Gaucher Disease and Parkinsonism: A Rare Disease Provides a Window into a Common Neurodegenerative Disorder

Ellen Sidransky, M.D.

Chief and Senior Investigator, Medical Genetics Branch, Molecular Neurogenetics Section
National Human Genome Research Institute, NHGRI

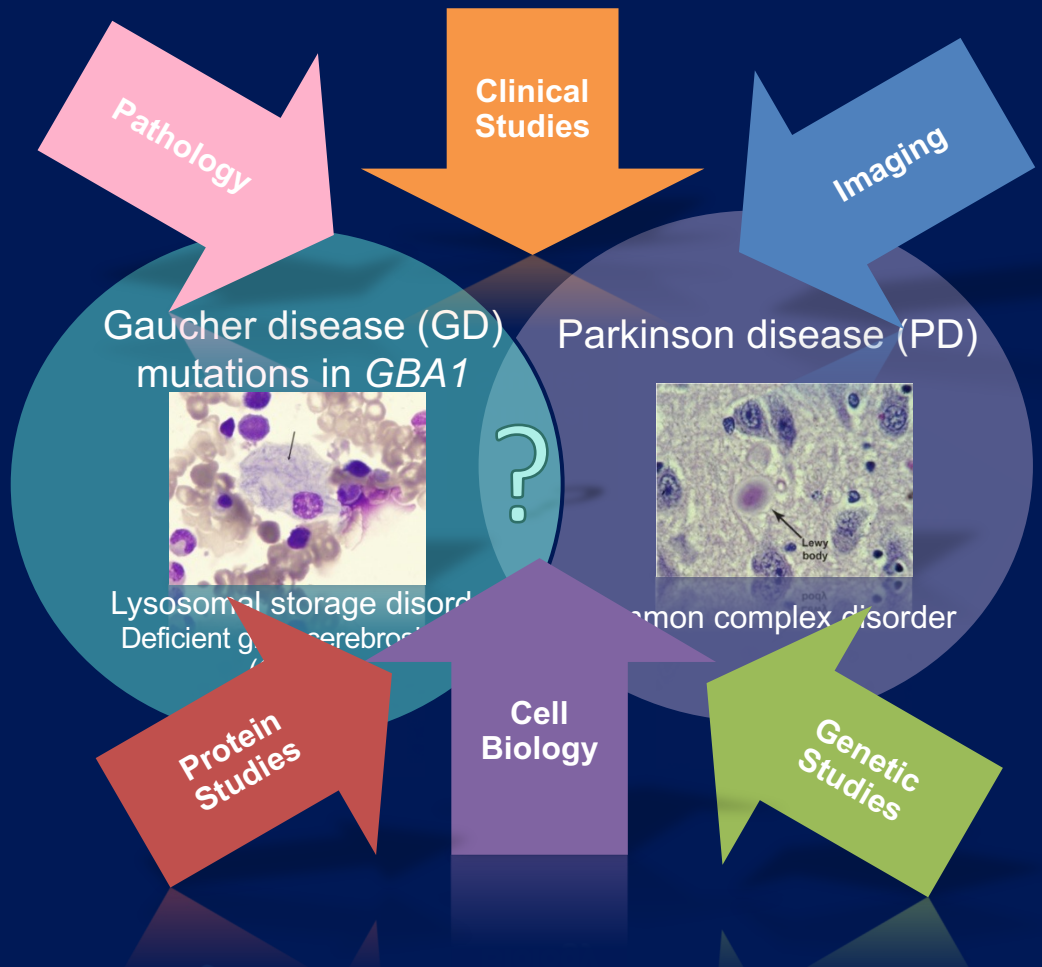
The **Forefront** of **Genomics**®

”I live in a very small house, but my windows look out on a very large world.” Confucius

National Human
Research Institut

The **Forefront** of **Genomics**®

Mendelian disorders provide a window into complex disease



Our knowledge about Gaucher disease can advance the field of Parkinson disease

NIH NHGRI

Questions:

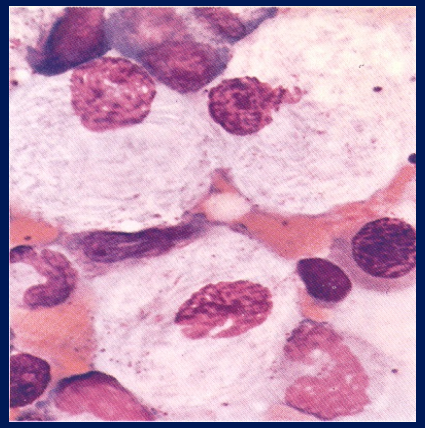
Isn't Gaucher disease enough?

???????

What more do we need to worry about?

GBA1- gene mutated in Gaucher disease

$$\text{Glucocerebroside} + H_2O \xrightarrow[\text{(GCase)}]{\text{Glucocerebrosidase}} \text{Ceramide} + \text{Glucose}$$



NIH NHGRI

Vast clinical variation is encountered in GD

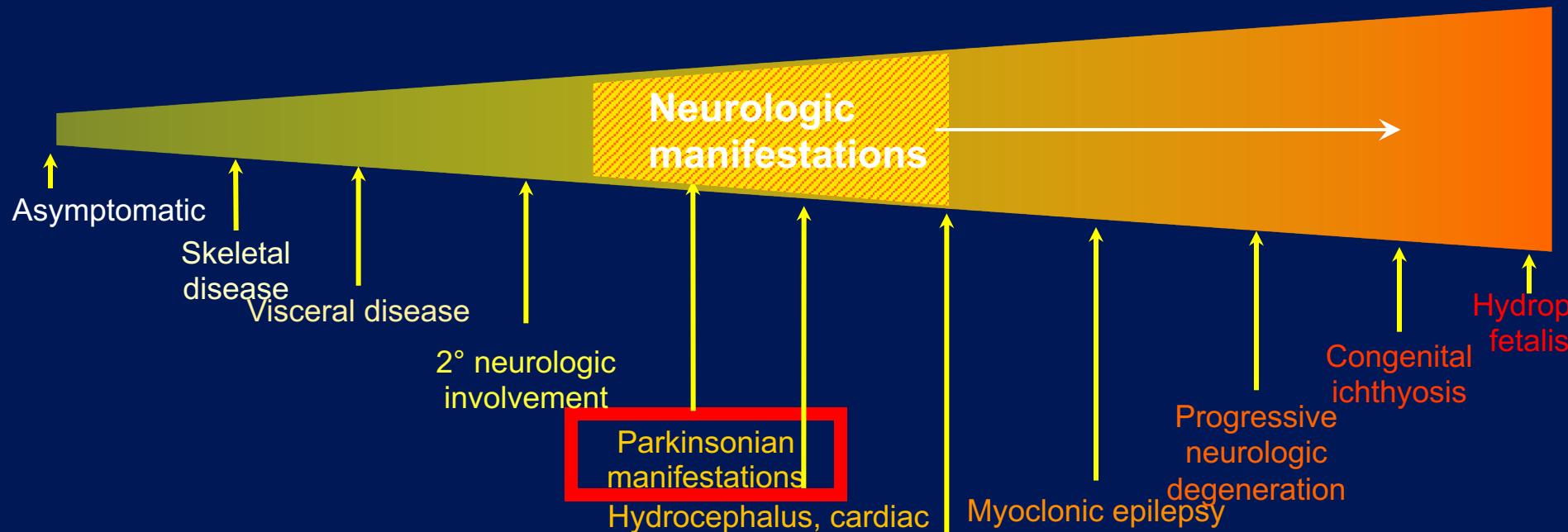
Non-neuronopathic

Neuronopathic

GD1

GD3

GD2



Gaucher disease: a spectrum of phenotypes

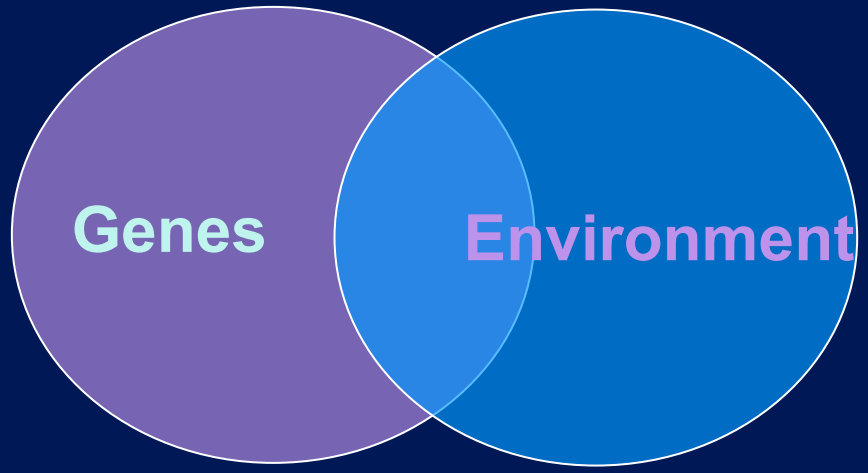
Rare disease
Carrier rate=
1/100 general population
1/14 Ashkenazi Jews

NIH NHGRI

Parkinson disease is common

- 2% of the population over 65 years
- 40,000 new cases/year
- 1 million people in the US

Contribution of both genetic and environmental factors

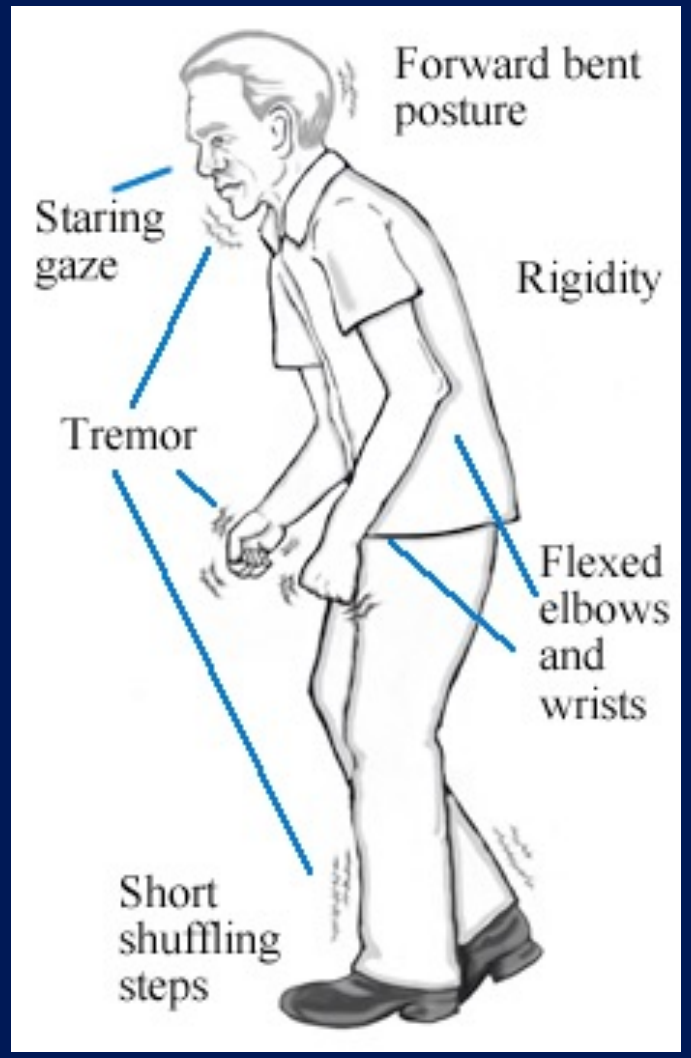


NIH
NHGRI

Parkinson disease (PD)

Includes: Bradykinesia (slowness of movement)
And at least one of the following:

- Muscular rigidity
- 4-6 Hz rest tremor
- Postural instability



Parkinsonism - term describing motor features of Parkinson disease

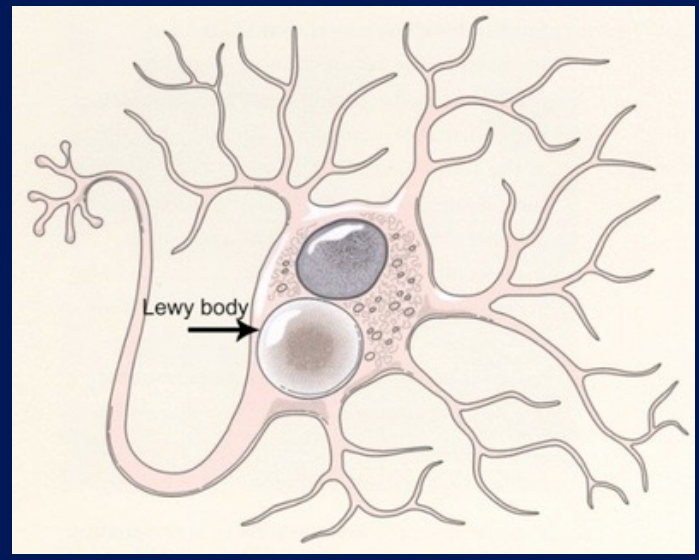
Dementia with Lewy bodies (DLB)

More severe cognitive deficits and more rapid disease progression

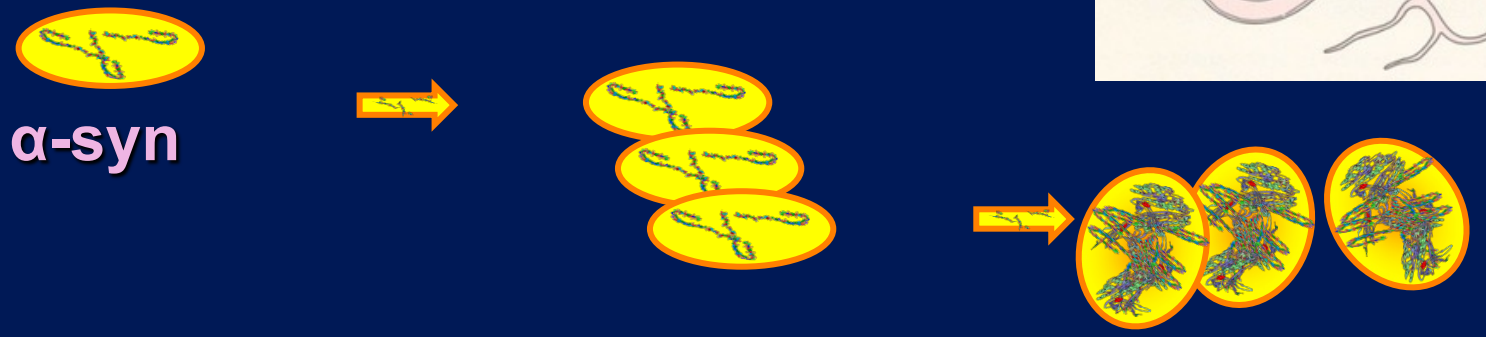
Disorders with parkinsonism- referred to as Lewy body disorders or synucleinopathies

NIH NHGRI

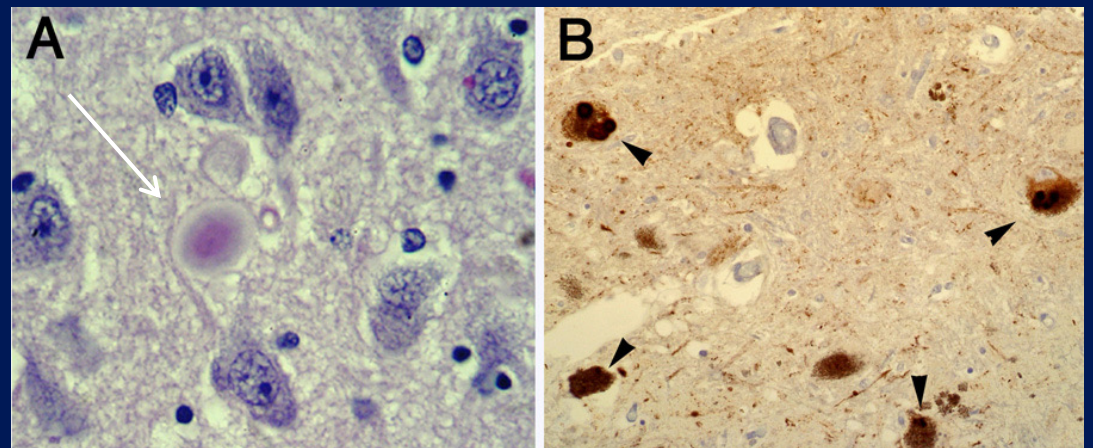
Lewy bodies are inclusions containing aggregates of proteins in neurons



Alpha-synuclein- a protein that aggregates and is found in Lewy bodies



Lewy bodies are found in brain autopsy samples from patients with parkinsonism



H&E, 400X

α-synuclein antibody, 200X

NIH NHGRI

The Parkinson story began my clinic in 1996, with a single patient with GD who developed parkinsonism…

- Mild Gaucher disease- diagnosed at age 19
- Tremor at age 42; rigidity, masked facies, difficulty initiating movements and rapid deterioration of gait
- Progressive dementia - death at age 54

Was this a co-incidence?

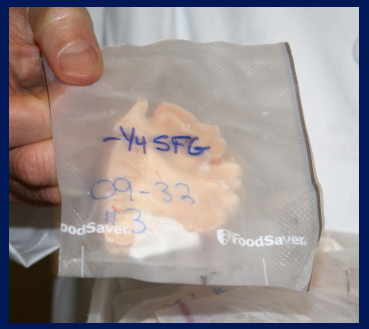
- Other cases found in literature (Neudorfer *et al* 1996*)* and other clinics
- In 2003, we published a series of 17 similar patients (Tayebi *et al*, 2003) from around the world

NIH NHGRI

The plot then thickens…….

Dr. Kathy Newell, Neuropathologist

- Autopsy performed in Boston
- Contributed frozen brain samples:



Serendipitous finding!

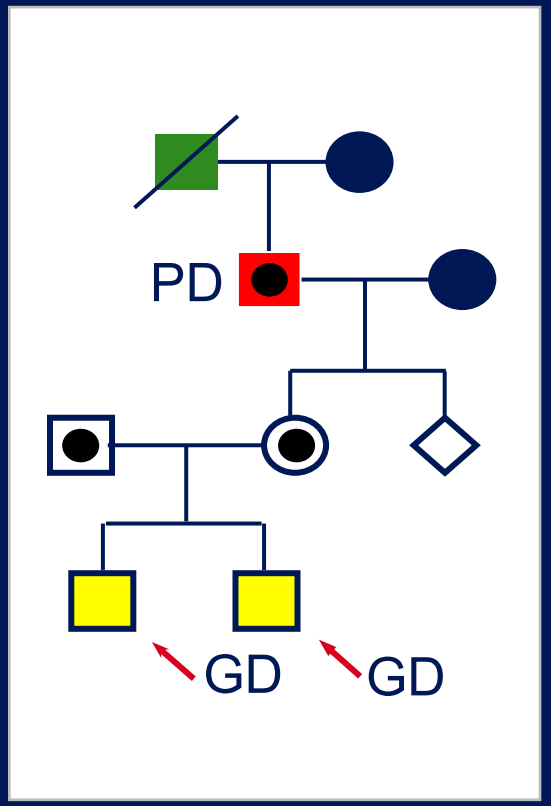
- Brain bank study:12/57 had variants in *GBA1*
- None found among 44 control brains

Study was very hard to get published!

NIH NHGRI

Family histories reveal parkinsonism in heterozygotes

- In a prospective study, 12 of 45 Gaucher probands had relatives with parkinsonism *(J Med Genet 2004)*
- Often, a parent or grandparent who was an obligate Gaucher carrier
- Similar findings from other Gaucher centers including Jerusalem



Heterozygotes are at increased risk for parkinsonism

NIH NHGRI

International multi-center study of *GBA1* mutations in PD

- 16 centers - 4 continents
  >10,000 *GBA1* genotypes from patients with PD and controls
- Subjects with PD are >5 times more likely to have a mutation in *GBA1*
- *GBA1 carriers had earlier PD onset and more cognitive deficits*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE Oct 2009

Multicenter Analysis of Glucocerebrosidase Mutations in Parkinson's Disease

E. Sidransky, M.A. Nalls, J.O. Aasly, J. Aharon-Peretz, G. Annesi, E.R. Barbosa, A. Bar-Shira, D. Berg, J. Bras, A. Brice, C.-M. Chen, L.N. Clark, C. Condroyer, E.V. De Marco, A. Dürr, M.J. Eblan, S. Fahn, M.J. Farrer, H.-C. Fung, Z. Gan-Or, T. Gasser, R. Gershoni-Baruch, N. Giladi, A. Griffith, T. Gurevich, C. Januario, P. Kropp, A.E. Lang, G.-J. Lee-Chen, S. Lesage, K. Marder, I.F. Mata, A. Mirelman, J. Mitsui, I. Mizuta, G. Nicoletti, C. Oliveira, R. Ottman, A. Orr-Urtreger, L.V. Pereira, A. Quattrone, E. Rogaeva, A. Rolfs, H. Rosenbaum, R. Rozenberg, A. Samii, T. Samaddar, C. Schulte, M. Sharma, A. Singleton, M. Spitz, E.-K. Tan, N. Tayebi, T. Toda, A.R. Troiano, S. Tsuji, M. Wittstock, T.G. Wolfsberg, Y.-R. Wu, C.P. Zabetian, Y. Zhao, and S.G. Ziegler

Second multi-center study in dementia with Lewy bodies (DLB) ***JAMA Neuro 2013***

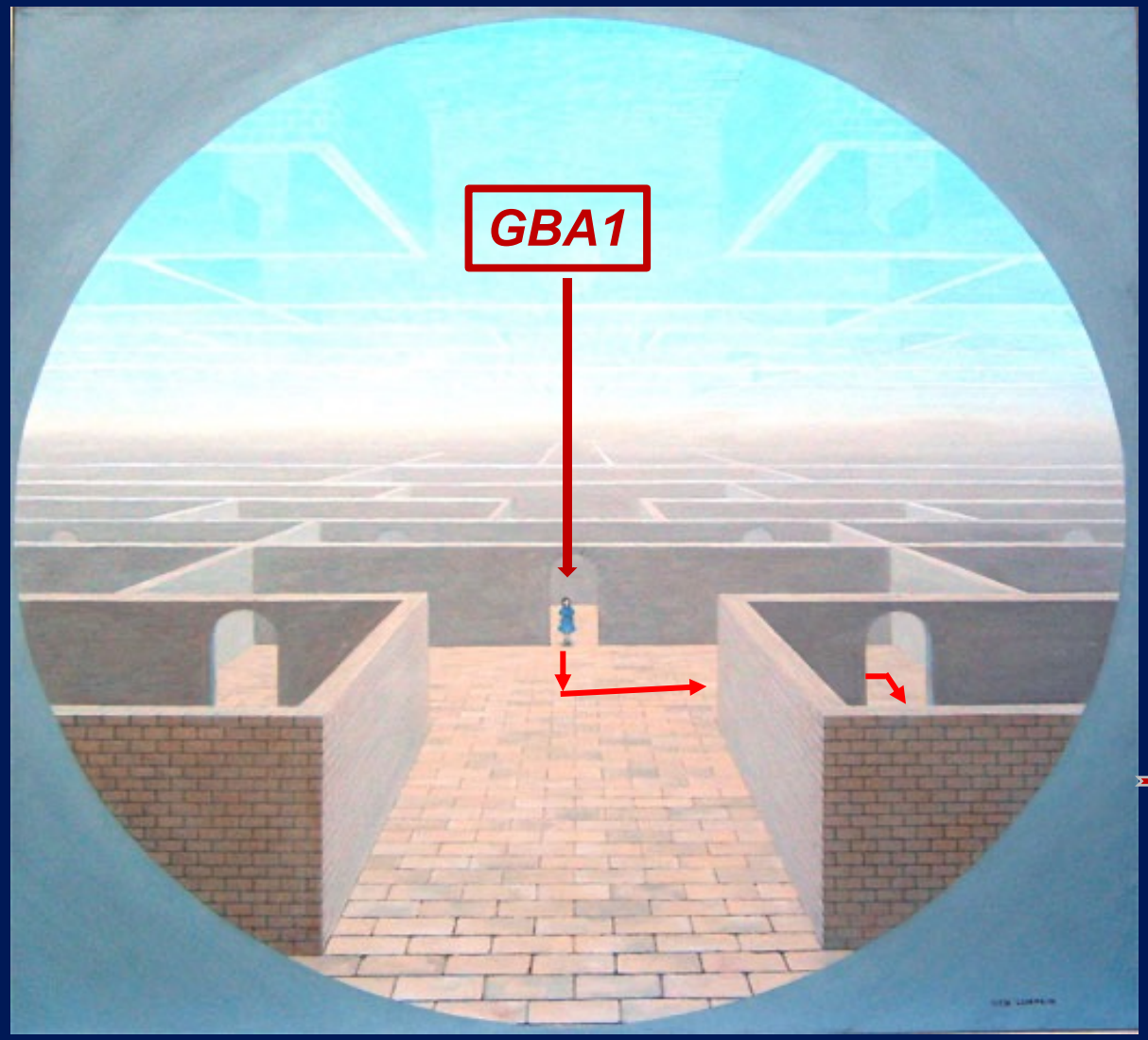
11 centers : 721 cases with DLB, 1962 controls

Odds ratio = 8.28

Gaucher mutations also play a role in DLB!

NIH NHGRI

Finding a gene gives us a starting point



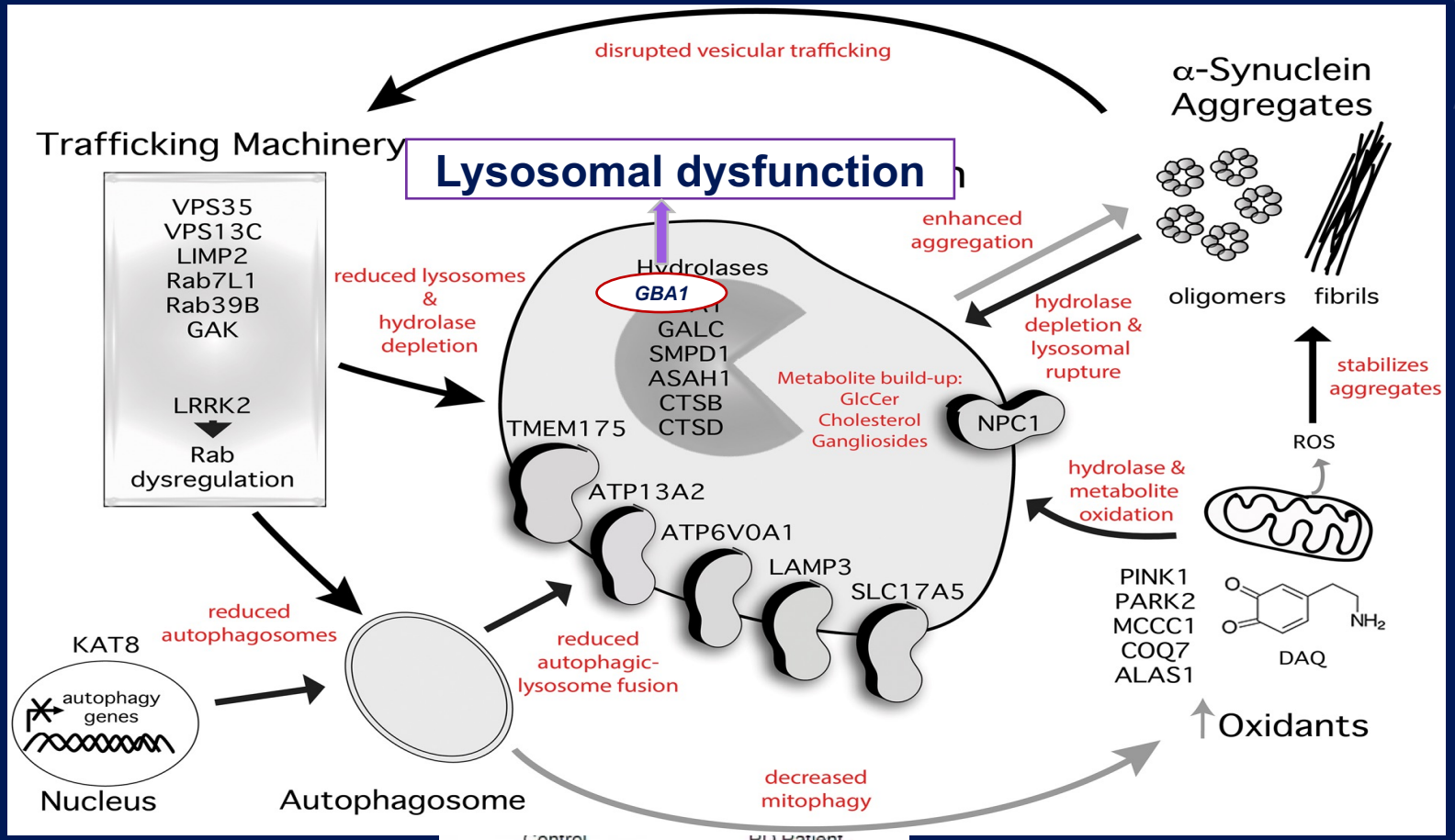
Parkinson disease

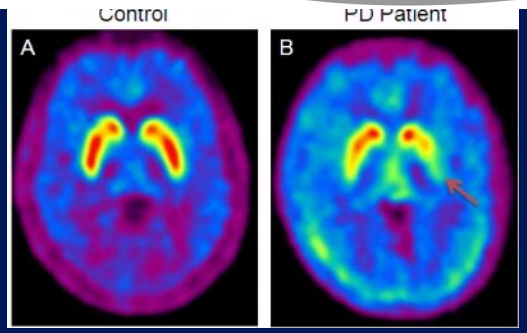
NIH
NHGRI

Pathways to Parkinsonism

Genes

Finding a gene can direct attention to a new pathway



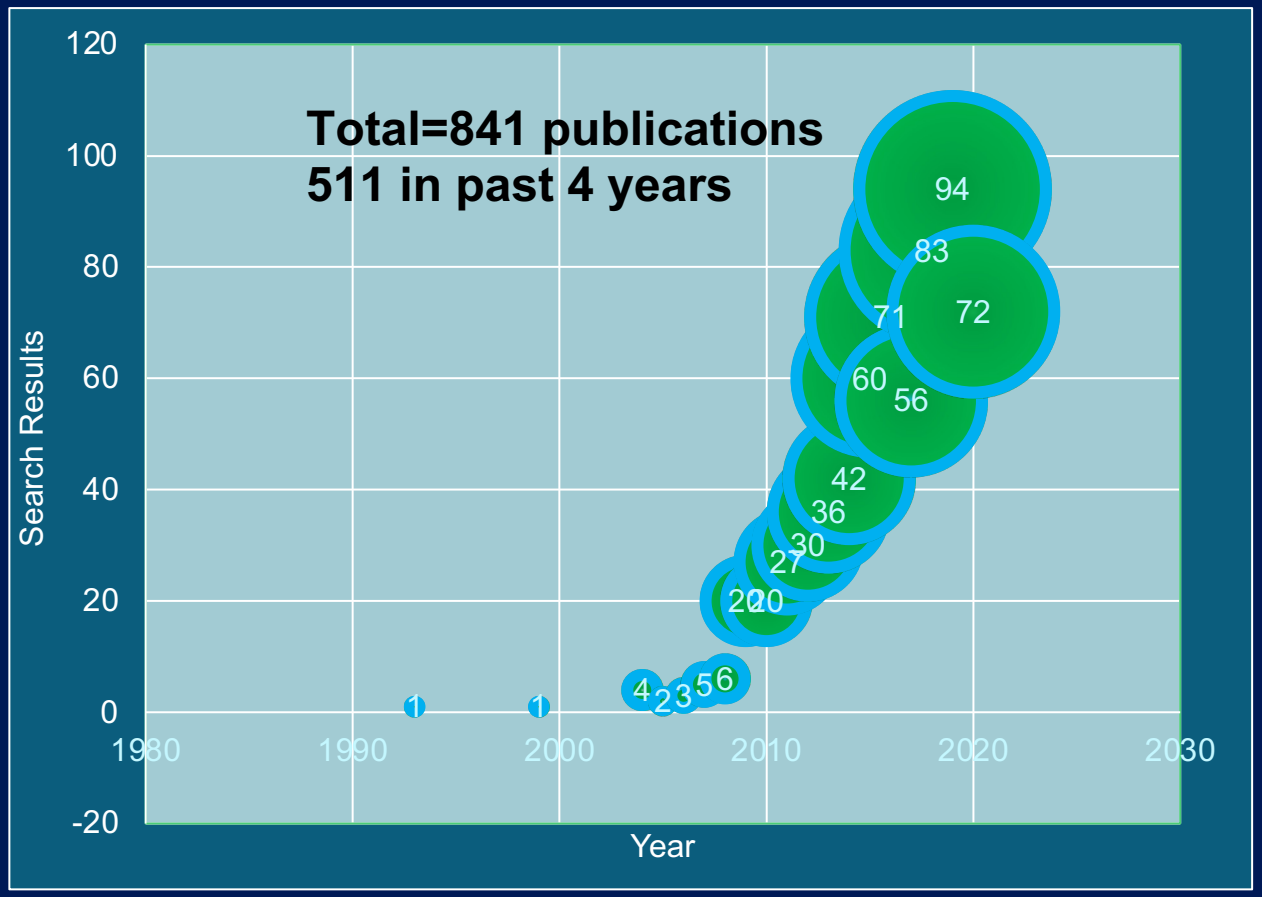


Many of the genes identified fall into <u>lysosomal</u> pathways

Adapted from Klein <u>Brain</u> 2018

NIH NHGRI

The number of publications on *GBA1* and Parkinsonism has rapidly grown!



"*GBA1*" and "Parkinson" PubMed search: results per year

Searching for GBA1 you will find more papers about PD than GD!

Great interest by the pharma industry

NIH NHGRI

NIH patient study: Can we find early clinical and imaging features predictive of parkinsonism in patients with *GBA1* mutations?

Dr. Grisel Lopez

Included:

- *GD/PD*
- *GD carriers with PD*

- *GD with & FH of PD*
- *GD carriers & FH of PD*

Clinical Studies

- Physical exam
- Neurologic exam (UPDRS)
- Neurocognitive evaluation
- Olfactory testing
- Screens for non-motor symptoms

Imaging Studies

- MRI (structural abnormalities)
- PET Scans (L-Dopa metabolism)
- Trans-cranial sonogram (TCS) (ultrasound study)

NIH NHGRI

Clinical study: Initial findings

13-year study longitudinal evaluations, single neurologist & neuropsychologist

11-year long PET study

> 500 visits; >850 observations

Our patients with PD

Often, findings resemble ordinary PD → Some have DLB features (clinical and pathologica)l → Similar levadopa response → Earlier age of PD onset (1.7- 6 yr) Mean=49y

Positive family history more likely → Non-motor symptoms common- low UPSIT → Progression faster → More cognitive dysfunction

However, among our patients we have seen exceptions.
Some of our patients have a slower progression and no cognitive problems

NIH NHGRI

Clinical study: Initial findings

Our patients <u>without</u> PD

13-year study longitudinal evaluations, single neurologist & neuropsychologist

93 individuals studied

55 GD:

38 carriers

In our at-risk cohort of 93 individuals followed for up to 13 years, we have seen <u>only one</u> develop PD- clearly <u>not</u> the majority!

NIH NHGRI

Focus on siblings

Ten sib pairs with GD

Only one with PD

Unaffected sib

- **Sibs seen 1-4 times over 1-12 years: complete battery of evaluations**
- **Thus far, no early indications of parkinsonism or changes in PET scans seen in non-PD sib** *(Mov Disorders, 2020)*
- **Many samples-plasma, serum, DNA, RNA, fibroblasts, RBCs, WBCs collected & stored**

Being used to identify risk *or* protective alleles for PD

NIH NHGRI

Remember…

Most Gaucher patients and carriers do *NOT* develop parkinsonism!

GBA1 mutation = risk factor

Challenge: To identify factors/genes increasing (or decreasing) risk for PD by

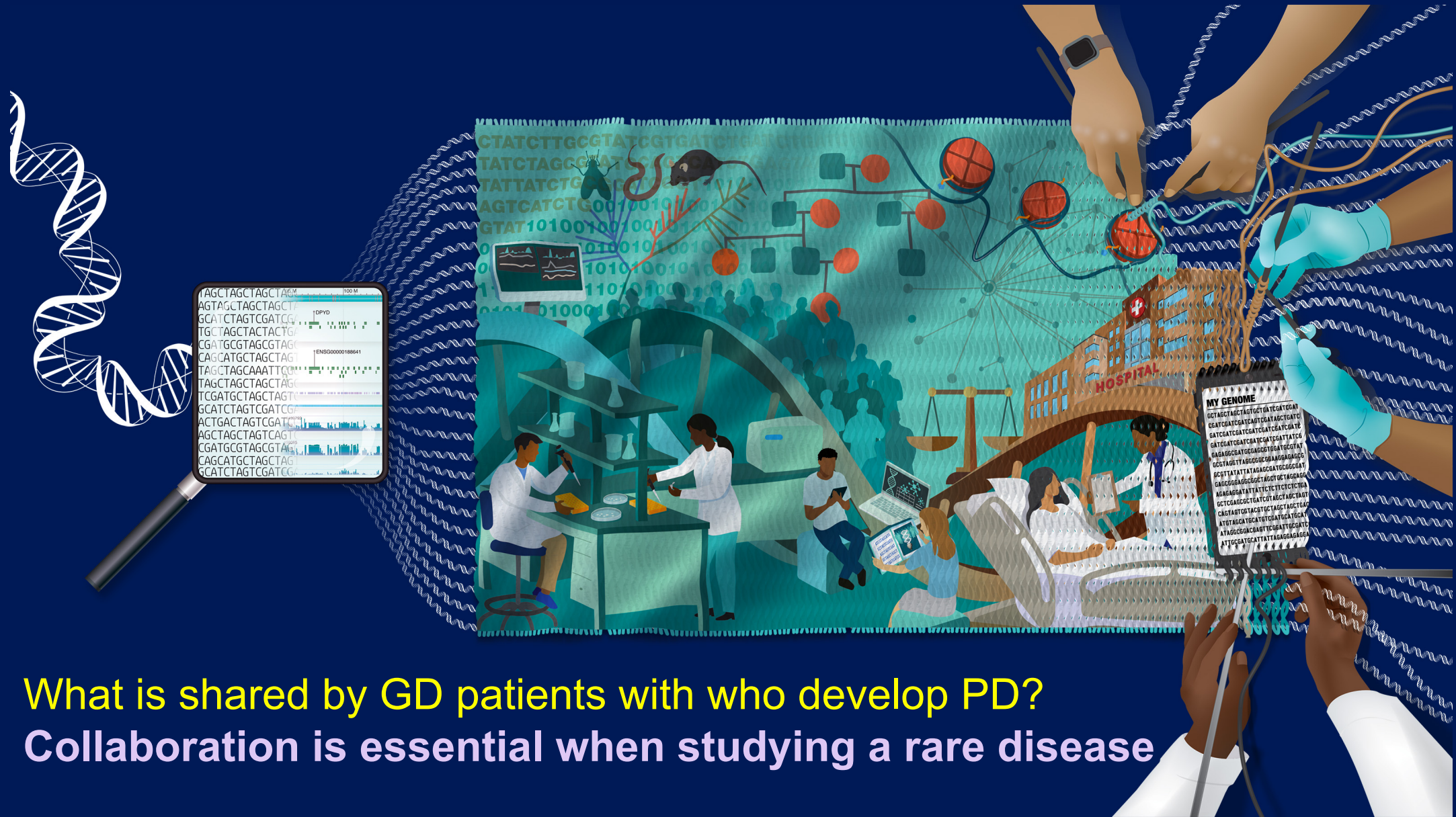
Clinical evaluations

+

Genomic approaches

NIH NHGRI

New technologies are enabling us to unravel the factors contributing to our complex individual tapestries



What is shared by GD patients with who develop PD?

Collaboration is essential when studying a rare disease

NIH NHGRI

Brain samples

- Exceptionally valuable and rare source of material for research investigations
- Collected at autopsy- takes planning and coordination
- Often stored by regional Brain Banks
- Comparing samples from individuals with Gaucher disease with & without Parkinson disease may help us to better understand what is going on

Can the Gaucher-Parkinson link lead to improved therapy?

Gaucher drugs (Enzyme Replacement & Substrate Reduction therapy) work, but are very expensive, inconvenient and do not cross the blood-brain-barrier

Other strategies:

- Substrate reduction that crosses into the brain
- Gene therapy to the brain
- Strategies to get enzyme into the brain
- GCase chaperones

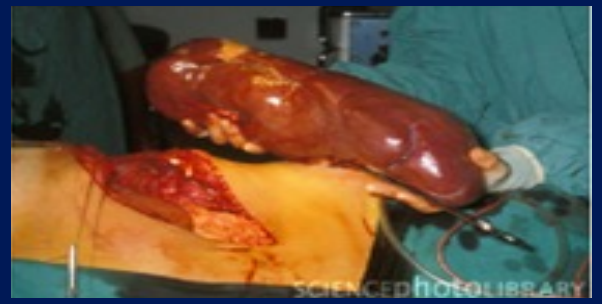
Disease-modifying therapy for Gaucher and Parkinson diseases: promote GCase folding to recover lysosomal function

NIH NHGRI

GCase chaperones as therapy for GD

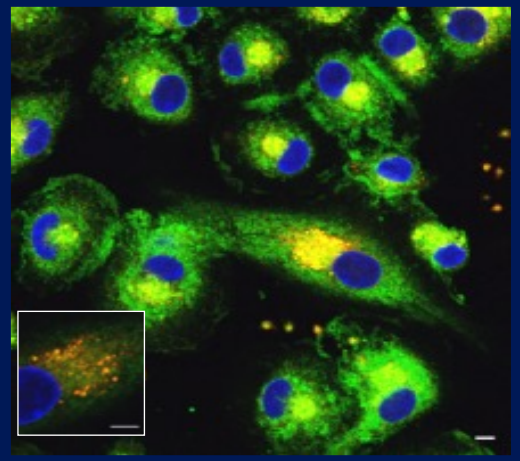
High-throughput screening approach

15 year collaboration with J. Marugan ,W. Zheng, and C. Austin, NCATS

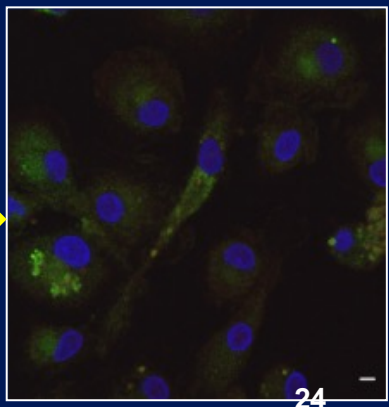


- Patient spleen- source of mutant GCase (N370S/N370S)
- HT Screen performed with 250K compounds
- New compounds identified: First non-inhibitory chaperones
- Lead compounds (758 and 607) identified

GD iPSC macrophages: compounds enhance enzyme activity, reverse lipid storage and restore macrophage function

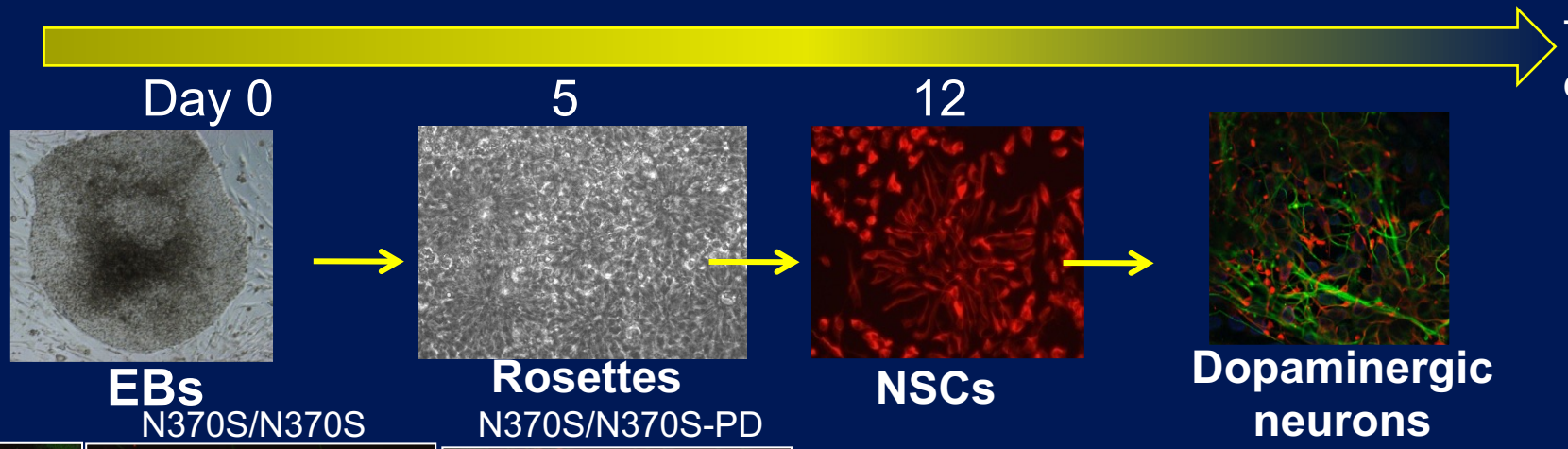


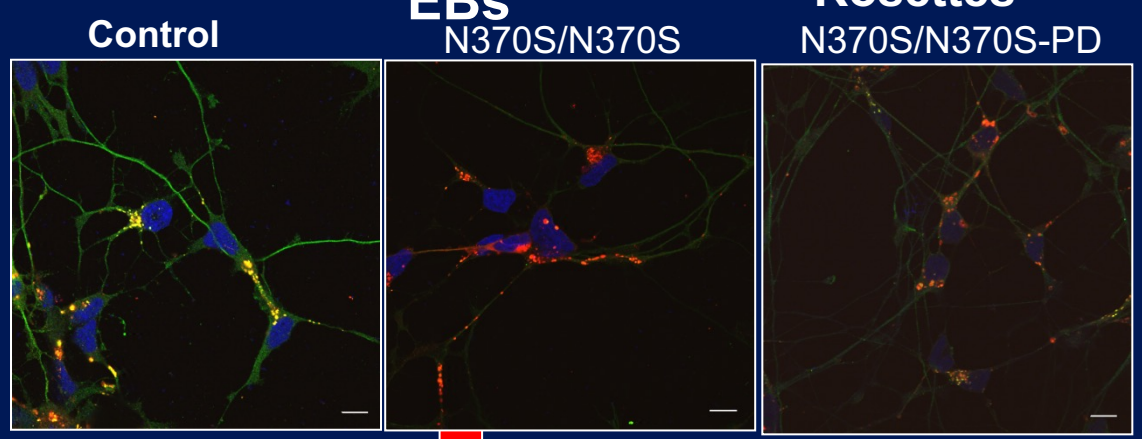
+ small molecule chaperone 758



NIH NHGRI

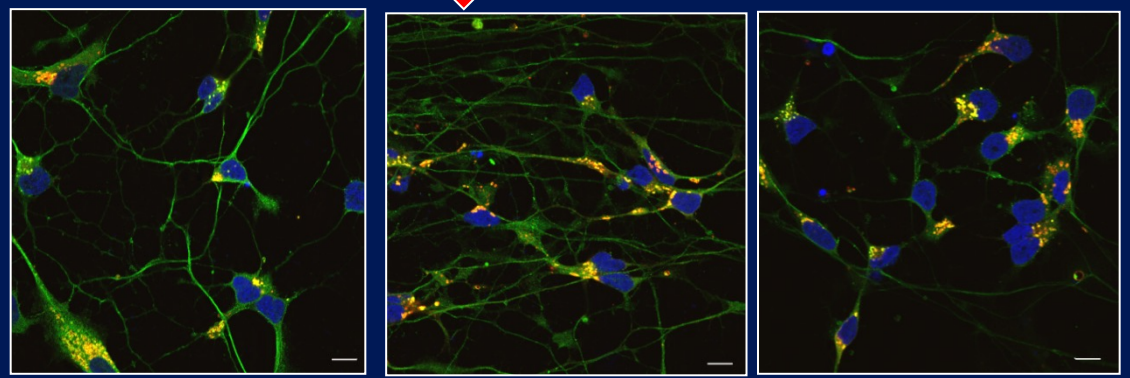
iPSC-derived neurons are made from patient fibroblasts





GCase
Lamp2

+NCGC607

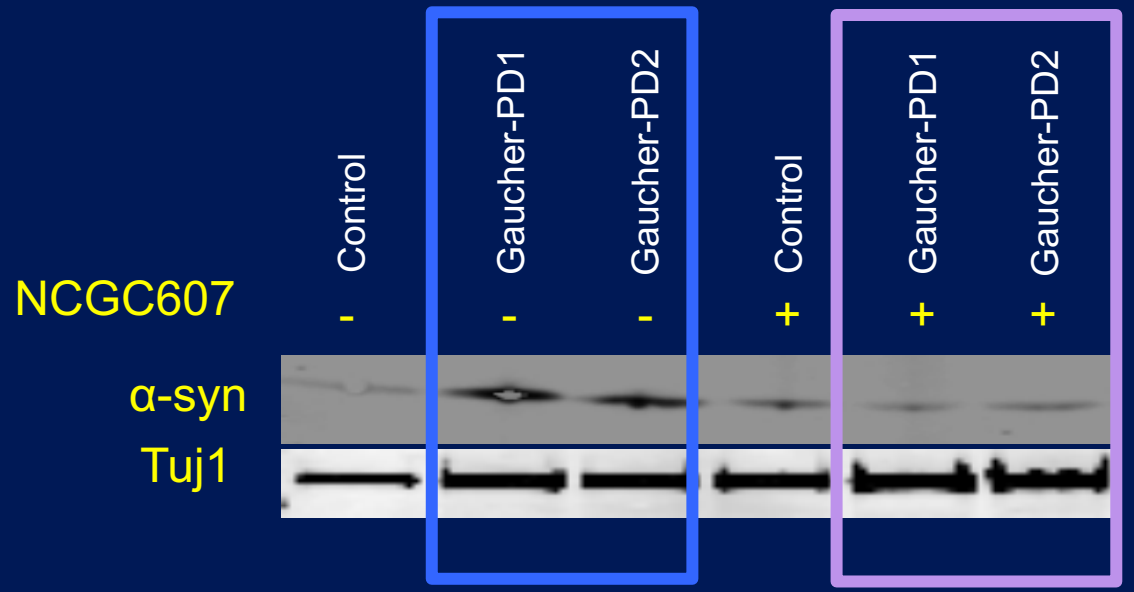


GD iPSC-dopaminergic neurons have decreased GCase and store the lipid

The neurons mimic what is seen in patients
Findings reversed with 607

α-synuclein levels in iPSC dopaminergic neurons from patients with Gaucher disease and PD

Elevated levels of α-synuclein seen



Suggests that drugs that increase GCase may work to treat Parkinson disease: Lots of work ahead!

α-synuclein levels are reduced when cells were treated with our lead GCase chaperone 607

NIH NHGRI

Take-home messages:

- Mutation in the Gaucher gene, *GBA1* is a risk factor for Parkinson disease, even in carriers
- However, most patients and carriers will never develop Parkinson disease
- Learning more about this connection will improve our understanding of both disorders
- New drug development for Parkinson disease may be beneficial for Gaucher disease

NIH
NHGRI

How to contribute to this research:

- Get involved in a study- NIH, Michael J Fox Foundation, other research centers
- Both patients with GD and carriers (with or without Parkinson disease) can be valuable
- Consider sample and tissue donations
- Keep up to date on new therapies: clinicaltrials.gov

NIH
NHGRI

NHGRI Clinical Team

Contact information:

Ellen Sidransky, MD: sidranse@nih.gov
Grisel Lopez, MD: glopez@mail.nih.gov

Clinical Coordinator-
Emory Ryan, MSN, CPNP-PC:
emory.ryan@nih.gov

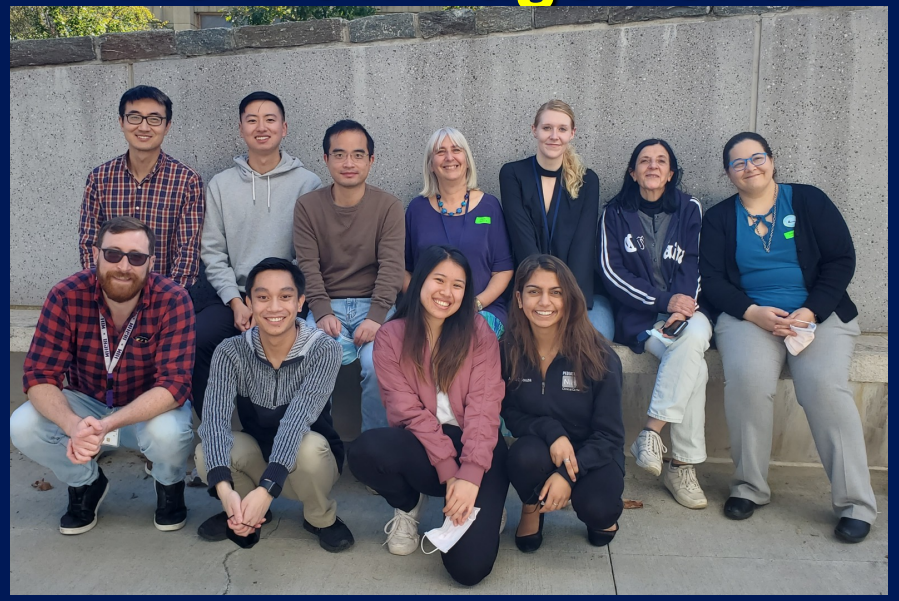
Were you ever seen at the NIH?
We'd love to update our records and research consents

NIH
NHGRI

Acknowledgements

Section on Molecular Neurogenetics

Nahid Tayebi
Grisel Lopez
Yu Chen
Tae Un Han
Bahafta Berhe
Emory Ryan
Barbara Stubblefield
Emily Daykin
Gani Perez
Geena Woo
Eric Garcia
Richard Sam
Adenrele Gleason



NCATS

Juan Marugan
Samarjit Patnaik
Wei Zheng
Noel Sunderland
Mark Henderson

Collaborators

Ari Zimran- Jerusalem
Edward Ginns- U. Mass
Dan Ory- Casma
Benoit Giasson- U. Florida
Raphael Schiffmann- Baylor
Peter Vangheluwe-Leuven
Loukia Parisiadou- NWU
Glenda Halliday- Australia
Ravi Jagasia- Roche
David Vocadio (SFU)
Mark Cookson- NIA
Jennifer Lee- NHLBI
Sonja Scholz- NINDS
Cornelis Blauwendraat -NIA
Daniel Eisenberg- NIMH
Karen Berman- NIMH
Andy Singleton- NIA
David Goldstein- NINDS
Ricardo Feldman-UMD
Michael Ward-NINDS

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

asap Aligning Science Across Parkinson's

ASAP Team

Peter Vangheluwe (KU LEUVEN)
Veerle Baekelandt (KU LEUVEN)
Joel Blanchard (Mount Sinai)
Joseph Lyons (AARHUS U)

The NHGRI Technology Transfer Office

The NHGRI Core Facilities

With special thanks to our patients, their family members and caregivers and their referring physicians