Research, Medical Faculty, University of Tübingen
- **Research focus:** **Genetics of Parkinson‘s disease and other Movement and Neurodegenerative Disorders**

Webinar outline

- Basics of Genetics of Complex Neurologic Diseases
- Genetic architecture of Parkinson's disease (PD)
- Monogenic forms of PD
- Genetic risk factors in sporadic PD
- Genetic testing in PD
- Emerging mutation-directed therapies in PD

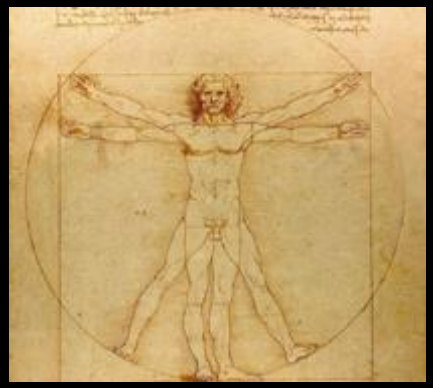
Learning objectives

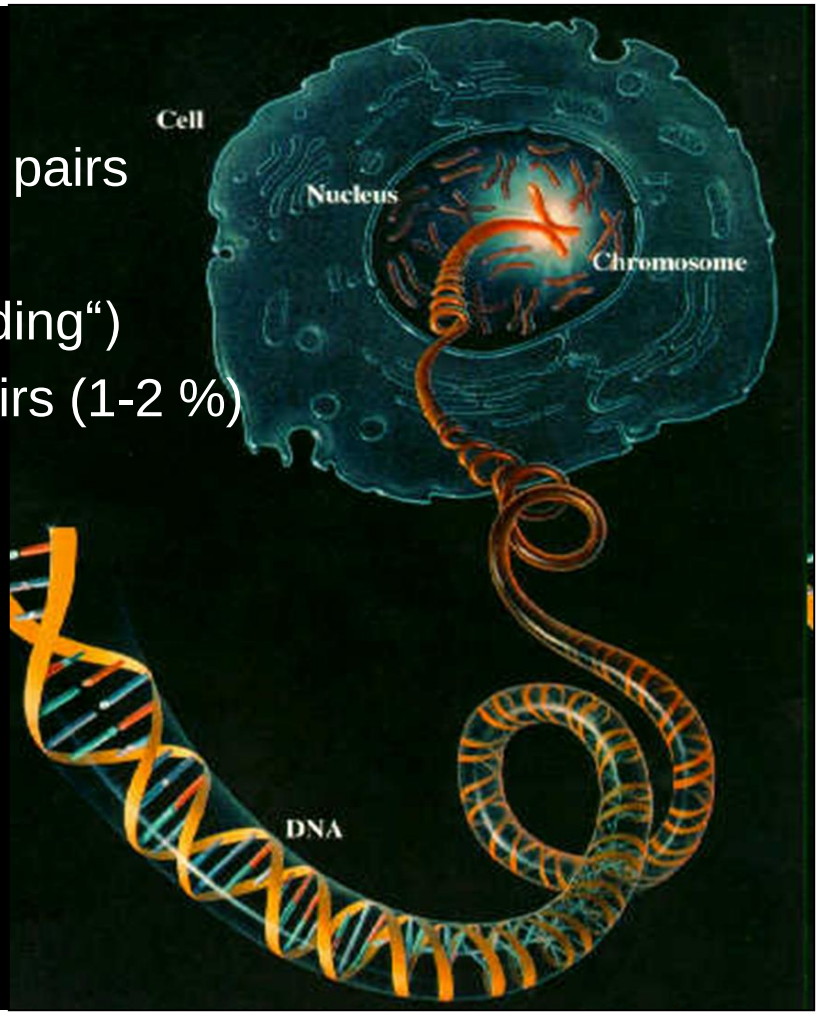
By the end of this webinar you will be able to:

- recognize patients with a high probability for a genetic form of PD and their specific features
- describe major pathogenic pathways identified in genetic forms of PD
- explain the concept of polygenic risk scores in sporadic PD
- discuss present state of targeted therapeutic trials in PD

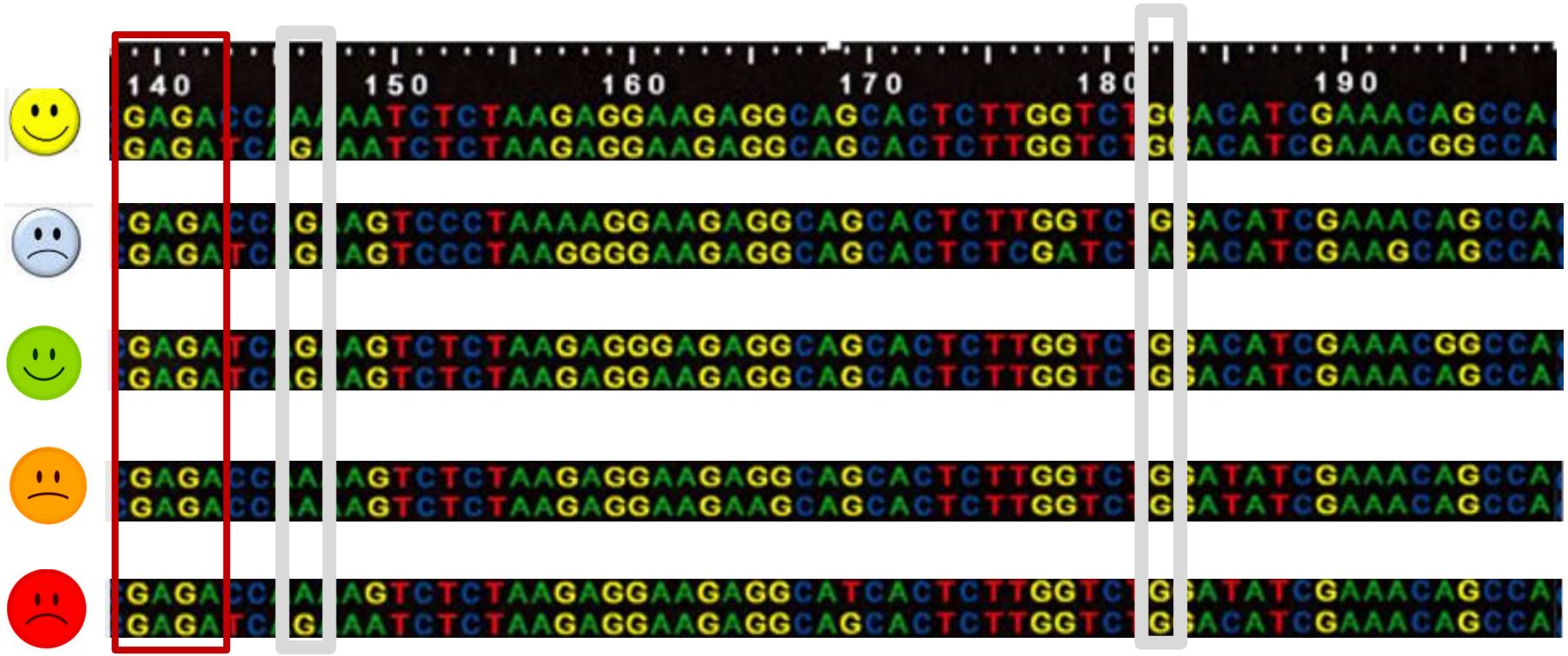
The Human Genome

- Genome: ~ 3.000.000.000 base pairs
- Genes: ~ 22.000
- Exome: ~ 180.000 exons („coding“)
- ~ 50.000.000 base pairs (1-2 %)





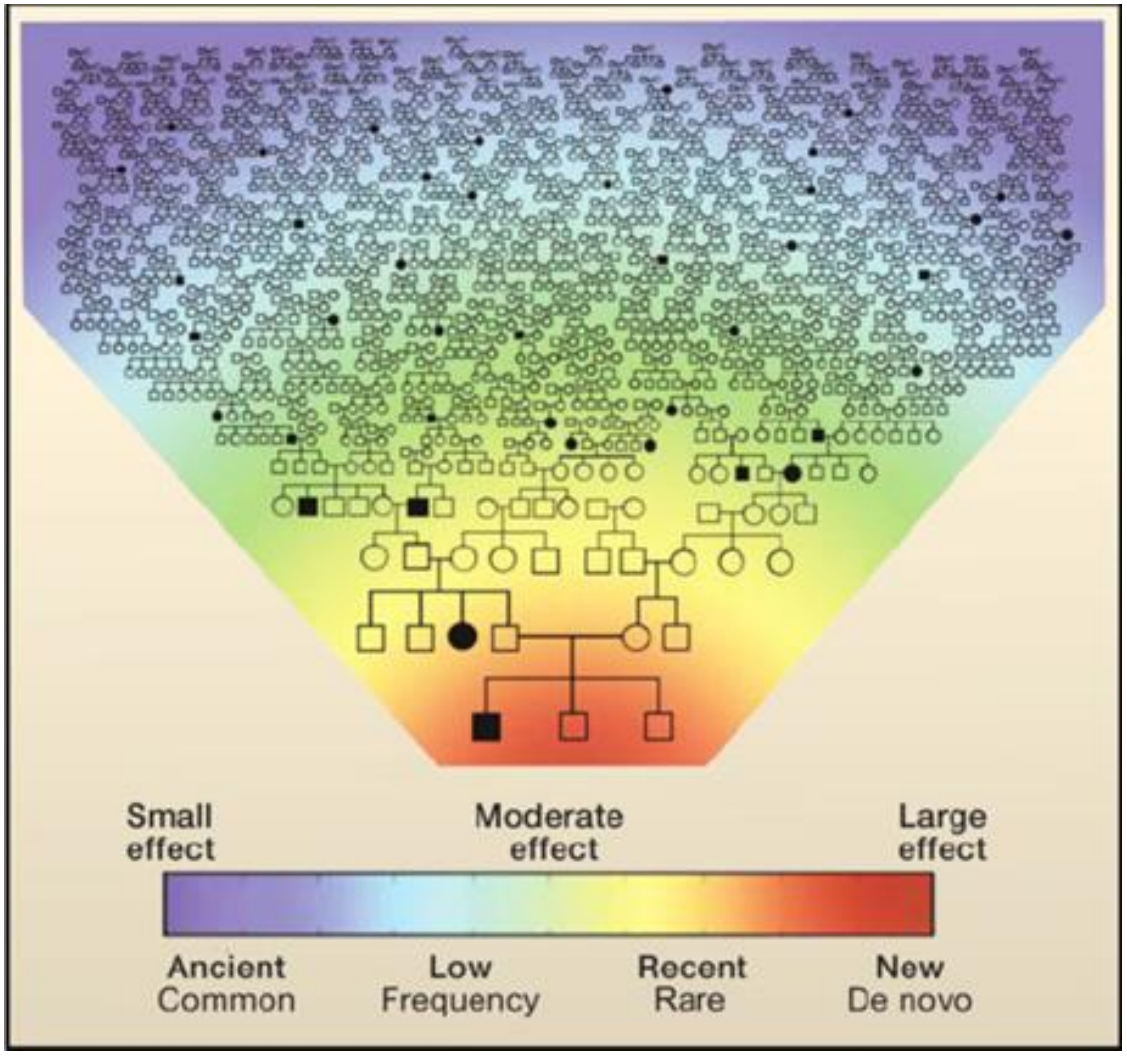
Human genomes differ



On average 1 of 500 to 1000 bases differ

A genome carries about 3 millionen varianten

Evolutionary age, frequency, effect strength



Lupski et al., Cell. 2011;147(1):32-43

Genetic architecture of complex diseases

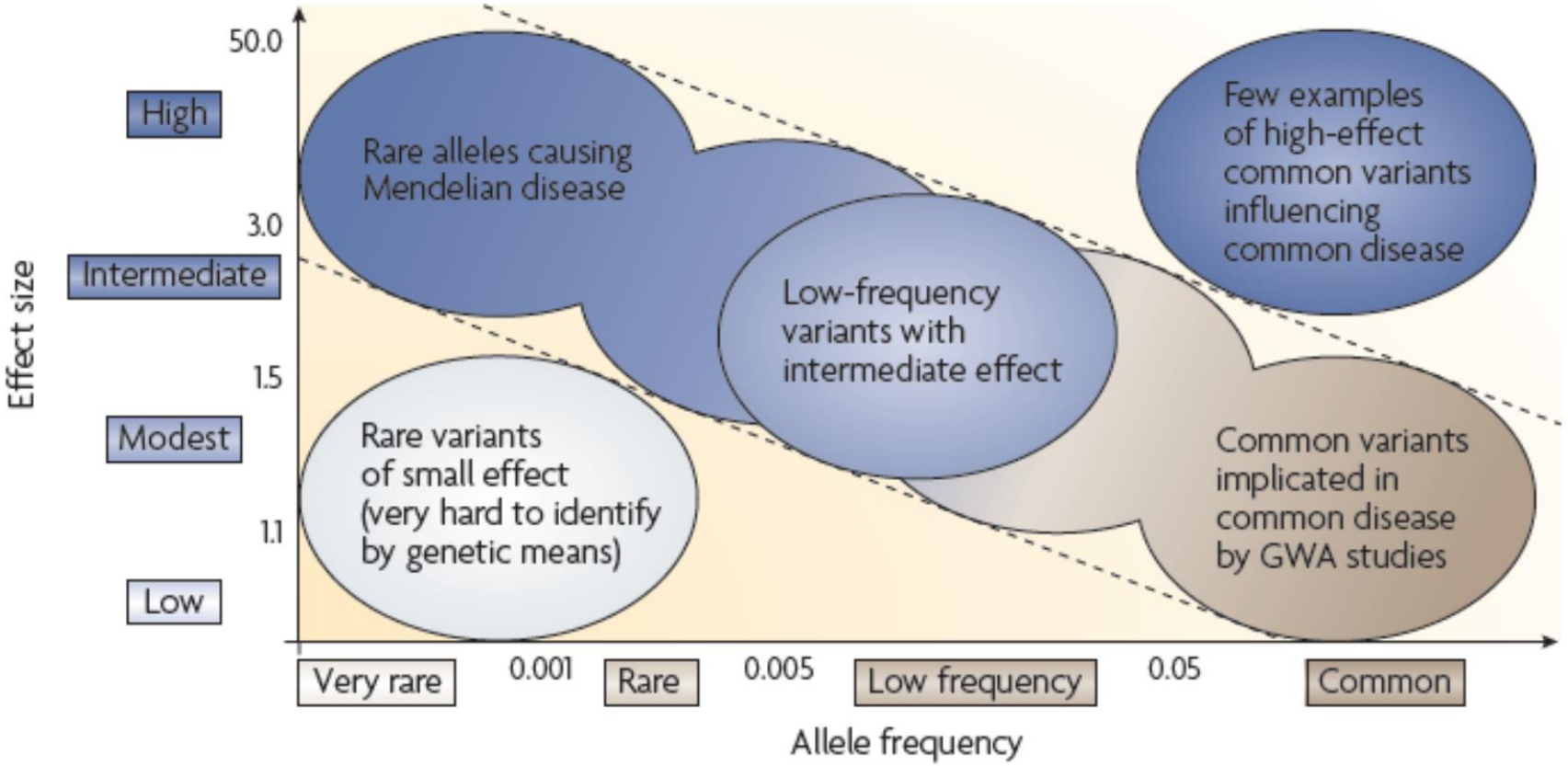


Figure 1 | **Feasibility of identifying genetic variants by risk-allele frequency and strength of genetic effect (odds ratio).** Reproduced, with permission, from *Nature* REF. 10 © (2009) Macmillan Publishers Ltd. All rights reserved. GWA, genome-wide association.

Genetic architecture of Parkinson‘s disease

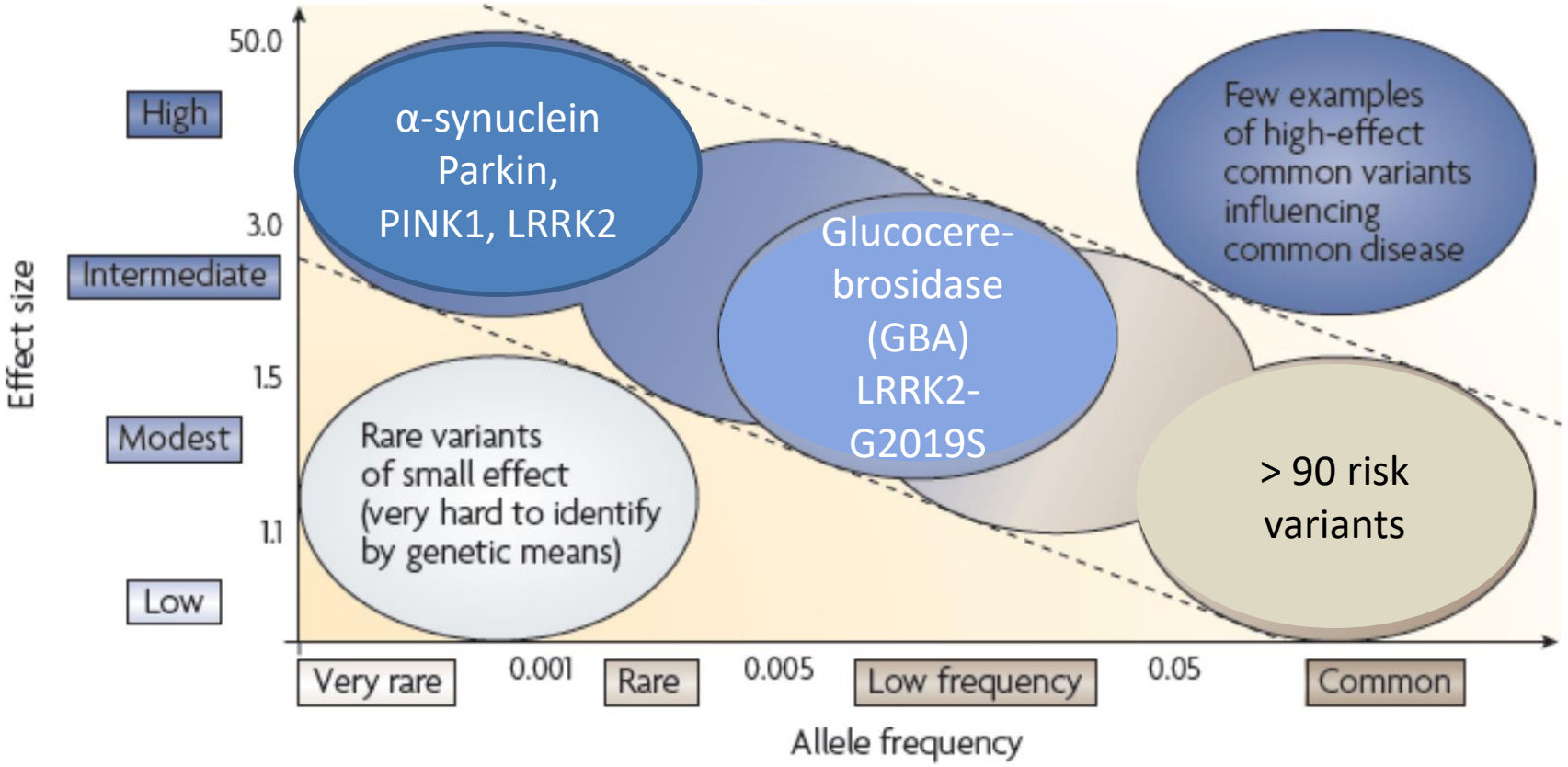
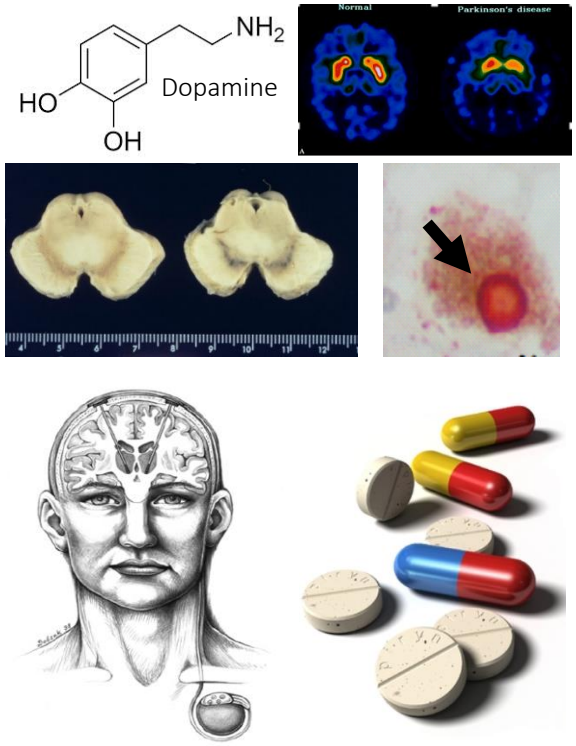
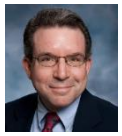


Figure 1 | **Feasibility of identifying genetic variants by risk-allele frequency and strength of genetic effect (odds ratio).** Reproduced, with permission, from *Nature* REF. 10 © (2009) Macmillan Publishers Ltd. All rights reserved. GWA, genome-wide association.

Parkinson‘s disease: the basics



The beginning of PD genetics: 1997



Larry Golbe, …,Roger Duvoisin:
A large kindred with autosomal dominant Parkinson's disease
(Ann Neurol 1990)

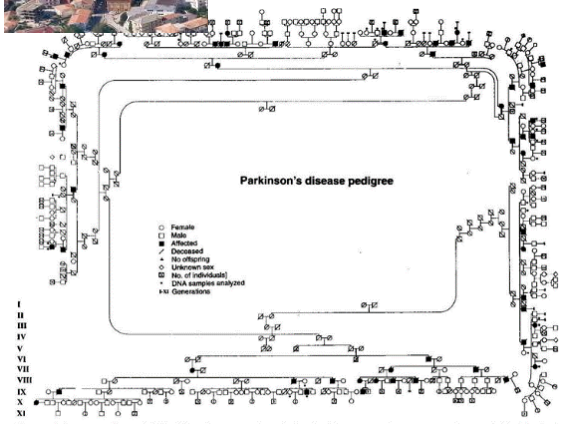
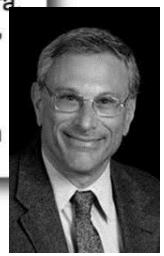


Fig. 1. A large family with PD. The clinical and pathological features of some members of this kindred were previously reported (*11*).

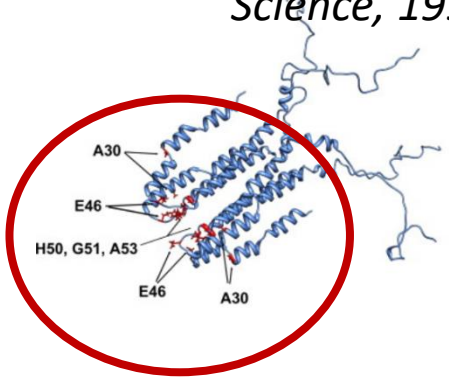
- Parkinsonism
- Onset ~ 44 years
- Rapid progression
- Dementia common

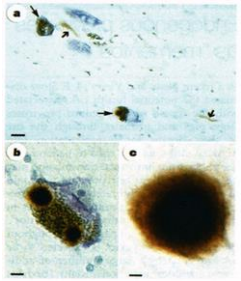
Mutation in the α-Synuclein Gene Identified in Families with Parkinson's Disease

Mihael H. Polymeropoulos,* Christian Lavedan†, Elisabeth Leroy†, Susan E. Ide, Anindya Dehejia, Amalia Dutra, Brian Pike, Holly Root, Jeffrey Rubenstein, Rebecca Boyer, Edward S. Stenroos, Settara Chandrasekharappa, Aglaia Athanassiadou, Theodore Papapetropoulos, William G. Johnson, Alice M. Lazzarini, Roger C. Duvoisin, Giuseppe Di Iorio, Lawrence I. Golbe, Robert L. Nussbaum



Science, 1997





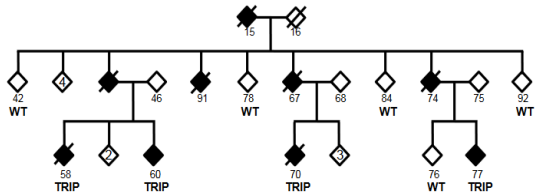
998

α-Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with Lewy bodies

(ubiquitin/sarkosyl-insoluble filaments/immunoelectron microscopy)

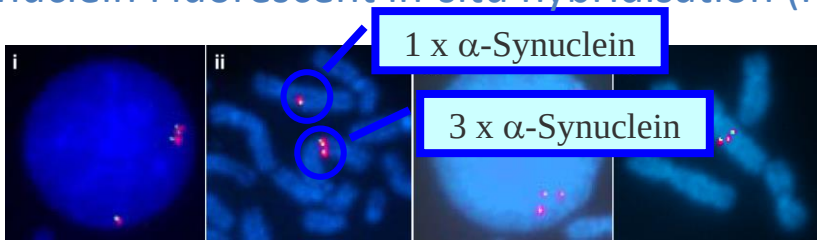
MARIA GRAZIA SPILLANTINI*, R. ANTHONY CROWTHER†, ROSS JAKES†, MASATO HASEGAWA†, AND MICHEL GOEDERT†‡

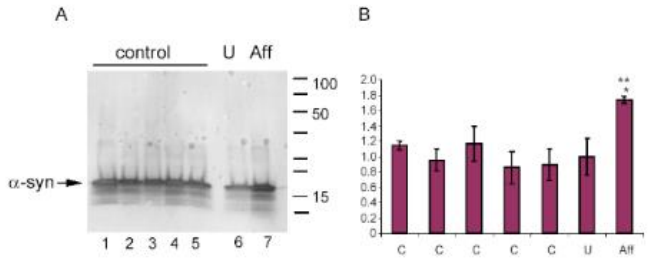
Gene dosage effect



„Iowa-kindred“

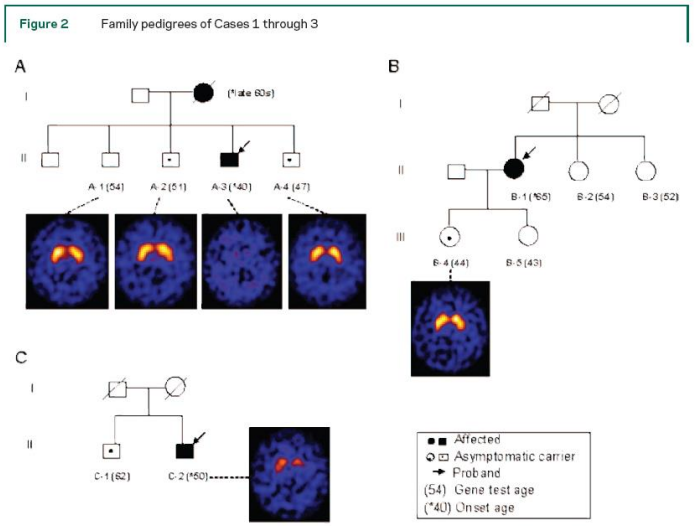
α-synuclein Fluorescent in-situ hybridisation (FISH)





Singleton et al., Science, 2004

α-Synuclein gene duplication is present in sporadic Parkinson disease



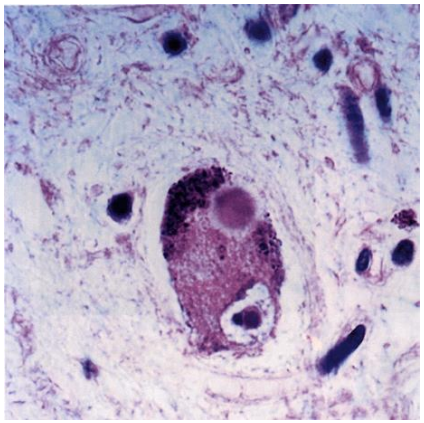
(A) Family pedigree of Case 1 (A-3). Genetic testing was not done in the affected mother. Of the five brothers, four were tested for the mutation, and three brothers (A-2, A-3, A-4) had the duplication. [123I]N-ω-Fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)-tropane ([123I]FP-CIT) SPECT shows virtually no uptake of [123I]FP-CIT in Case 1. The mutation negative brother and asymptomatic mutation carriers show normal [123I]FP-CIT uptake. (B) Family pedigree of Case 2 (B-1). The 44-year-old daughter (B-4) of the proband is an asymptomatic carrier and shows normal [123I]FP-CIT uptake. (C) Family pedigree of Case 3 (C-2). His brother is an asymptomatic carrier. [123I]FP-CIT SPECT of the proband shows decreased [123I]FP-CIT uptake, which is asymmetrical and more marked in the putamen.

Ahn et al., 2008

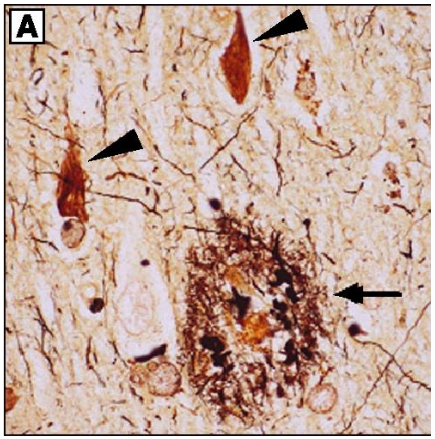
α-Synuclein point mutations or multiplications in << 1% of PD patients

Point mutations and gene dosage

α-SYN point mutations	α-SYN overexpression	APP point mutations	APP overexpression



Parkinson‘s disease



Alzheimer‘s disease

α-Synuclein point mutations or multiplications in << 1% of PD patients

Monogenic forms of Parkinson‘s disease

1997 → 2017

„pure PD“

„Complicated“ PD

	Inheritance	locus	onset	Lewy Bodies	gene
PARK1	Dominant	4q21			α-Synuclein
PARK2	Recessive	6q25			Parkin
PARK3	Dominant	2p13	~ 60	+	SPR ?
PARK4	Dominant	4q21			α-Synuclein
PARK5	Dominant	4p15			Ubiquitin hydrolase L1 ?
PARK6	Recessive	1p35	~ 30	+	PINK1
PARK7	Recessive	1p36	~ 30		DJ-1
PARK8	Dominant	12q			LRRK2
PARK9	Recessive	1q36			ATP13A2
PARK10	Dominant	1p32	late	?	?
PARK11	Dominant	2q36	late	?	GIGYF2 ?
PARK12	x-linked	Xq25	late	?	?
PARK13	Dominant	2p13	late	?	OMI/HtrA2
PARK14	recessive	22q13.1	early	+	PLA2G6
PARK15	recessive	22q12	early	?	FBXO7
PARK16	risk gene	1q36	late	?	?
PARK 17	dominant	16q11	late	?	VPS35
PARK 18	dominant	3q27			EIF4G
No PARK #	risk gene	1p31			GBA

Protein aggregation

Mitochondrial quality control

Vesicle sorting and transport

Lysosomal function

Dominant („gain of function“)

Recessive („loss of function“)

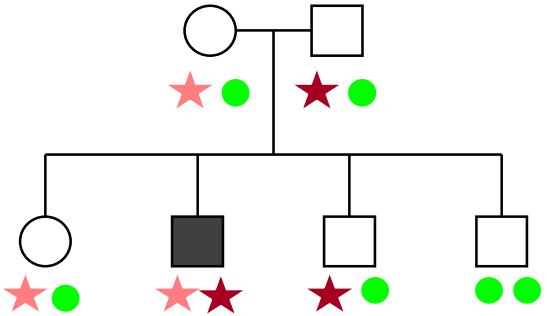
…PARK23 ….

Young-onset (juvenile) Parkinson‘s disease

Compound heterozygous Parkin mutations

Age 38
Onset at 31 years
Levodopa-responsive PD
Dyskinesias
MOCA 29

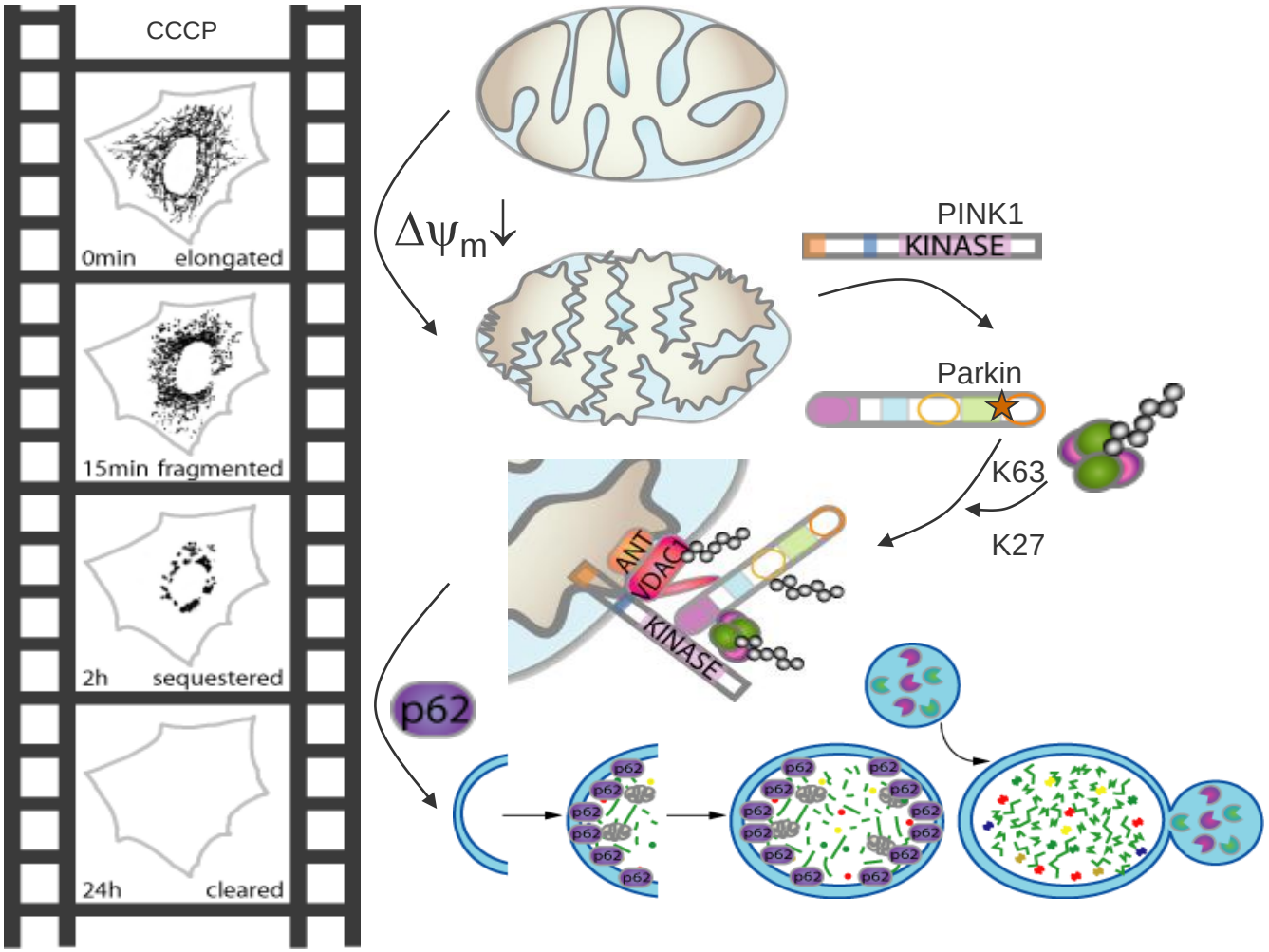
No family history



Autosomal-recessive Parkinson‘s disease

Parkin	➢ > 100 mutations ➢ 75% if onset < 20 ➢ 25% if onset < 30 ➢ 5 – 10% if onset < 40	Mostly NO aSYN pathology
PINK1	➢ > 20 mutations ➢ 1 – 2 % in early-onset PS	1 report of widespread aSYN pathology
DJ-1	➢ 4 mutations ➢ rare	aSYN pathology
ATP13A2	➢ rare ➢ complicated PS	No pathology reported
PLA2G6	➢ rare ➢ complicated PS	aSYN pathology Iron accumulation
FBXO7	➢ rare ➢ complicated PS	No pathology reported

Parkin / PINK1 function



PINK1 kinase

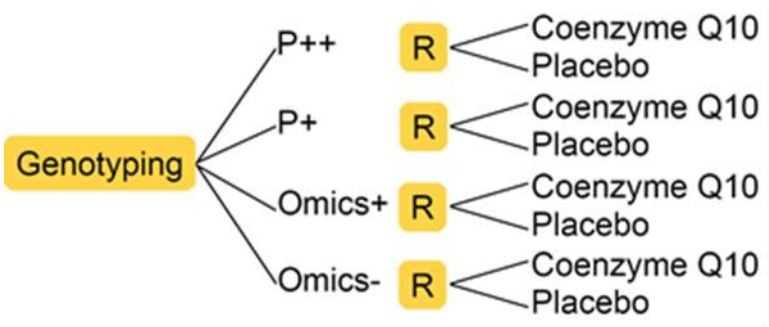
Parkin E3
ubiquitin ligase

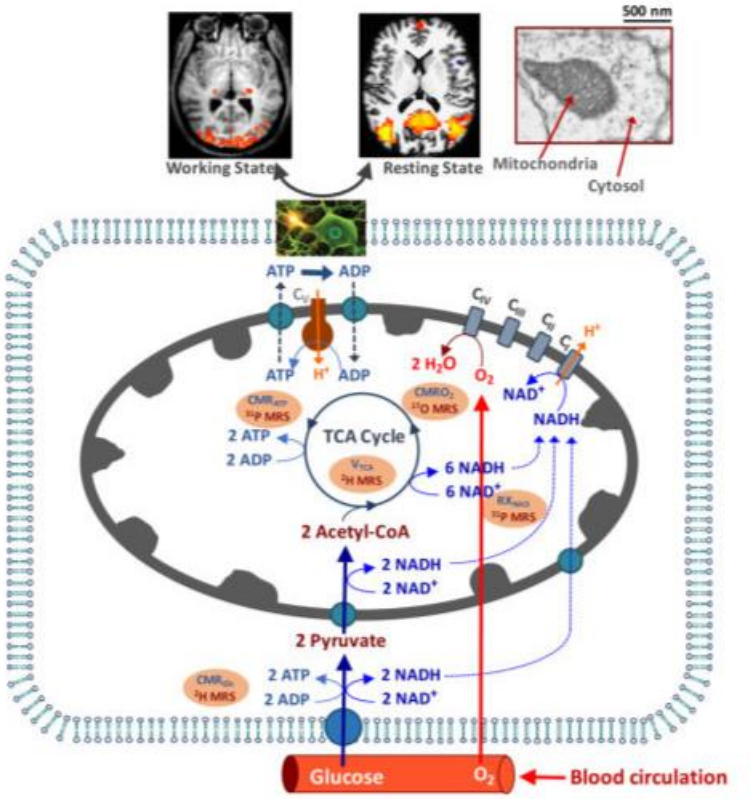
Parkin-K63 polyUb
VDAC1-K27 polyUb

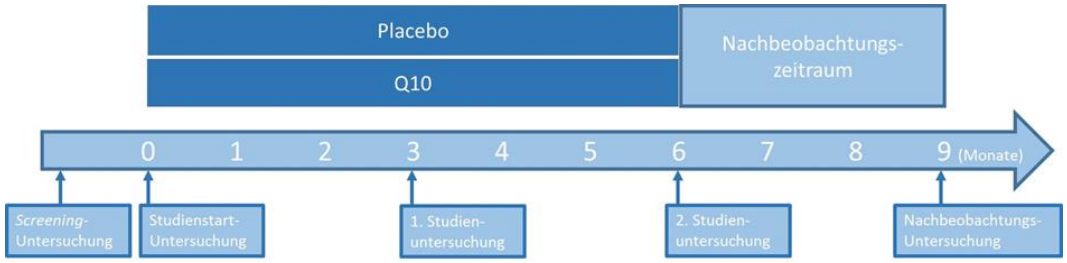
Aggresome markers

p62/SQSTM1
LC3

Clinical trial: Coenzyme Q10







Age 64
Onset at 55 years
Treated with
pramipexole 3.1 mg / d

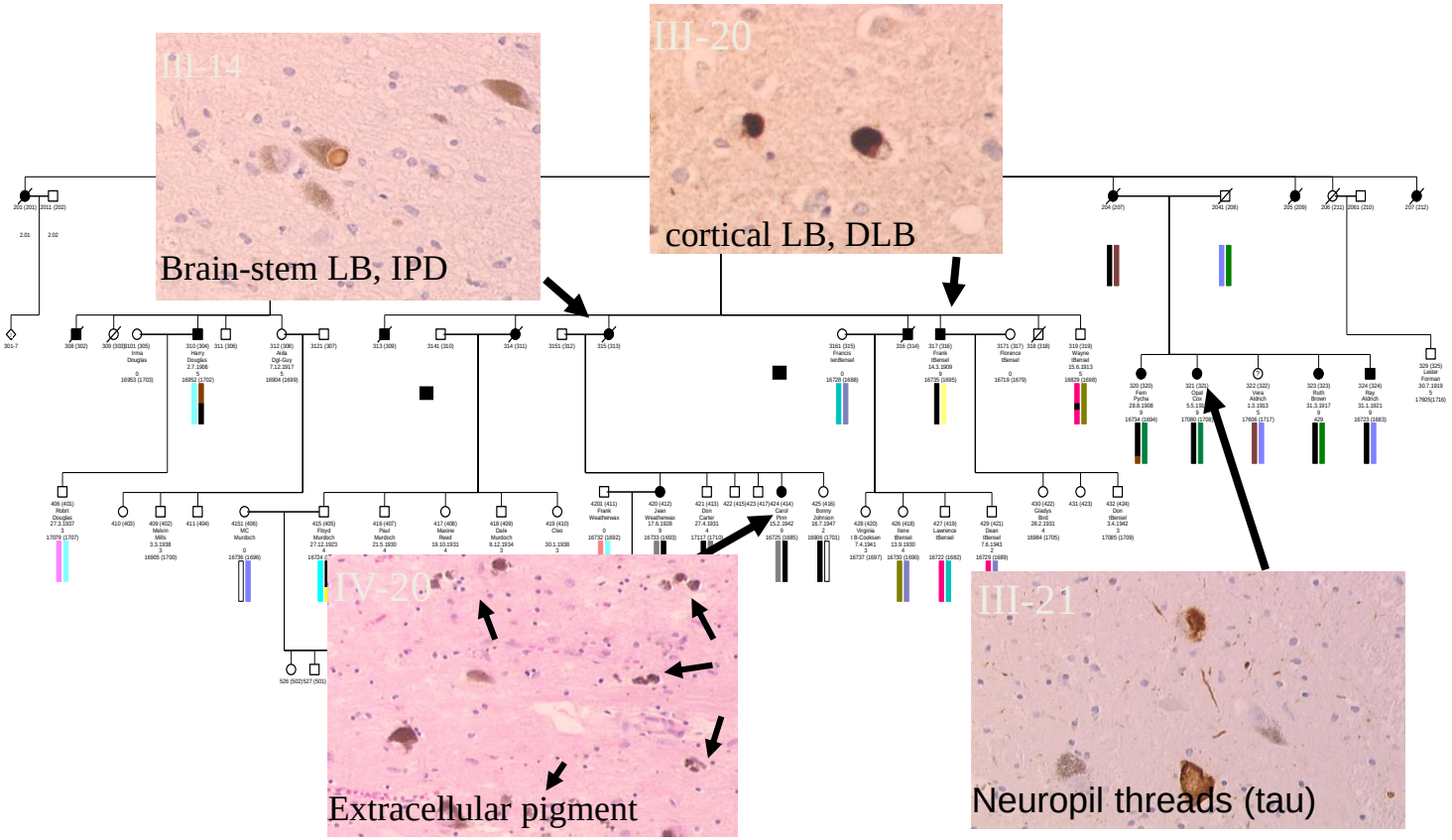
No dyskinesias

MOCA 29

No Family history of
PD

LRRK2 G2019S mutation

LRRK2: pleiomorphic pathology



Prevalence of LRRK2-G2019S in *sporadic* PD

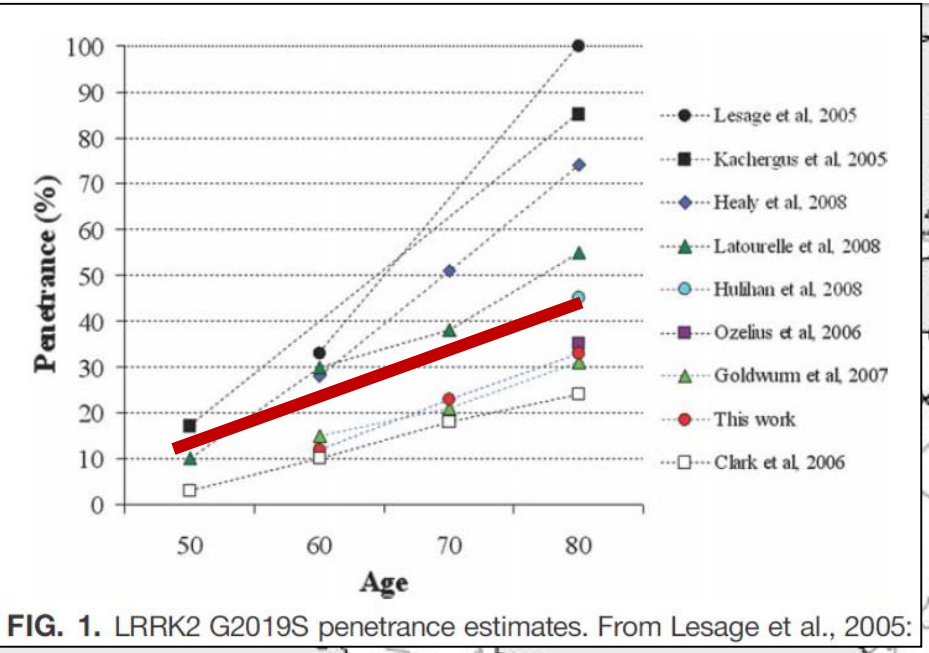
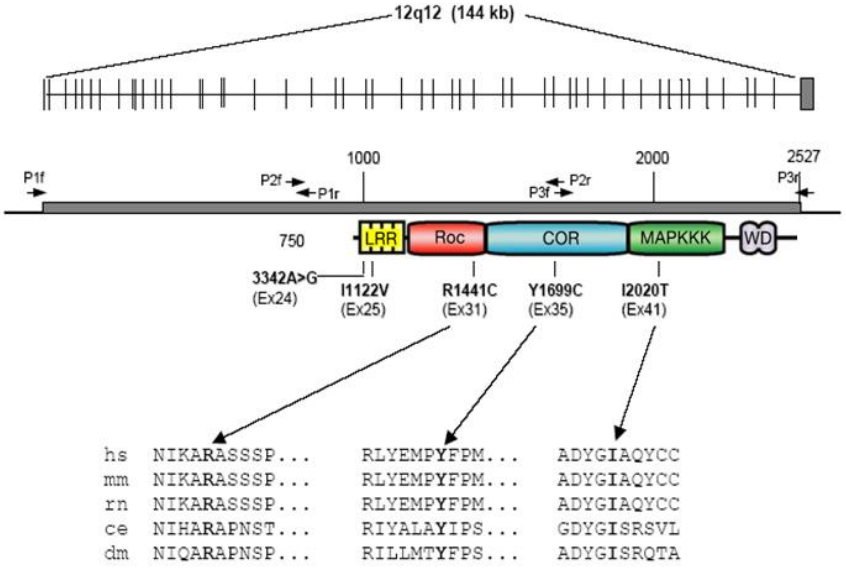
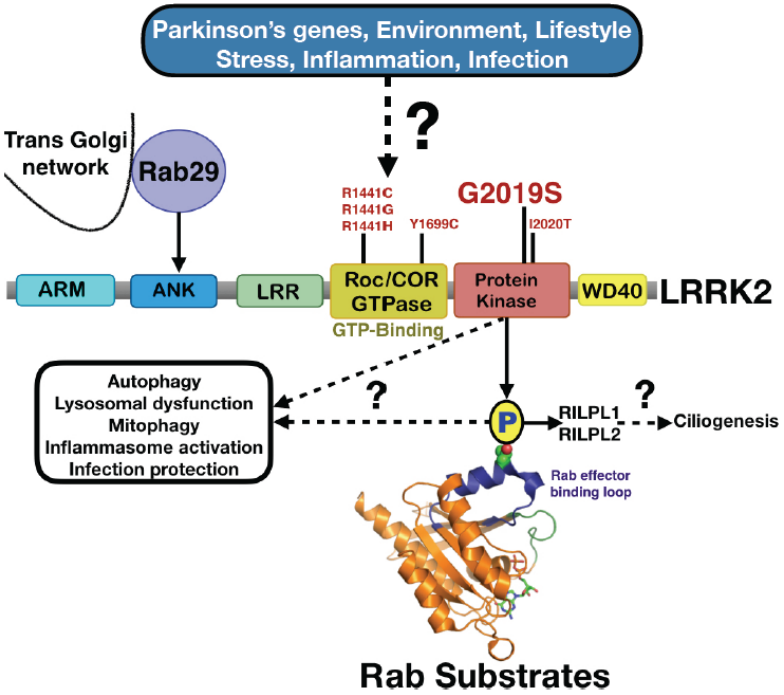


FIG. 1. LRRK2 G2019S penetrance estimates. From Lesage et al., 2005:

LRRK2 kinase function

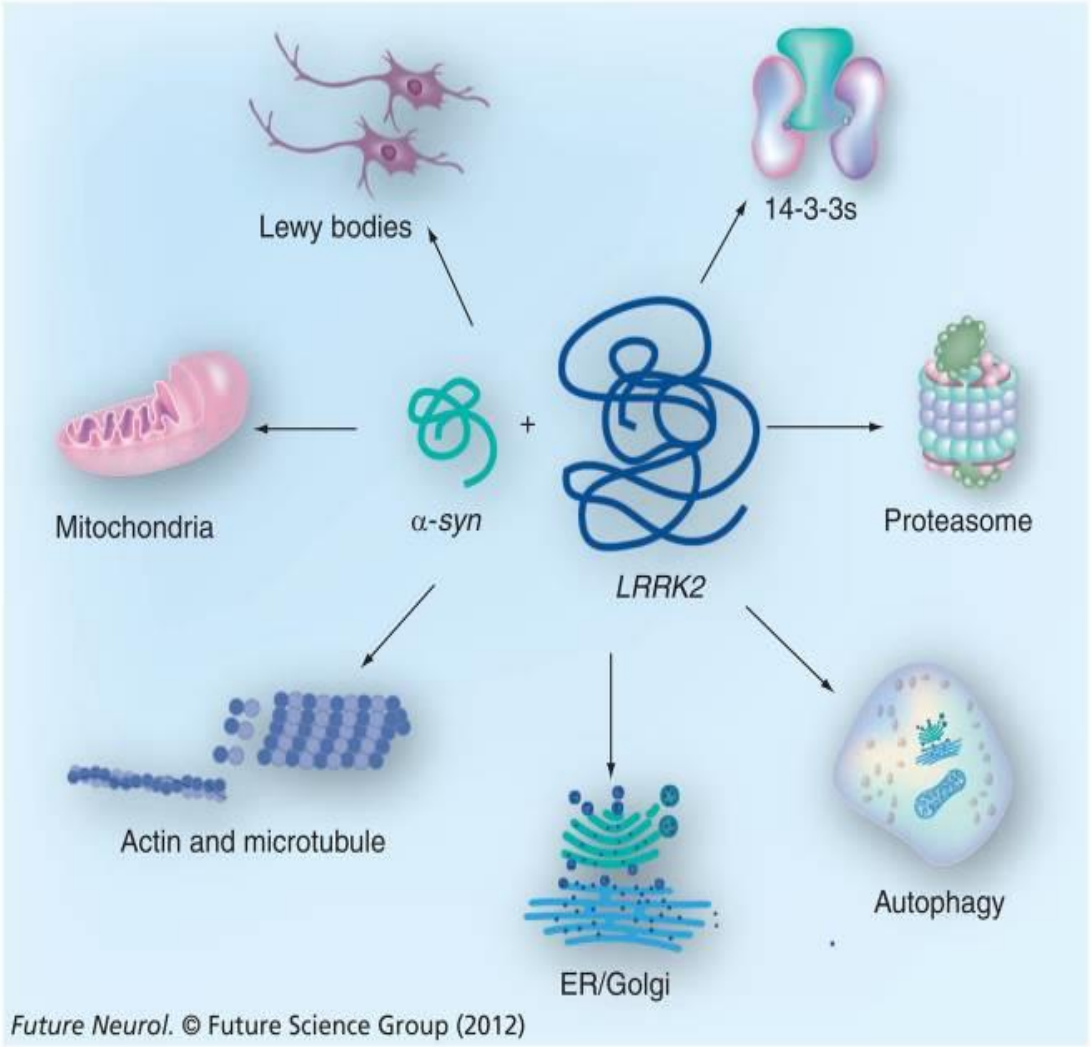




LRRK2: Leucine rich repeat Kinase 2

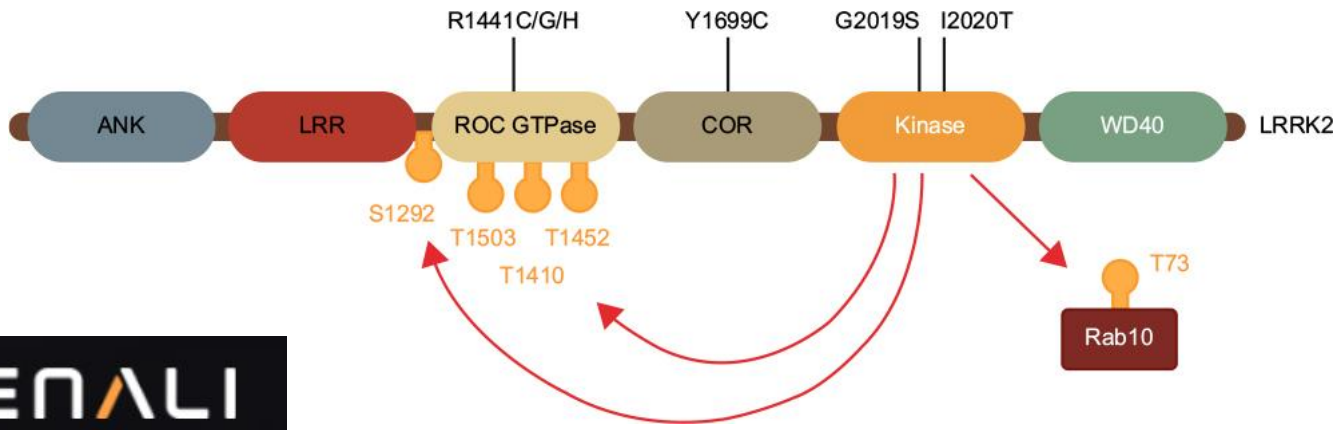
Alessi and Sammler, Science 2018

LRRK2 function



Institutional Logo,
‚Speakers' picture or
disease related picture

LRRK2 kinase inhibition



DENALI

Denali Therapeutics Announces Positive Clinical Results From LRRK2 Inhibitor Program for Parkinson's Disease

August 1, 2018

- *Healthy volunteer study of DNL201 meets all objectives in phase 1 clinical study, including CSF exposure levels and LRRK2 inhibition, as well as pathway engagement, at doses that were safe and well tolerated*
- *DNL201 will advance to Phase 1b in Parkinson's disease patients with and without a genetic LRRK2 mutation*

Age: 70 years
Aao: 60 years

Rapid progression

Cognitive impairment

Orthostatic dysfunction

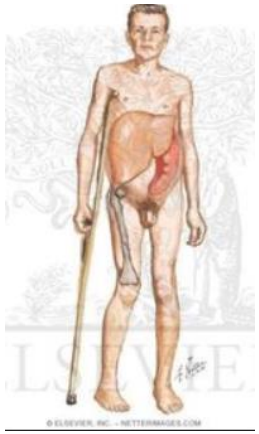
Brother PD

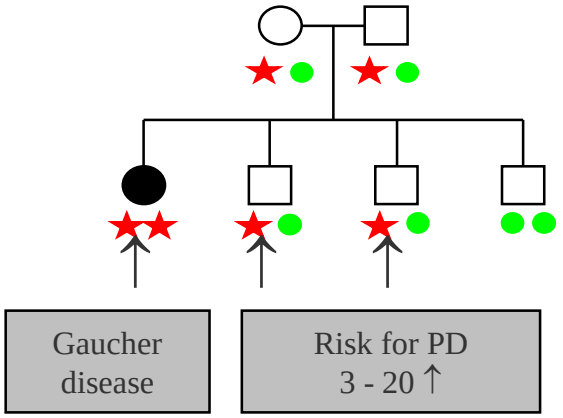
GBA L444P mutation

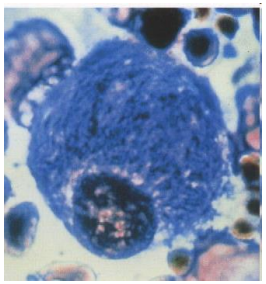
Gaucher disease and Parkinson

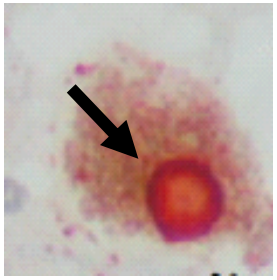
Gaucher disease

- Non-neuronopathic type I
  - Hepatosplenomegaly
  - Thrombocytopenia
- acute neuronopathic type II
  - Hepatosplenomegaly
  - Cognitive decline
- subacute neuronopathic type III
  - Myoclonus
  - Oculomotor disturbances
  - Dementia

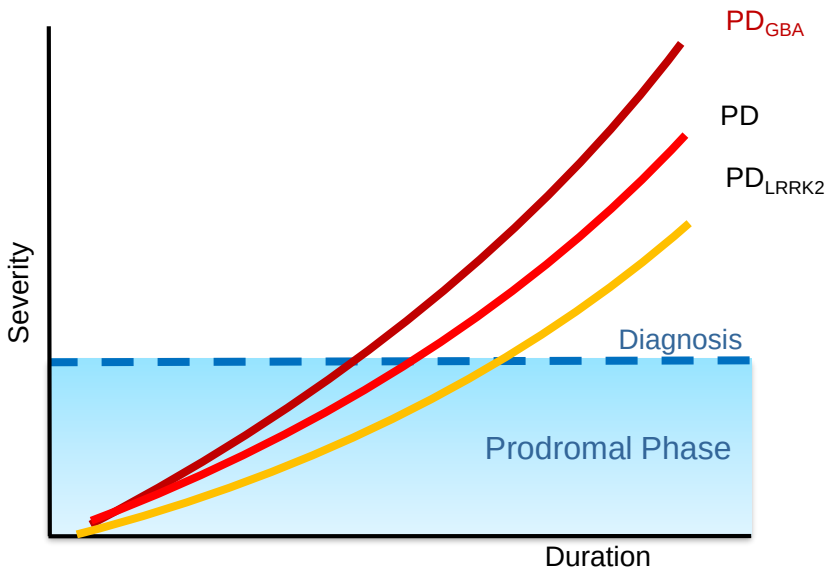








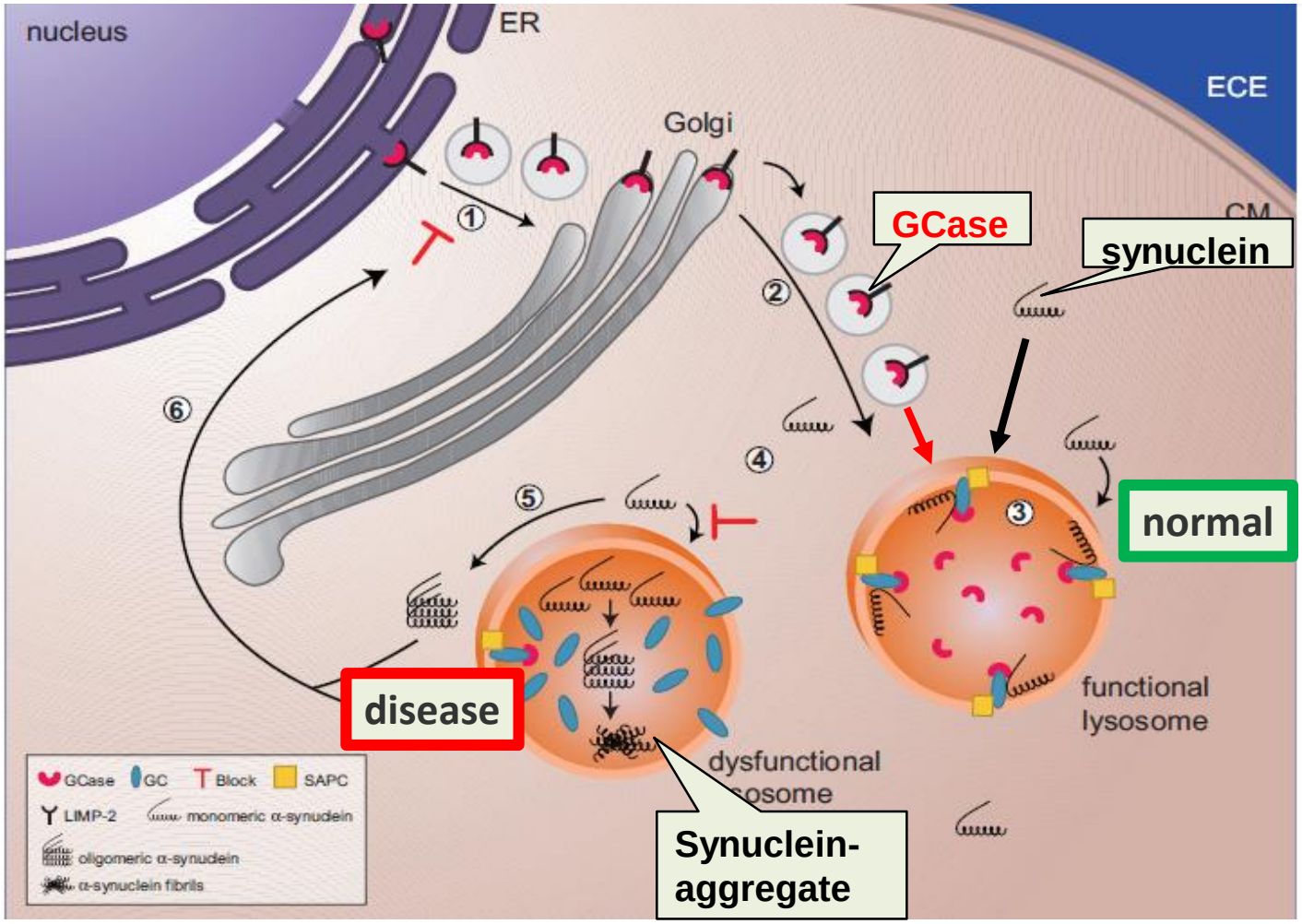
PD with mutations in GBA



- Earlier age of onset
- More rapid progression
- More „non-motor“ symptoms
  - Dementia
  - Autonomic symptoms

Brockmann et al., Neurology 2011
Brockmann et al., Movement Disord 2015

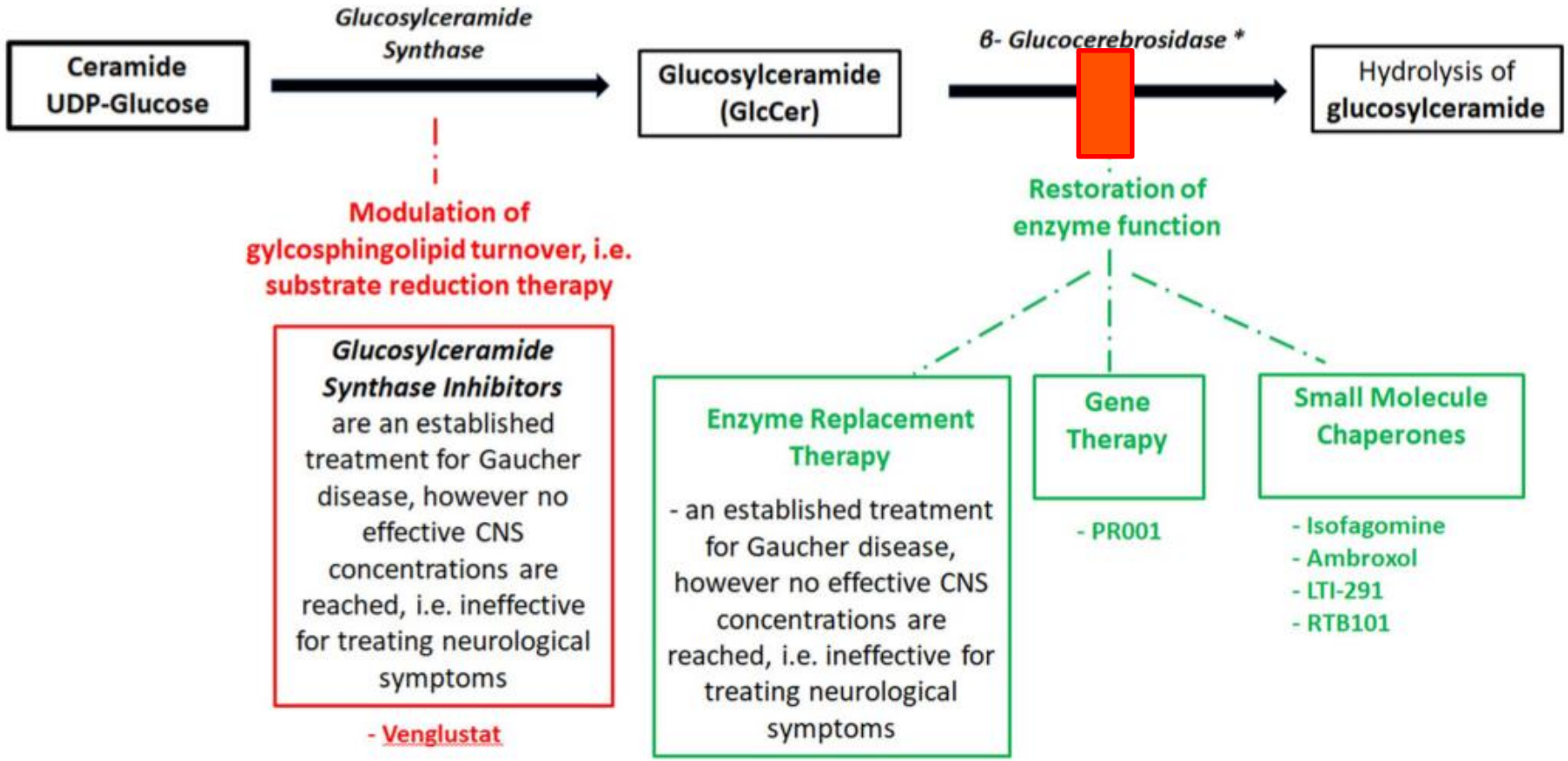
GBA function



Siebert et al., Brain 2014

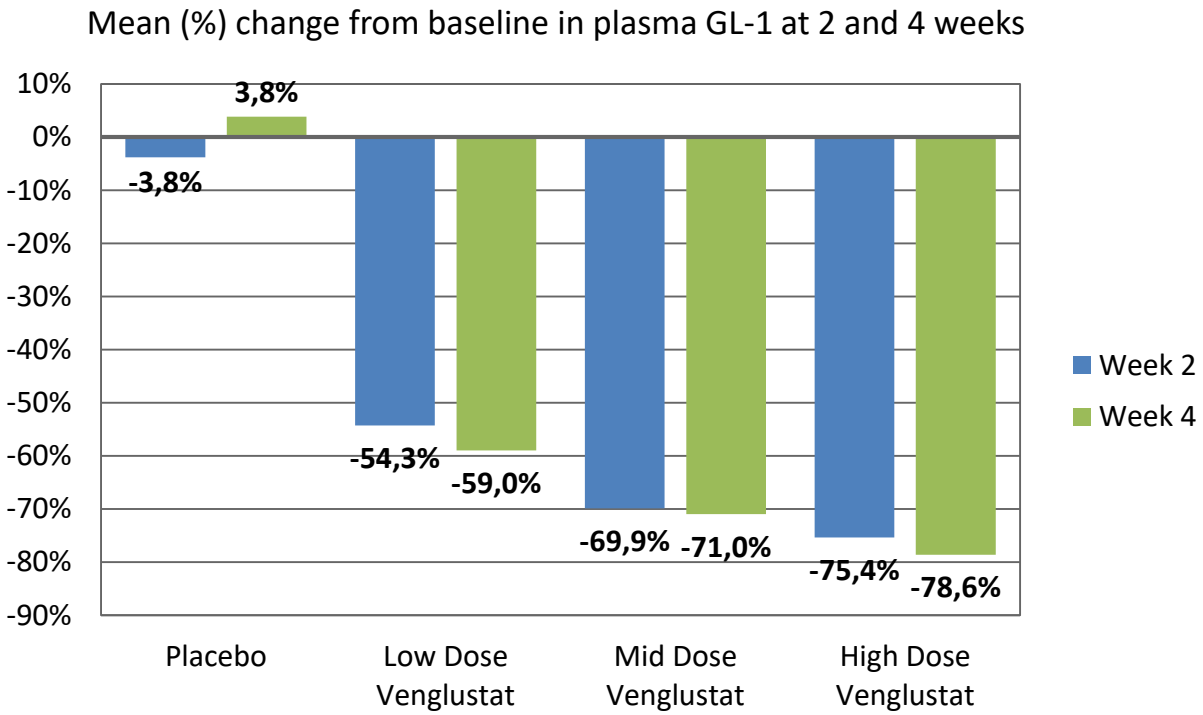
GBA-directed treatment

Journal of Neurology (2020) 267:860–869



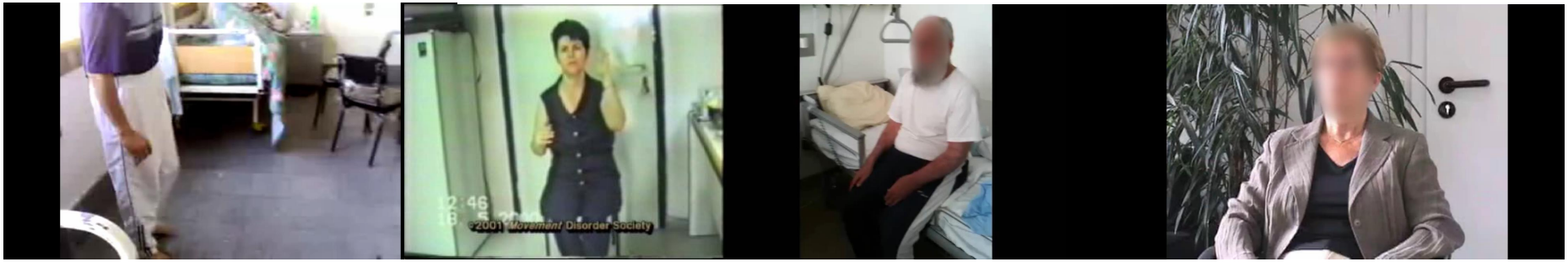
Schneider and Alcalay, 2020

Moves-PD (Sanofi)

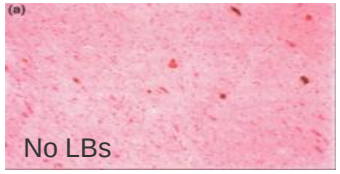


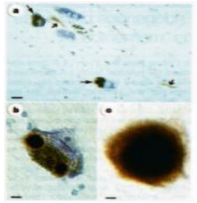
- **Substrate reduction achieved**
- **Primary endpoint (clinical improvement over placebo) not achieved**

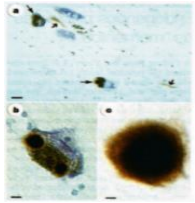
Parkinson‘s disease heterogeneity



Onset 24y | Onset 44y | Onset 59y | Onset 64y







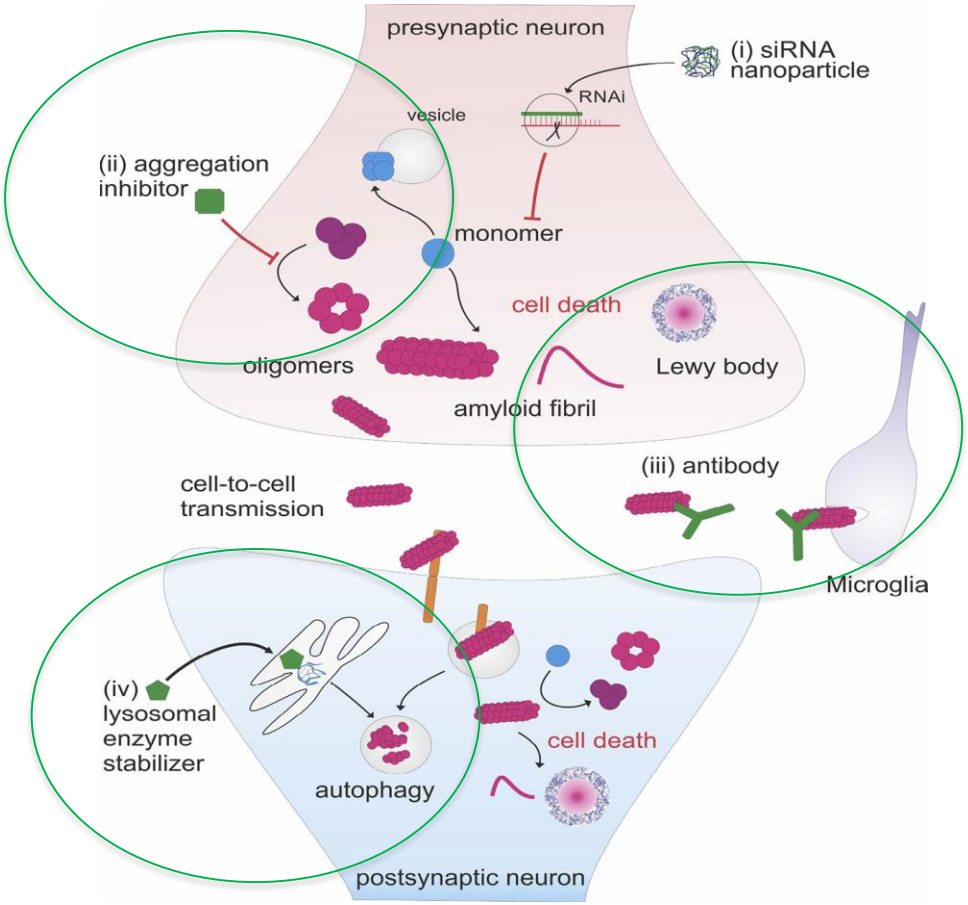
parkin
PARK2

SNCA
PARK1

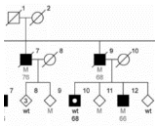
GBA

LRRK2
PARK8

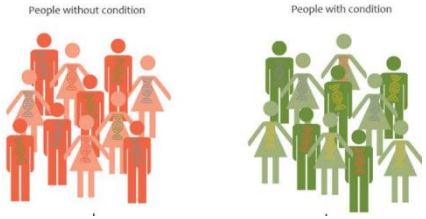
Targeted treatment in PD



sporadic Parkinson‘s disease

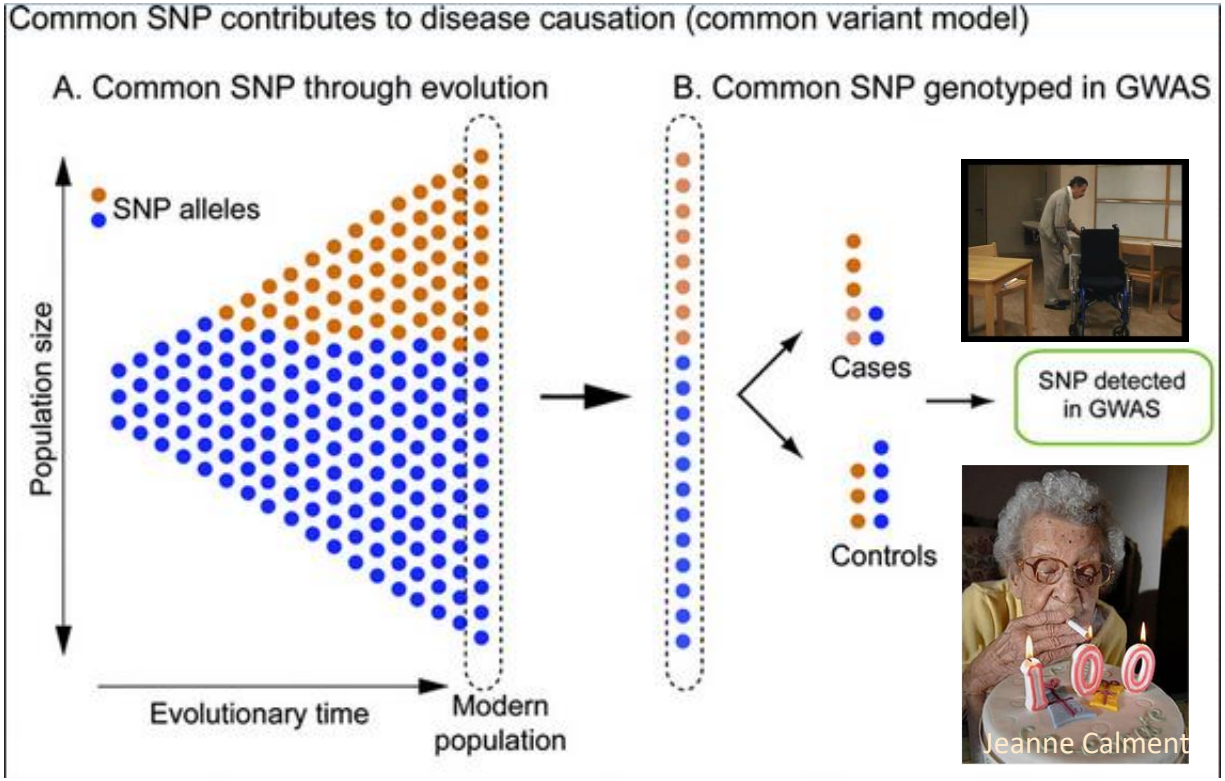


Family studies



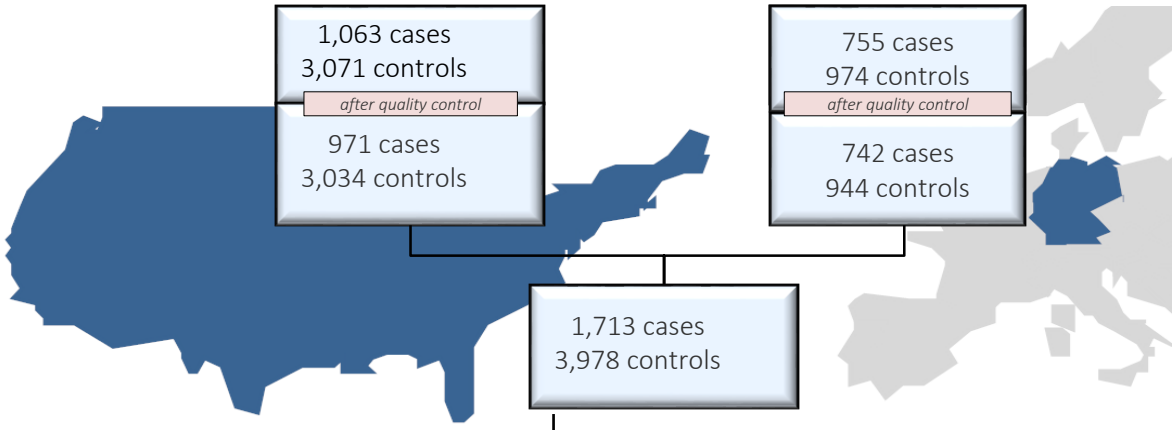
Genome-wide
association studies

Association studies



Institutional Logo,
‚Speakers' picture or disease related picture

Genome-wide association study



GWAS Stage 1

545,000 SNPs / sample

after quality control

463,187 SNPs / sample

GWAS Stage (Replication) 2

384 SNPs / sample

after quality control

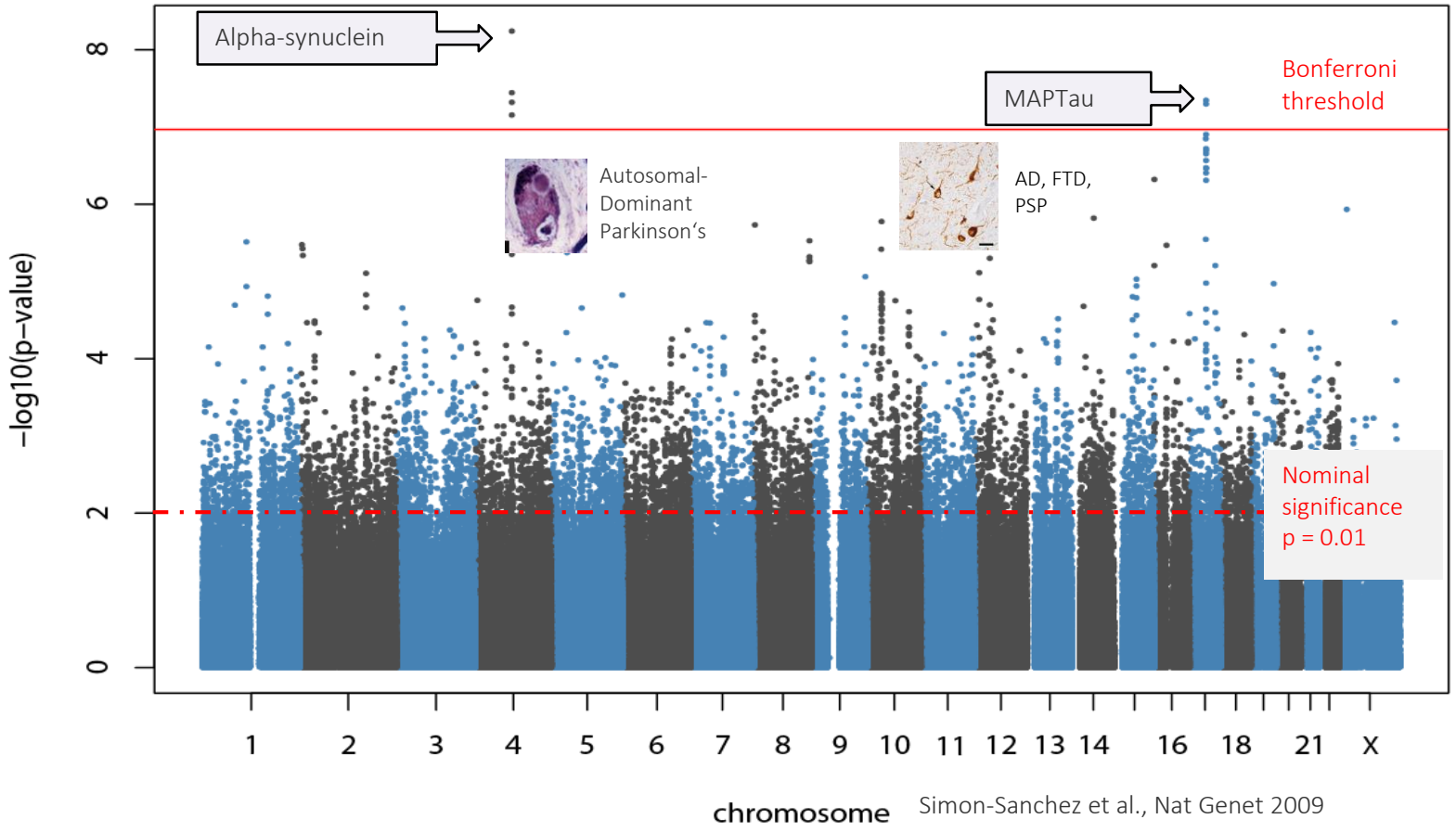
345 SNPs / sample

Total

5,226 cases & 8,210 controls

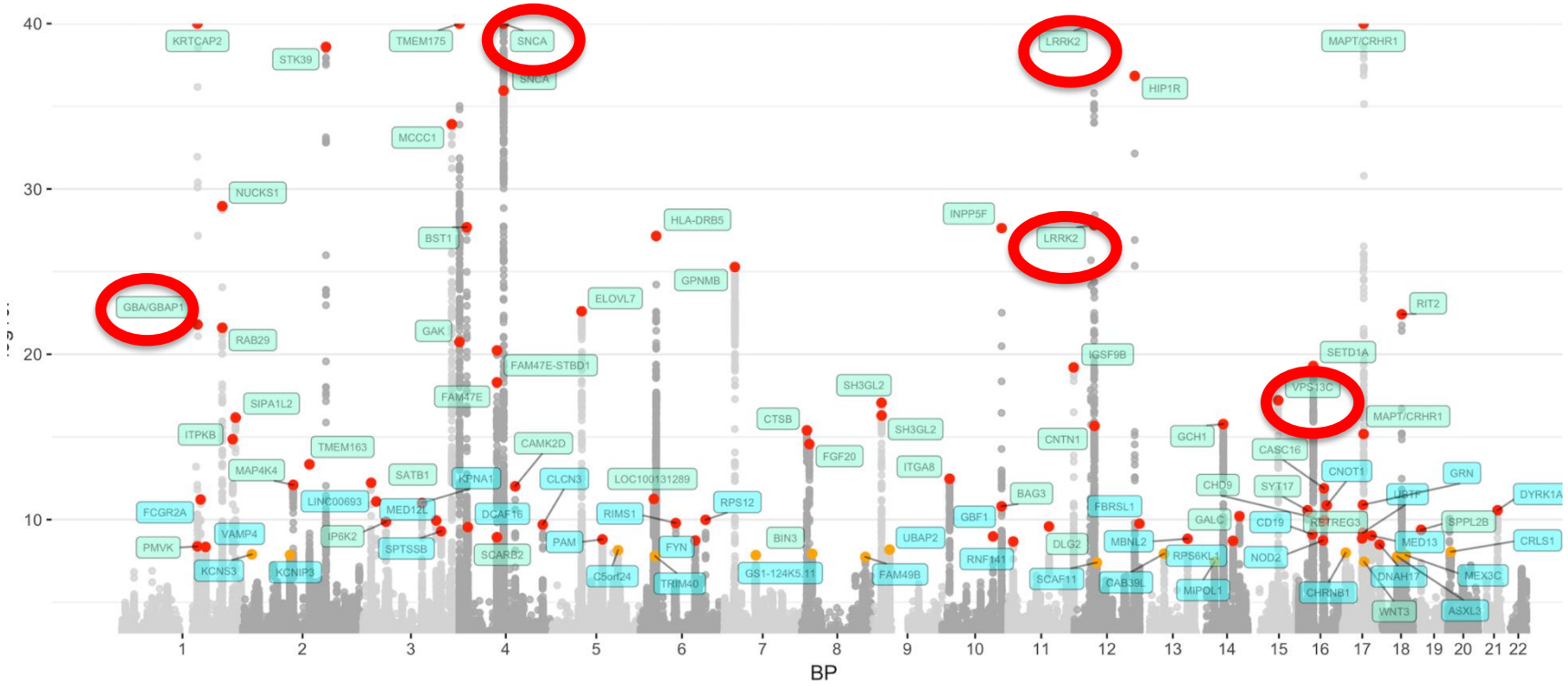
Simon-Sanchez et al., Nat Genet 2009

2009: 1,713 *sporadic* PD cases & 3,978 controls



Simon-Sanchez et al., Nat Genet 2009

Most Recent GWAS

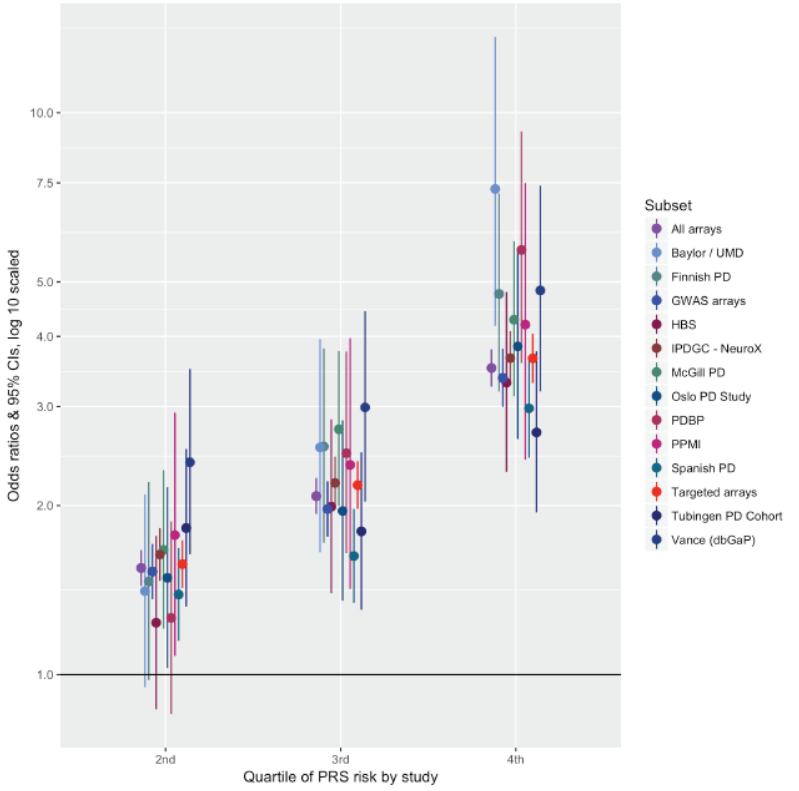


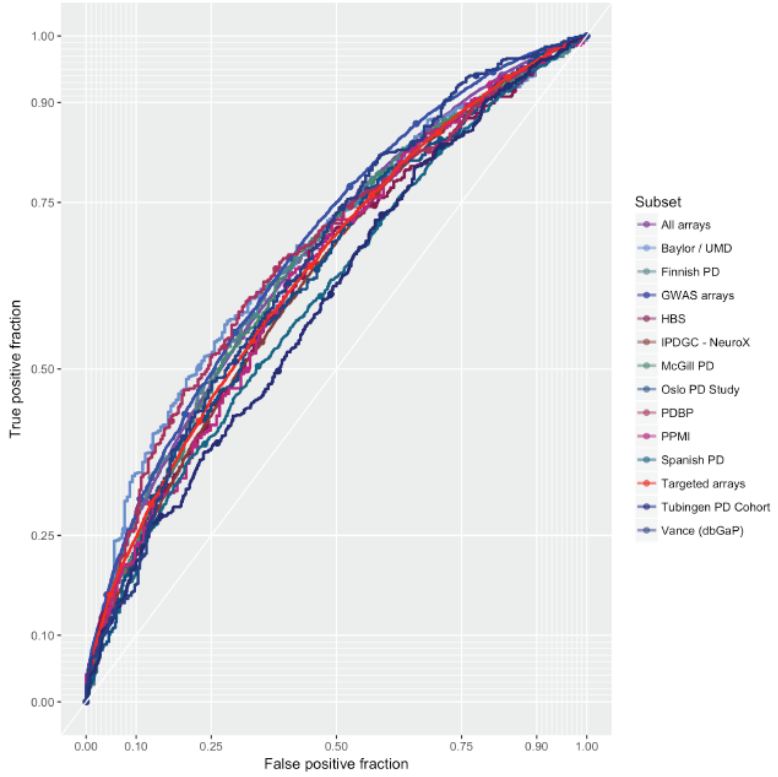
37.7K cases, 18.6K 'proxy-cases' and 1.4M controls
> than 80 loci with genome-wide significance

Nalls et al., Lancet Neurology 2019

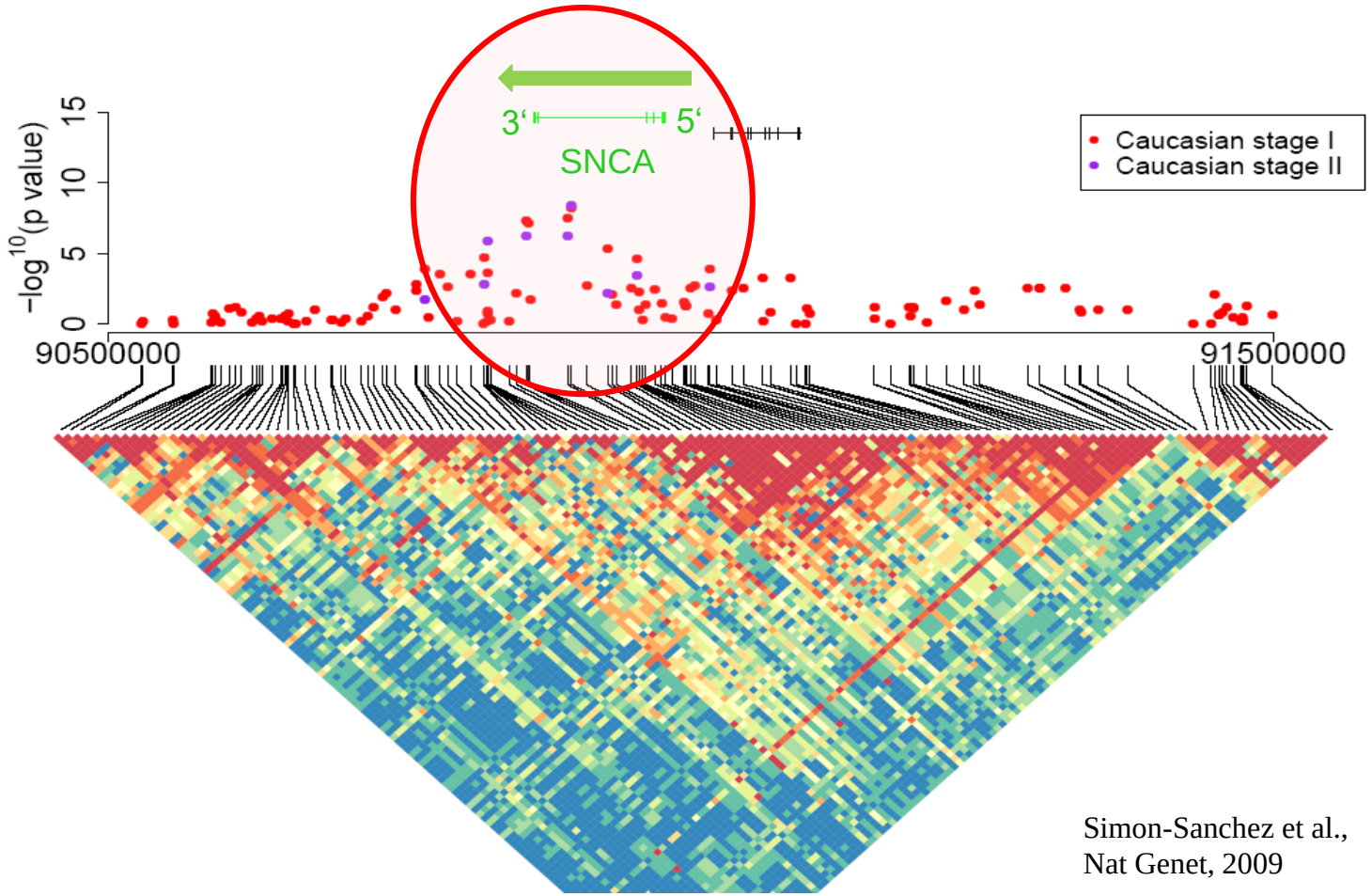
Institutional Logo,
‚Speakers' picture or disease related picture

Polygenic risk scores



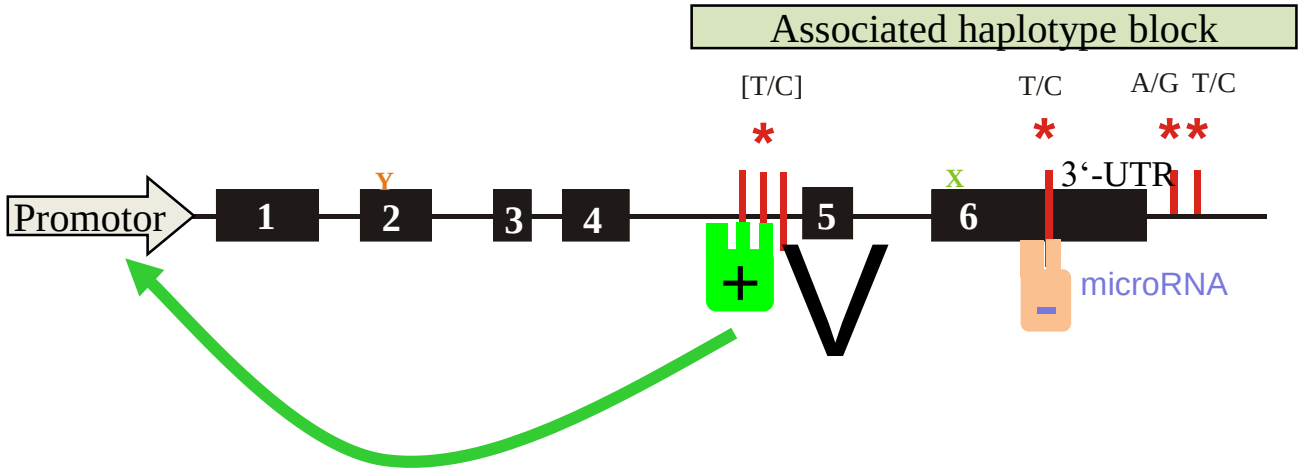


Structure of the a-synuclein GWAS signal

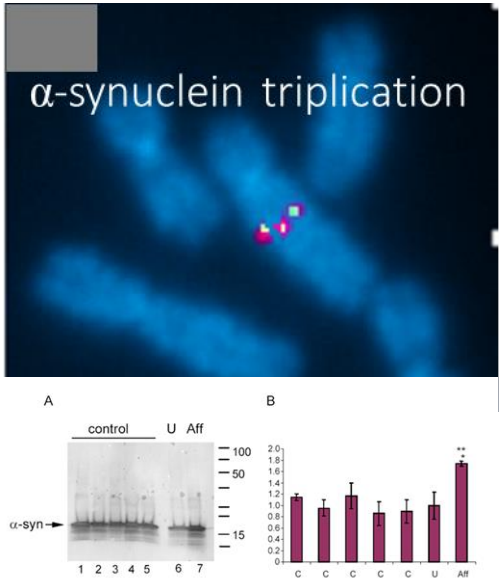


Simon-Sanchez et al., Nat Genet, 2009

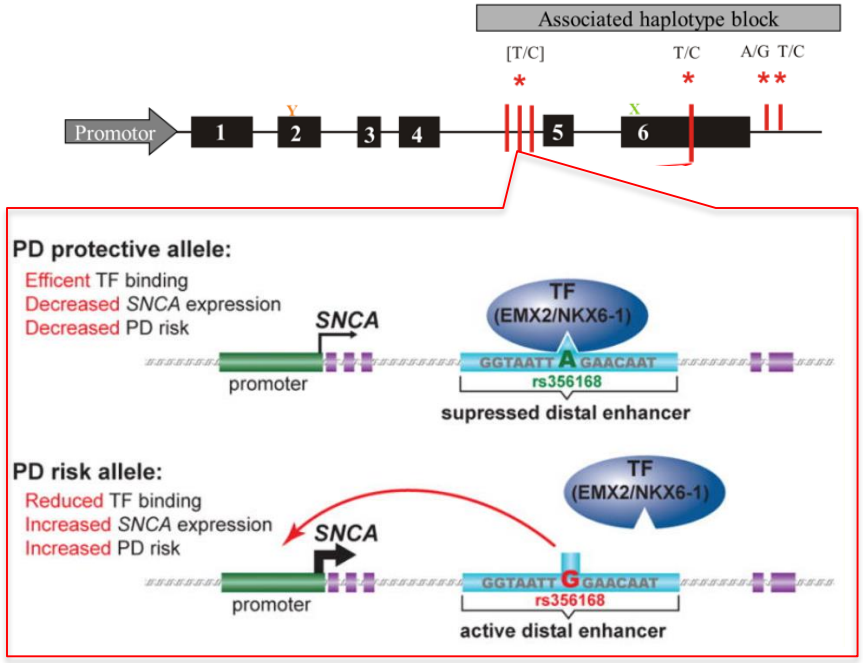
Potential effects of genetic SNCA variants



alpha-synuclein: potential mechanism of action in familial and sporadic PD



Singleton et al., Science, 2004



Soldner et al., Nature 2016

Institutional Logo,
‚Speakers' picture or disease related picture

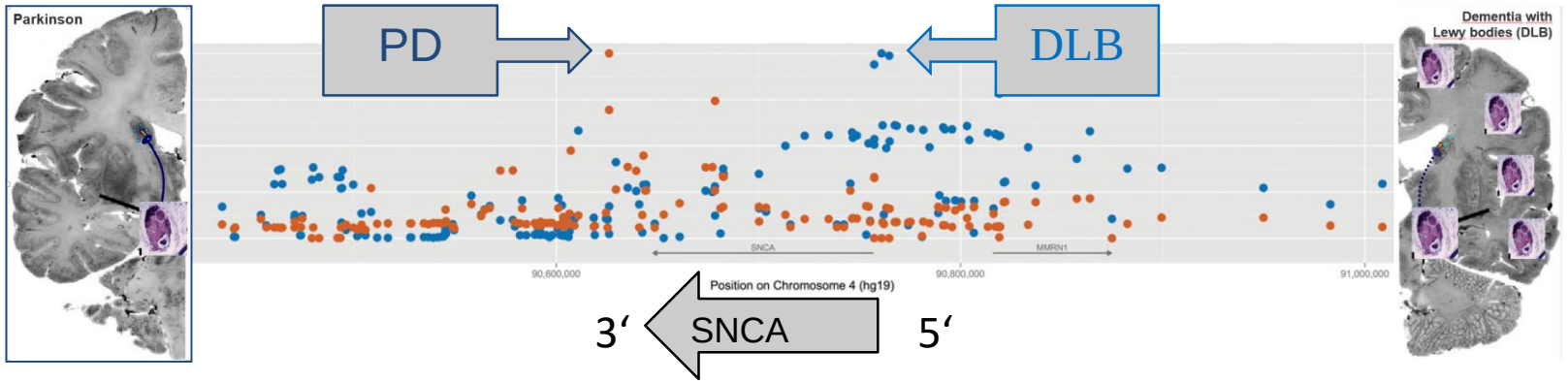
Common variability and phenotype

Human Molecular Genetics, 2014, Vol. 23, No. 23 **6139–6146**
doi:10.1093/hmg/ddu334
Advance Access published on June 27, 2014

Genetic analysis implicates *APOE, SNCA* and suggests lysosomal dysfunction in the etiology of dementia with Lewy bodies

Jose Bras[1,*], Rita Guerreiro[1], Lee Darwent[1], Laura Parkkinen[4], Olaf Ansorge[4],

- association study of 54 regions, previously implicated in PD or AD
- in 788 DLB cases / 2624controls



Key Points /Conclusions

- PD has a complex genetic architecture with common and rare variants influencing different aspects of the phenotype
- Genetic forms show different molecular pathways to disease
- Risk variant patterns are associated with distinct clinical features (endophenotypes ?)
- Therapeutic potential in risk variants of intermediate effect strength

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European Reference Network for rare or low prevalence complex diseases

Network Neurological Diseases (ERN-RND)

European Reference Network for rare or low prevalence complex diseases

Network Neuromuscular Diseases (ERN EURO-NMD)

ean european academy of neurology

European Reference Network | Neurological Diseases (ERN-RND)

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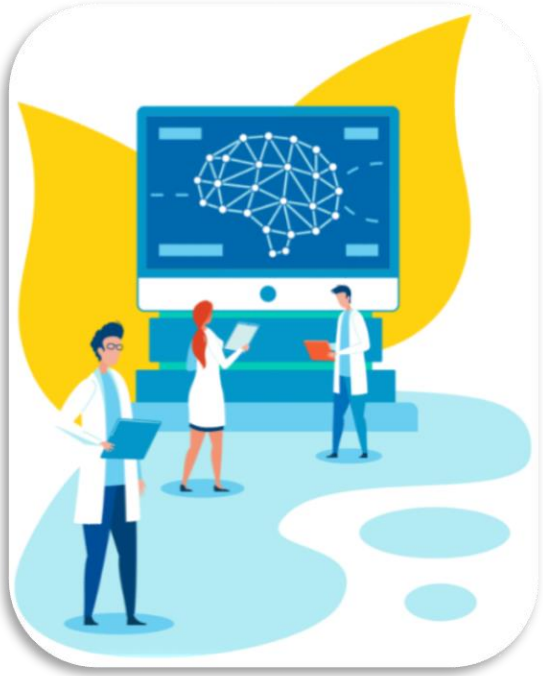

THANK YOU

Next webinar:

‚Treatable dystonias & dystonia in inborn errors of metabolism’

28. September 2021