Clinical evolution in PD and the spread of pathology: insights from the GBA story

Tony Schapira
Department of Clinical and Movement Neurosciences
UCL Queen Square Institute of Neurology

Background

Catabolism of glycosphingolipids in humans: enzymes involved and enzyme-related diseases

Multicenter Analysis of Glucocerebrosidase Mutations in Parkinson’s Disease


Clinical considerations

The Evolution of PD

Prodromal features:
Olfactory loss, RBD, depression, constipation imaging

50–60% dopaminergic neurons lost

Dopaminergic neuronal function
Motor clinical dysfunction
Non-motor clinical dysfunction

Diagnosis
No symptomatic treatment
With symptomatic treatment

Schapira et al Nature Neurosci 2017
**GBA and PD**

- Homozygous vs heterozygous
- Up to 30% have PD by age 80 years
- 10-15% PD patients have *GBA* mutations
- Also associated with DLB (>PD)
- N370S and L444P are the commonest mutations. E326K common in PD but does not cause GD

Schapira Mol Cell Neurosci. 2015

---

**GBA-PD: clinical**

- Clinical features – slightly earlier onset, more cognitive impairment, faster progression*
- Pathology – identical
- Imaging – identical to idiopathic PD
- Pharmacology – same response to treatment including motor complications, 17% DBS patients *GBA* positive
- GBA +ve individuals may exhibit prodromal PD

Schapira Mol Cell Neurosci. 2015
CC2  Please confirm the proposed citation
Chris Cammack; 25/01/2016
GBA mutations accelerate PD progression

Progression to Dementia

- Non-carriers
- GBA-carriers
- GBA-MM
- GBA-SM

Log-rank test:
- Non-carriers vs GBA-carriers < 0.001
- GBA-SM vs GBA-MM < 0.001

Adapted from Cilia et al., Ann. Neurol. 2016

GBA-PD: clinical

- Clinical features – slightly earlier onset, more cognitive impairment, faster progression
- Pathology – identical
- Imaging – identical to idiopathic PD
- Pharmacology – same response to treatment including motor complications, 17% DBS patients GBA positive
- GBA +ve individuals may exhibit prodromal PD

Schapira Mol Cell Neurosci. 2015
GBA Prodrome

Asymptomatic GBA carriers develop…

• Impaired olfaction
• Subtle motor deficits
• Cognitive dysfunction
• RBD
• Depression
• Constipation

…significantly more than matched controls

Mullin et al Mov Dis 2019
Avenali, Toffoli et al JNNP 2019

Figure 1(A) (left) Coloured areas depicted on the single-subject brain template illustrates clusters of voxels with significantly increased $^{11}$C-PK11195 binding in the brainstem region of GBA carriers compared to control subjects. Non brainstem clusters are masked. $GBA1^+$ n=9 control n=20 . Figure 1(B) (right) Red colored areas depicted on the brain surface template illustrates clusters of voxels with significantly increased $^{11}$C-PK11195 binding in cortical regions of GBA carriers compared to control subjects. $GBA1^+$ n=9 control n=20.

Mullin et al 2019
Mullin et al. 2019

Fig 1. Box plots of PK11195 uptake in the left and right substantia nigra of control and GBA carrier participants

$\text{PK11195 uptake in the substantia nigra of GBA carriers and controls}$

$p=0.0008$  \hspace{1cm}  $p=0.0016$

left control \hspace{1cm} left GBA \hspace{1cm} right control \hspace{1cm} right GBA

Mullin et al. 2019

Fig 2. Scatter plot of correlation of UPSIT score (x) PK11195 uptake (y) in left (red) and right (blue) substantia nigra amongst GBA carriers

Spearman’s rank, left $p=0.0058$, right, $p=0.0317$

Mullin et al. 2019
Biochemistry

GCase in PD Brain

GCase activity is reduced in PD brain without GBA mutations

• Substantia nigra: 58%* ↓ GCase in GBA mutation positive brains and 33%* ↓ in sporadic PD
• Striatum: 48%* ↓ GCase in GBA mutation positive brains

*p<0.01

The GCase – alpha-synuclein connection

GBA1 KO mice
GBA1 mt mice
GBA siRNA
GBA inhibitors

↓GCase  ↑SNCA

SNCA o/e cells, PD triplication cells, SNCA o/e mice PD brain

Schapira et al Lancet 2014

AAV-GBA, adeno-associated virus gene therapy; CβE, conduritol-β-epoxide; GCase, glucocerebrosidase; KO, knock-out; SNCA, alpha-synuclein

WT or L444P mice and AAV SNCA over-expression

Migdalska-Richards et al Brain Oct 2017
Intra-Striatal injection of alpha-synuclein pre-formed fibrils into normal and GBA mutant mice

(A) Perirhinal cortex
(B) Amygdala
(C) Substantia nigra

Migdalska et al 2020

GBA mutation increases spread of alpha-synuclein PFFs

(D) Striatum
(E) motor & cingulate cortices

Migdalska et al 2020
GBA mutation summary

- Commonest risk factor for PD (20-30x). Present in 10-15% PD
- 30% penetrance by 80y
- Cause prodromal PD symptoms
- Cause brain microglial activation before nigral cell loss
- Increase levels of A-syn
- Increase spread of A-syn
- Earlier PD onset, more cognitive dysfunction
- Faster progression

Therapeutic considerations
Therapeutic approaches for *GBA*-related PD

- Neuronal susceptibility
- Cognitive deficits

**GBA** mutation → GCase → α-synuclein homeostasis → ↓GCase → ↑GSLs → Glucosylceramide synthase (GCS) inhibitor (Ph 2 trial)

GSLs: Glycosphingolipids

The GCase – alpha-synuclein connection

↓GCase → ↑SNCA → ↑GCase → ↓SNCA → ↓TOXICITY

Ambroxol treatment...

- Fibroblasts – ABX increases GCase, reduces ERAD.
- Drosophila-GBA mutant – ABX increases brain GCase, reduces ERAD, protects DA neuronal loss, restores motor function
- Human dopaminergic neurons (iPSC) – ABX increases GCase, reduces alpha-syn
- Mouse – ABX increases brain GCase, reduces alpha-syn levels and spread
- NHP – ABX increases brain GCase

McNeill et al Brain 2014
Sanchez-Martin et al Scientific Reports 2016
Yang et al Stem Cell Reports 2017
Migdalska et al Annals of Neurology 2016
Migdalska et al Synapse 2016
ABX increases GCase in GBA dopaminergic derived neurons

Yang et al. Stem Cell Rep 2017

ABX, ambroxol; CβE, conduritol-β-epoxide; wt, wild-type

ABX reduces alpha-synuclein in GBA-derived dopaminergic neurons

Yang et al. Stem Cell Rep 2017 see also Mazzulli J Neurosci 2016

ABX, ambroxol; wt, wild-type
Ambroxol reduces A-SYN and p-A-SYN in SNCA/SNCA mouse brain

(A) phospho-α-synuclein (↓ 41%)  
α-synuclein (↓ 19%)  
β-actin (for α-synuclein)  
β-actin (for phospho-α-synuclein)

(B)  

(C) Migdalska et al Annals of Neurology 2016

Ambroxol in Modification of Parkinson Disease
AiM-PD

Stephen Mullin PhD, MRCP1,2 Laura Smith MSc.1 Katherine Lee MSc.1 Gayle D’Souza MSc.3 Phil Woodgate PhD1 Josh Efflein BSc.2 Jenny Hallqvist BSc.4 Marco Toffoli MD.1 Adam Streeter5 Joanne Hosking5 Wendy Heywood PhD4 Rajeshree Khengar PhD1 Phil Campbell MRCP1 Jason Hehir BSc.5 Sarah Cable BSc.1 Kevin Mills PhD, Henrik Zetterberg PhD, MD1,8,9,10, Patricia Limousin PhD, MD.1 Vincenzo Libri PhD, FRCP5 Tom Foltynie PhD, MRCP1 Anthony HV Schapira MD, DSc, FRCP, FMedSci1

Mullin et al JAMA Neurol in press
End points

6 month treatment, 1.2g
• Target engagement: increased GCase protein
• Safety
• CSF ambroxol levels
• Effects on GBA mutation pos and neg PD

Mullin et al JAMA Neurol in press

CSF Ambroxol levels

Mullin et al JAMA Neurol in press
CSF GCase protein and blood activity

End points

- Safety - confirmed
- CSF ambroxol levels – mean 11% of blood
- Target engagement: 35% increased CSF GCase protein
- Increased CSF total alpha-synuclein levels 13%
- Effects on GBA mutation positive and negative PD