GBA – personalised medicine for Parkinson disease: clinical and therapeutic stratification (GBA-PaCTS)

JPND/JPco-fuND2 Midterm Symposium

Brussels, November 28th 2024

Dr Marco Toffoli

GBA1 and Parkinson disease

- **Changes in the *GBA1* gene are found in:**
  - Less than 1% of the general population
  - 12% of people with a diagnosis of PD (up to 30% if Ashkenazi Jewish background)

- **The risk of developing PD is small**
  - Only about 3-10% of people with changes in *GBA1* will develop PD by the age of 80, so most people will not.

- **GBA1 pathology is relevant in all PD cases**
  - GCase activity is reduced in people with PD without GBA1 variants

Aims of the project

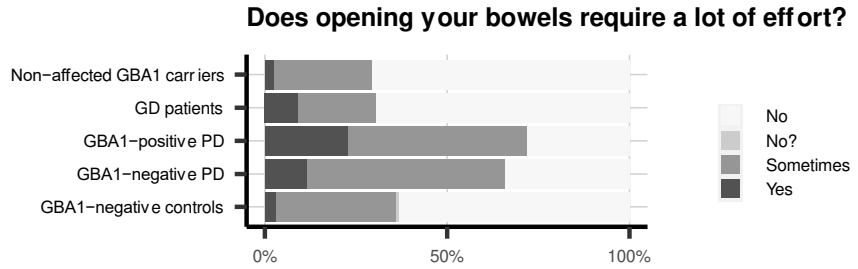
- **Recruit and harmonise** assessment strategies of GBA1-PD patients and GBA1 carriers across different countries (UK, Italy, Germany, Spain)

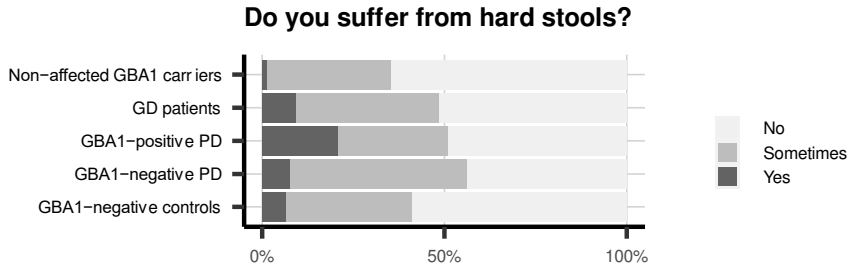
- **Collect multiple samples** from participants (saliva, blood, fibroblasts) to evaluate biochemical and inflammatory markers

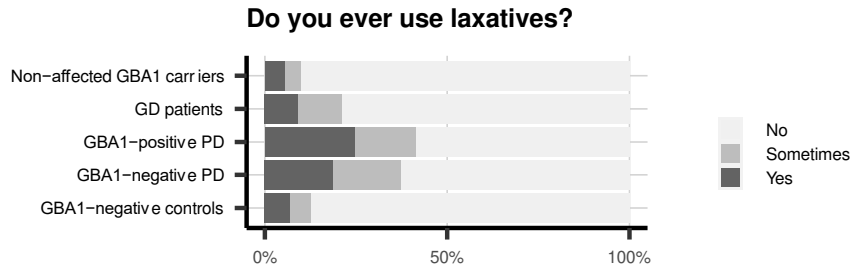
- Use ***in vitro*** (human iPSc, 3D organoids, primary neuronal cultures) and ***in vivo*** models to study biochemical consequences of GBA1 variants on α-synuclein spread, mitochondrial and immune function

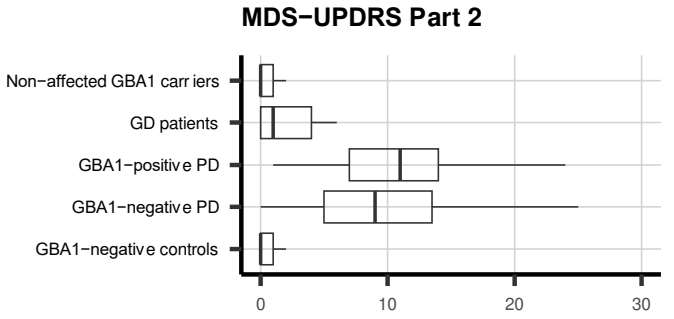
- Evaluate effect of GBA1 **targeted therapies** (Ambroxol) to reverse pathological events that can precipitate PD pathology

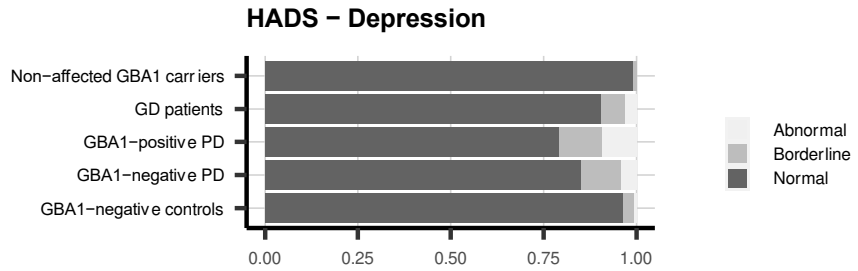
UK-Italian-Spanish cohort

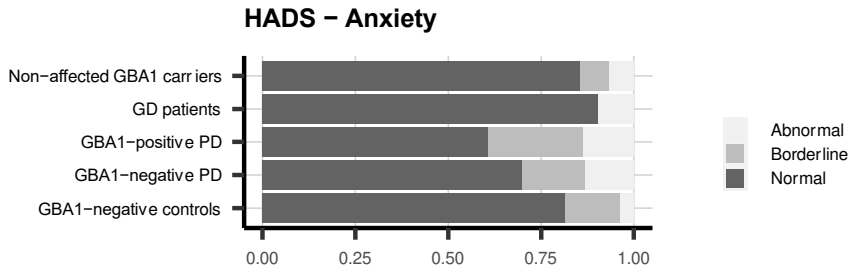


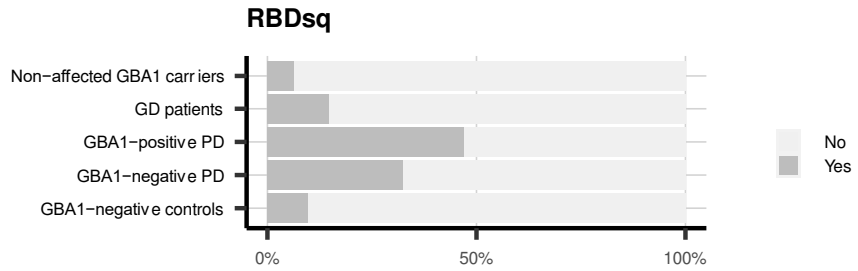


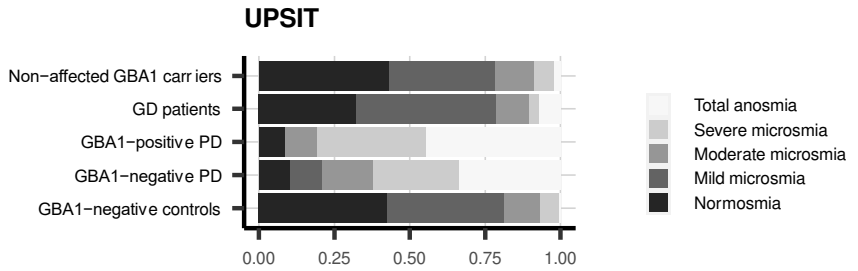






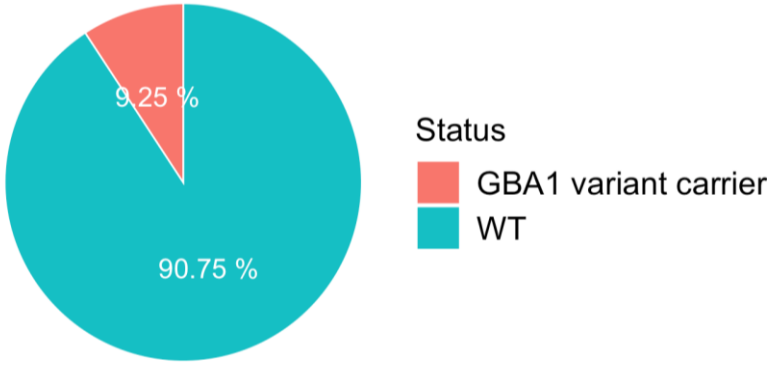




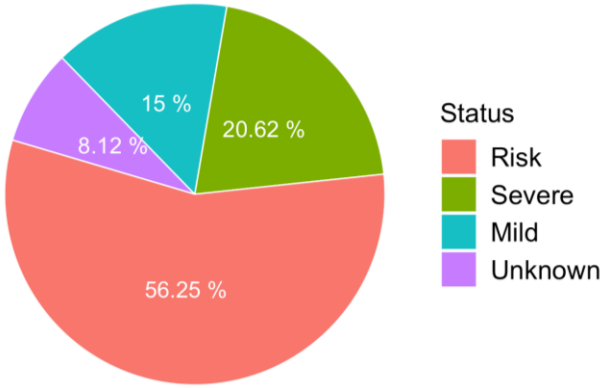


(Toffoli et al, Neurobiol Dis 2023)

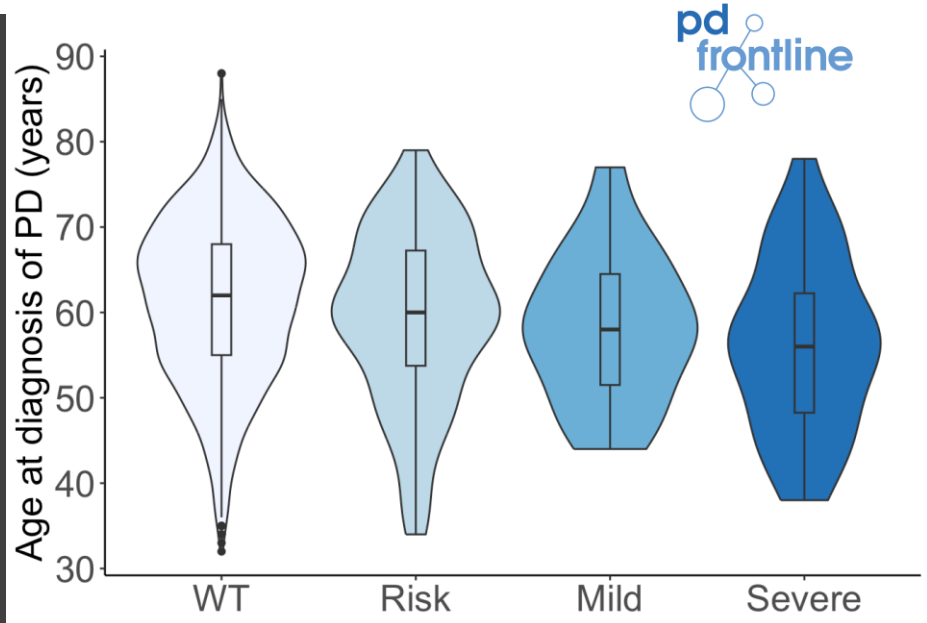
Characterisation of the *GBA1* gene in a large Parkinson disease cohort in the UK



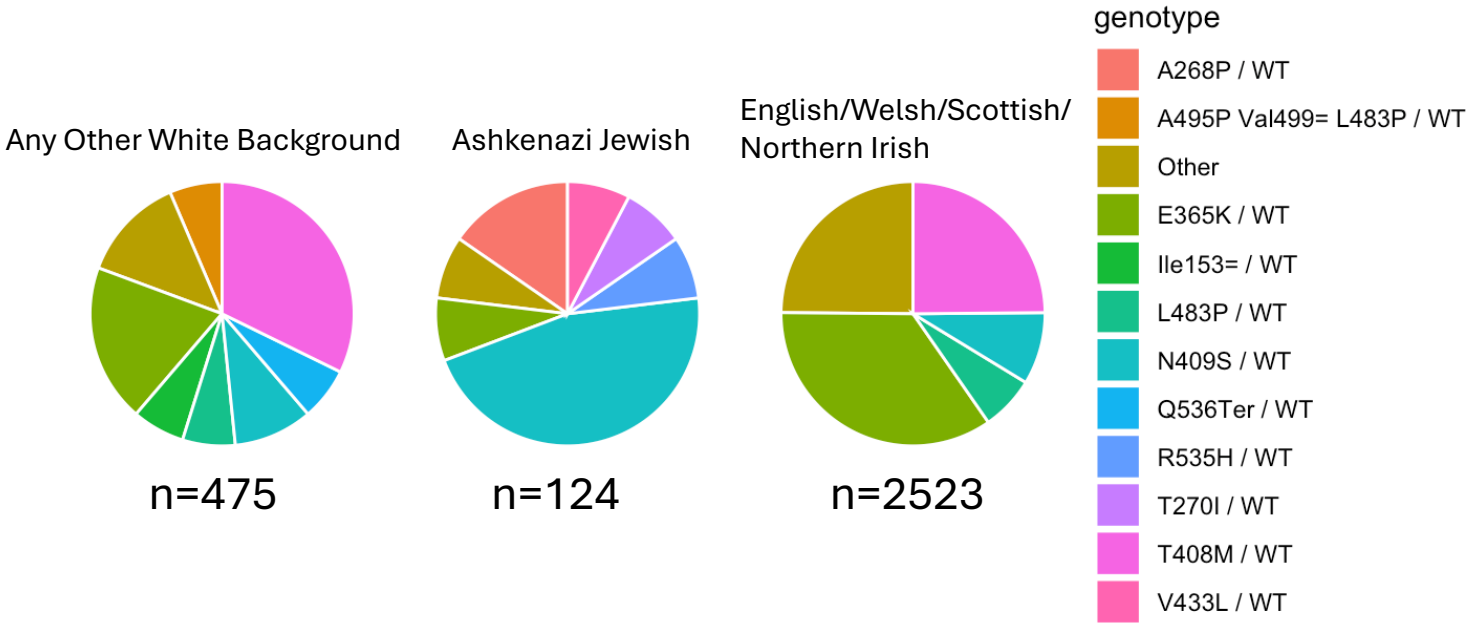
Prevalence of *GBA1* variants (n=3458)



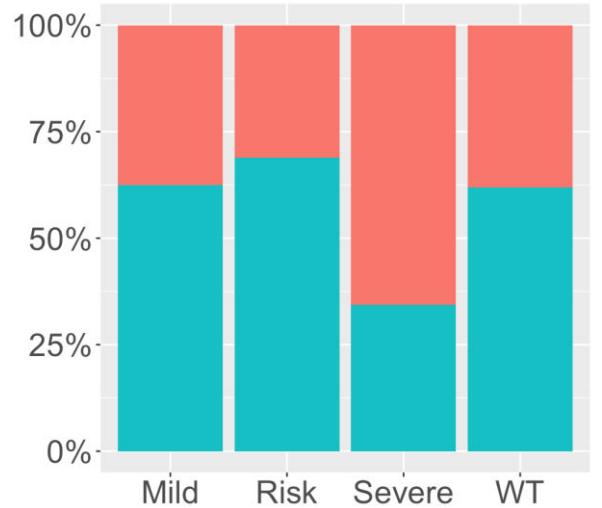
By variant type



GBA1 status vs age at diagnosis



GBA1 status vs ethnicity



GBA1 status vs sex

CURE PARKINSON'S

PARKINSON'S UK
CHANGE ATTITUDES
FIND A CURE.
JOIN US.

Inflammatory and biochemical markers

Role of Microglia:

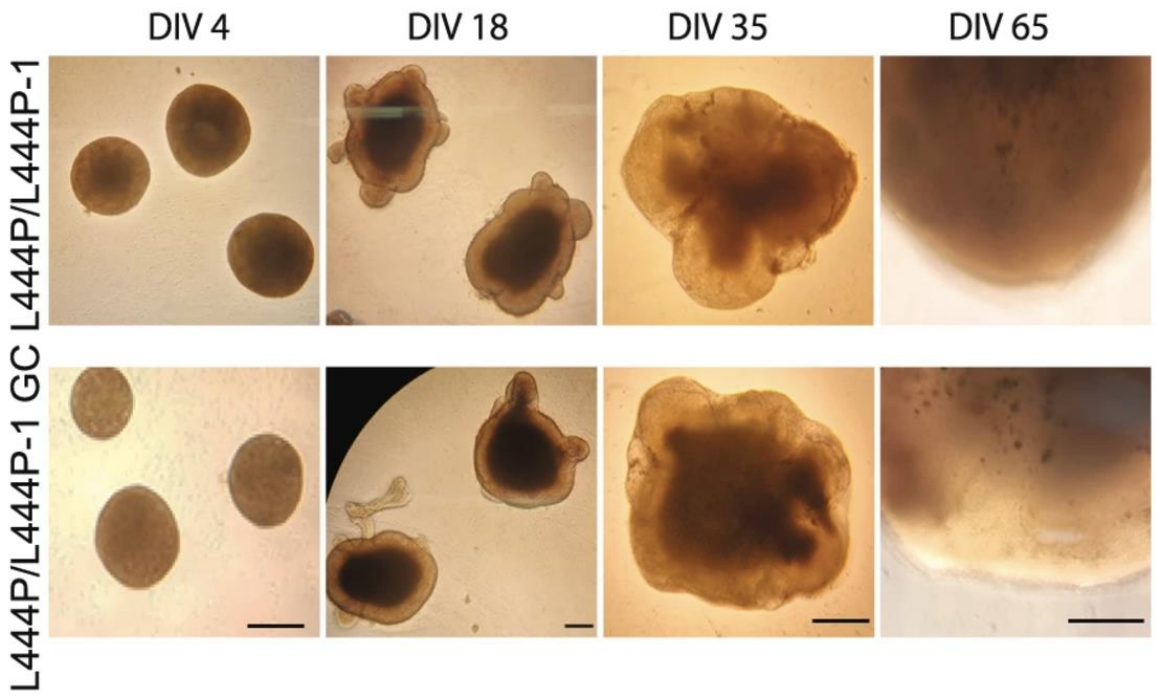
- Microglia are crucial in the early stages of GBA-associated Parkinson's disease (PD).
- GBA inhibition alters microglial morphology, function, and mRNA expression.
- These changes reduce microglial neuroprotection and increase neuronal vulnerability to PD-related triggers.

Sex-Specific Responses:

- GCase inhibition in female microglia disrupts the Nrf2 detoxification pathway, reducing neuroprotection.
- This aligns with clinical data showing:
  - Women have a lower risk of idiopathic PD.
  - This protective effect is lost in GBA mutation carriers.

(Brunialti et al., J Neuroinflammation, 2021; Brunialti et al., Cells, 2023; manuscript in progress)

GBA1 & A-SYN pathology in midbrain organoids



- Developed a model of GBA-PD α-Synuclein Pathology
- Significant transcriptional dysregulation in DA neurons of GBA1 mutants
- Altered mitochondrial ATP production.
- Dysregulated respiratory chain complex

(Helwig et al, Sci Adv. 2022; Tolve et al, Cell Rep. 2021; Baden et al, Nat Commun. 2023)

Ambroxol to reverse PD-related pathology

- **Ambroxol and Microglia-to-Neuron Communication**:
  - Ambroxol shows potential in modulating microglial phenotypes affected by GCase inhibition.

- **Effect of Ambroxol on Macrophages**:
  - Treatment increased GCase activity in PD-GBA+ patients, restoring it to healthy levels.
  - Reduced pro-inflammatory cytokines, especially TNF-α, in all groups (PD or GBA mutation presence didn't affect this result).

- **Limitations of Ambroxol**:
  - Failed to restore mitochondrial function in PD-GBA+ macrophages.
  - Persistent mitochondrial issues likely due to irreversible effects of GBA mutations.

(Brunialti et al., Autophagy, 2024; Yang et al, Hum Mol Genet. 2022*)*

Patients/Public Involvement: UK experience

- **Webinars**
  - RAPSODI Educational Events (yearly)
  - Cure Parkinson's Research Updates

https://www.youtube.com/channel/UCdsOHwDsn_yaunfAxAnkM7A
https://cureparkinsons.org.uk/2021/11/pd-frontline/

- **Online platform and newsletter**
- **Social media platform**
  - @RapsodiRFH, @PDFrontline #gettrialready

https://rapsodistudy.com/en
https://pdfrontline.com/en

- **Involvement of Jewish community across the UK**
- **Feedback from our patients**
  - *"If there was anything I could do to help in this research programme I would be there like a shot"*

THE JC
THE JEWISH CHRONICLE

JPND research

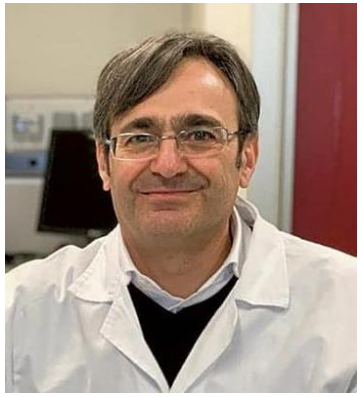
EU Joint Programme – Neurodegenerative Disease Research

Thank you for your attention

Prof Tony Schapira
(UCL)

Prof Michela Deleidi
(DZNE Tubingen)

Prof Fabio Blandini
(Mondino Foundation)



Prof Paolo Ciana
(University of Milan)

Prof Donato di Monte
(DZNE Bonn)

Prof José Luis Lanciego
(CIMA)