In at least half of Parkinson's disease (PD) patients, abnormal aggregation of α–synuclein fibrils starts from the intestinal neural plexus

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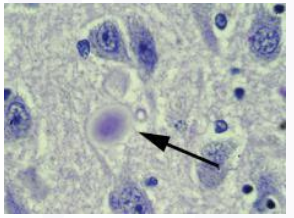
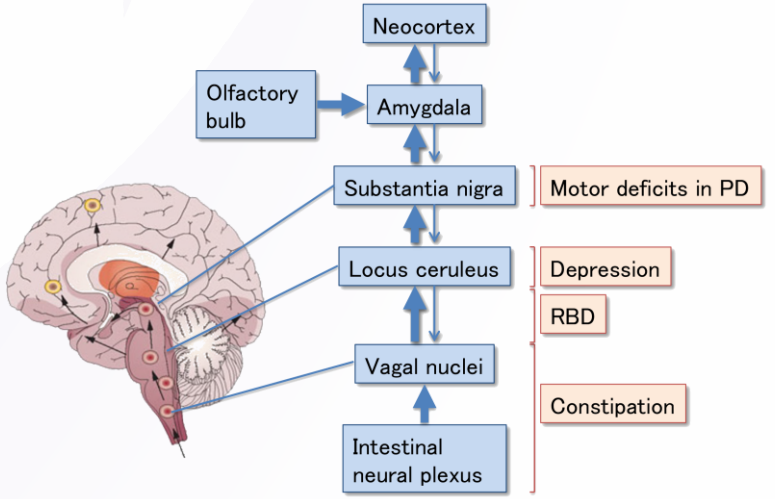
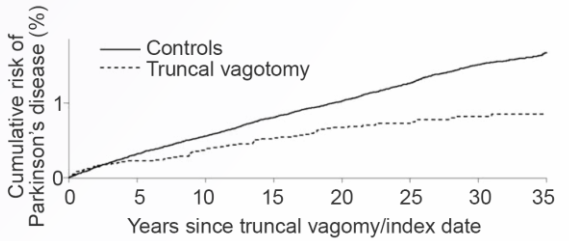
1. Abnormal aggregation of α-synuclein fibrils (Lewy bodies) ascends from the dorsal vagal nucleus to the substantia nigra in PD (*J Neurol* 249 S3: III/1, 2002).
2. Constipation, REM sleep behavior disorder (RBD), and depression precede 20, 10, and 5 years before the onset of PD (*Lancet* 386: 896, 2015).
3. Abnormal aggregation of α-synuclein fibrils is frequently observed in colon biopsies in PD (*Gastroenterol Res Pract* 2015: 476041, 2015).
4. Lewy bodies behave like prions (*Proc Natl Acad Sci USA* 112: E5308, 2015; *Science* 349: 1255555, 2015).
5. Enteroendocrine cells directly synapse to the vagal nerve (*Science* 361: eaat5236, 2018), and a synaptic pathway exists up to the substantia nigra and the striatum (*Cell* 175: 665, 2018).
6. Vagotomy reduces the risk of PD to ~50% in Denmark (*Ann Neurol* 78: 522, 2015) and Sweden (*Neurology* 88: 1996, 2017).
7. Inflammatory bowel diseases (Crohn disease and ulcerative colitis) increase the risk of PD 1.22-to-1.35 folds in five countries (*Inflamm Bowel Dis* 22: 1049, 2016; *JAMA Neurol* 75: 939, 2018; *Gut* 68: 3, 2019; *Inflamm Bowel Dis* 25: 111, 2019).

1

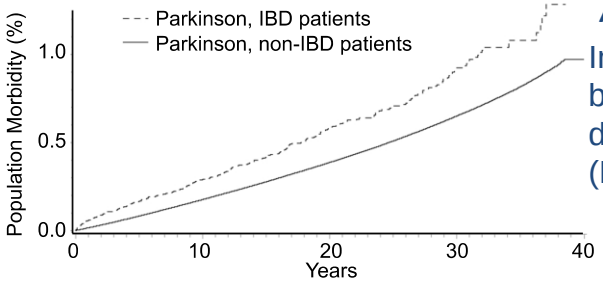


Lewy bodies in the substantia nigra





6
Vagotomy (Denmark)



7
Inflammatory bowel disease (Denmark)

In DLB, short-chain fatty acids (SCFA)-producing bacteria were decreased, and *Ruminococcus torques* and *Collinsella* were increased

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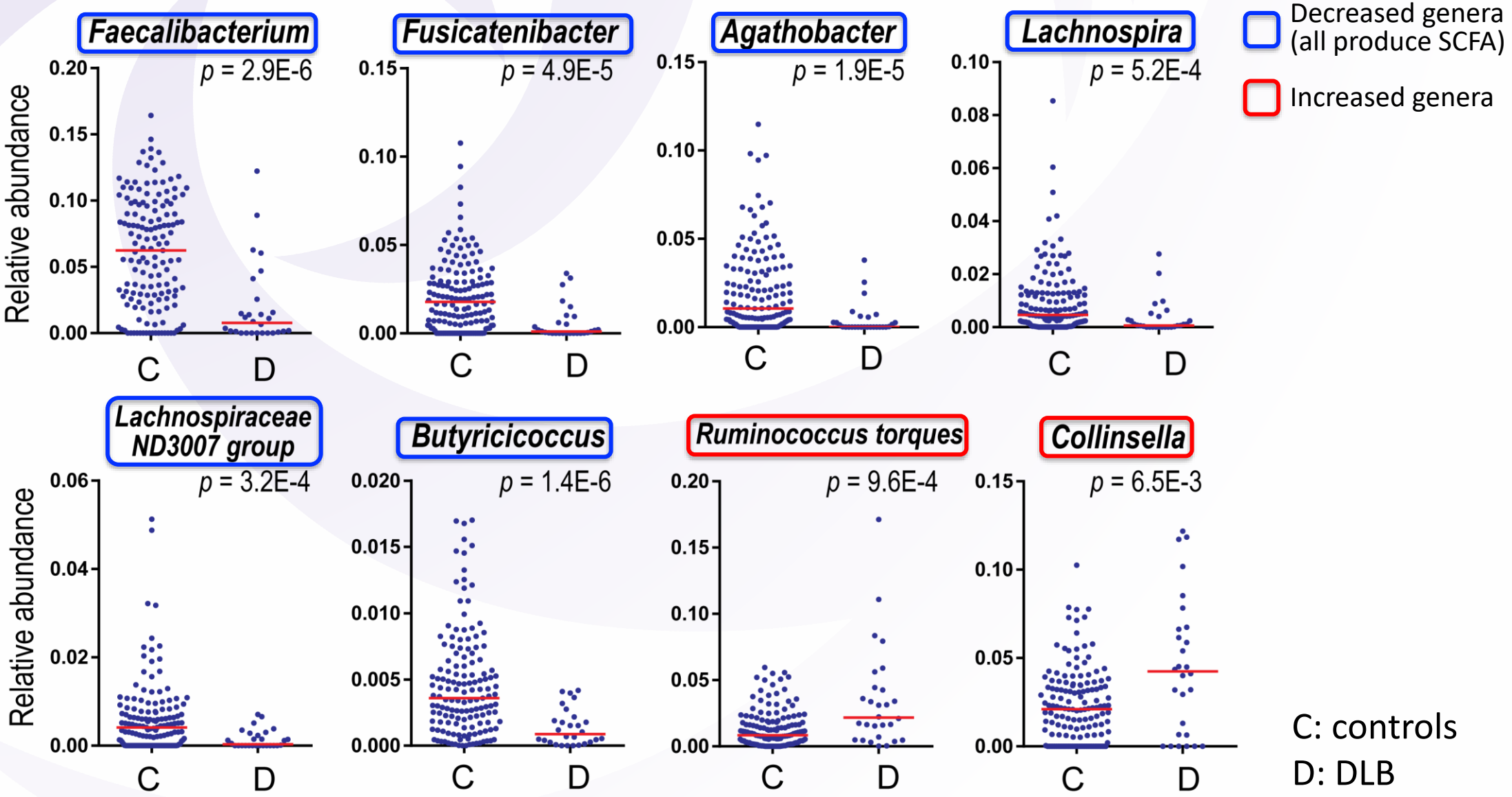

Differentiation of DLB and Parkinson's disease dementia (PDD) by a topological data analysis tool, *tmap*

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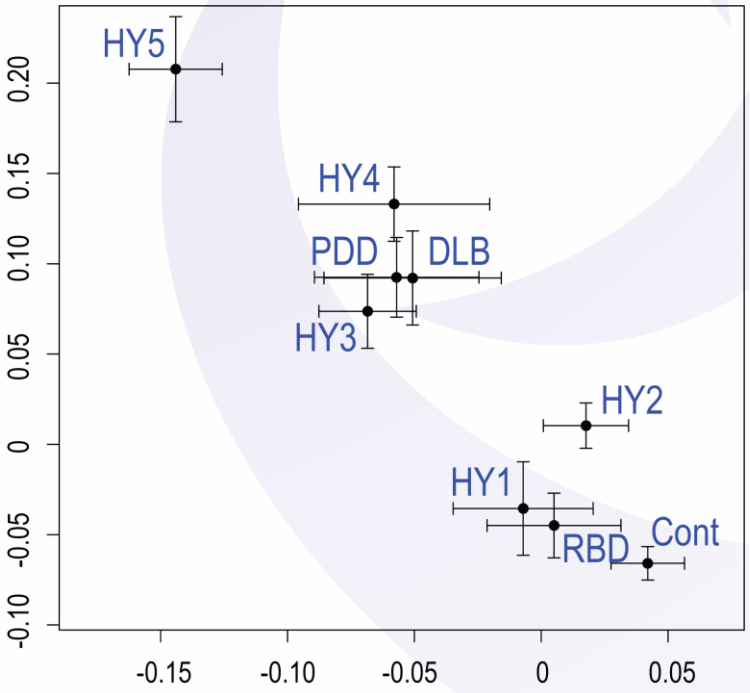
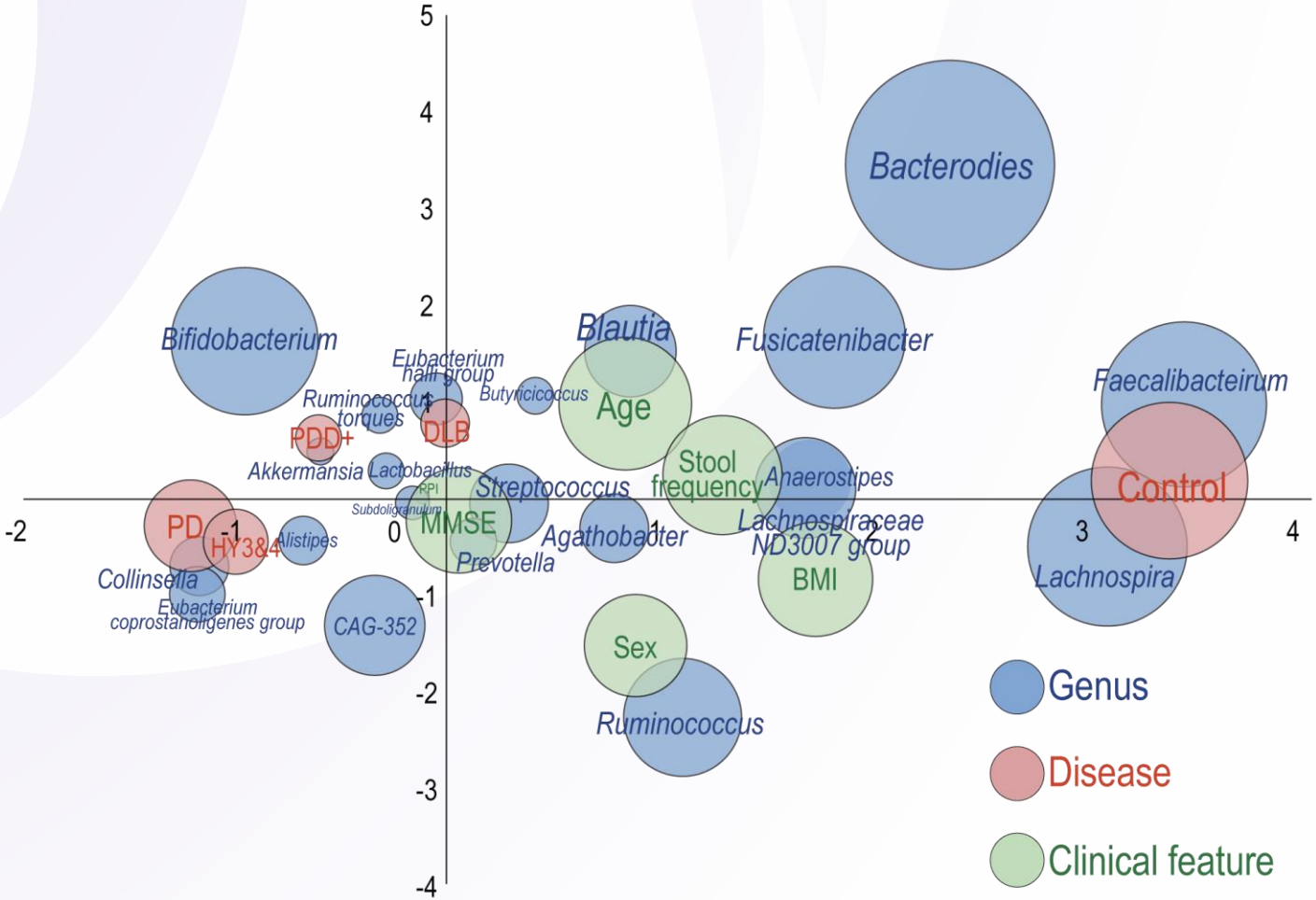
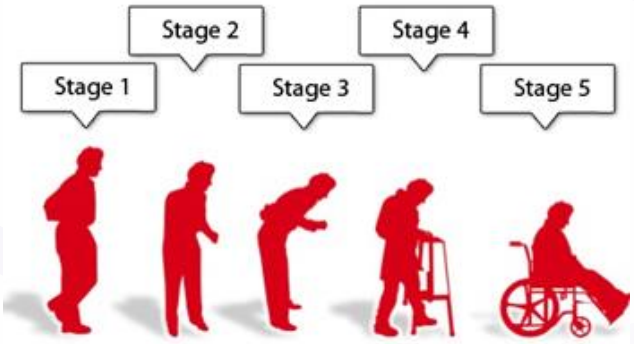
PCoA (center of gravity and SEM)







Hoehn & Yahr (HY) stages 1-5

RBD: idiopathic REM sleep behavior disorder
HY1-5: Hoehn & Yahr stages 1-5
DLB: dementia with Lewy bodies
PDD: Parkinson's disease dementia

Random forest model to differentiate dementia with Lewy bodies (DLB) and Parkinson's disease (PD) at Hoehn and Yahr stages 3&4 revealed three essential intestinal bacteria

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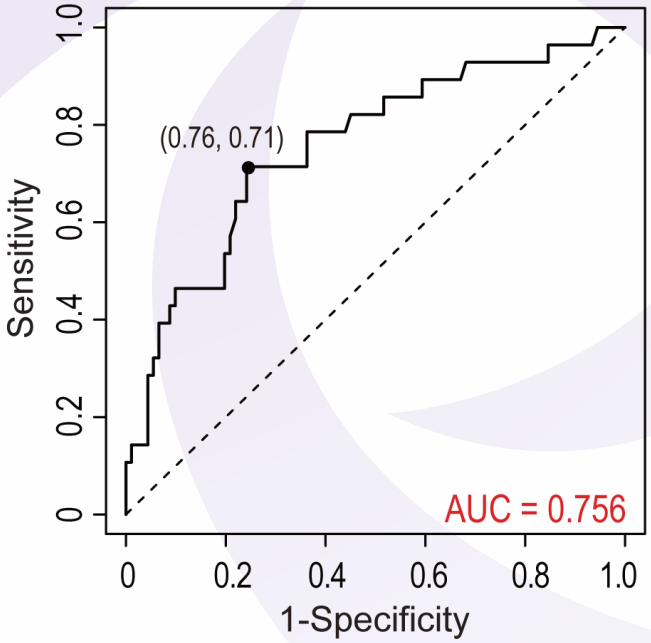
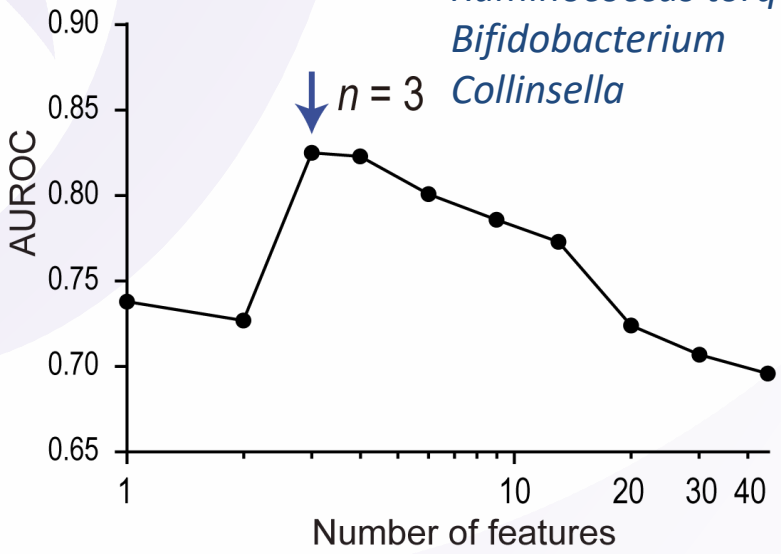
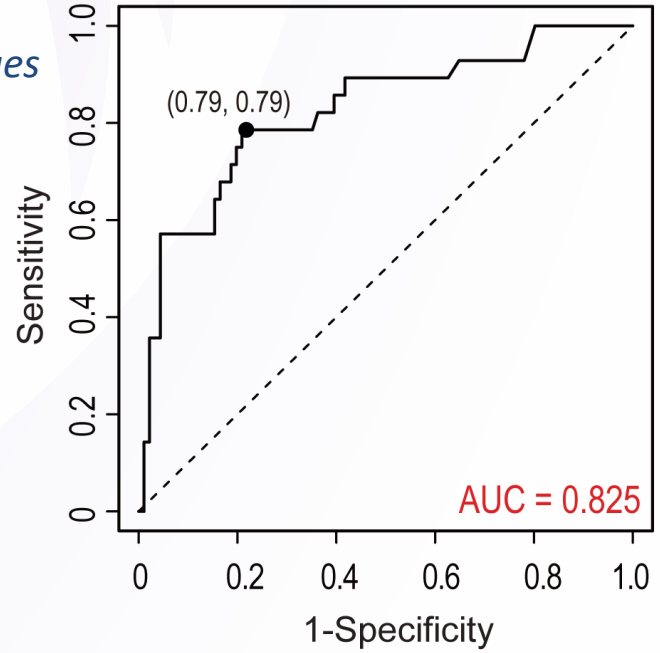
a) ROC curve by nested cross-validation



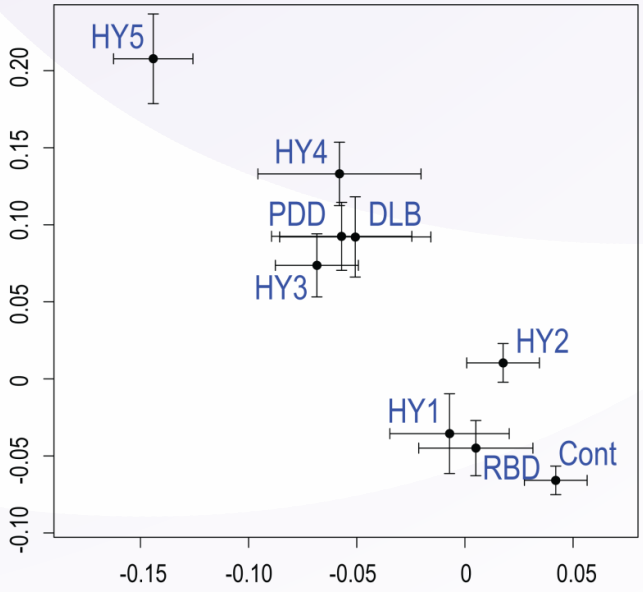
b) Feature elimination by recursive feature elimination (RFE)

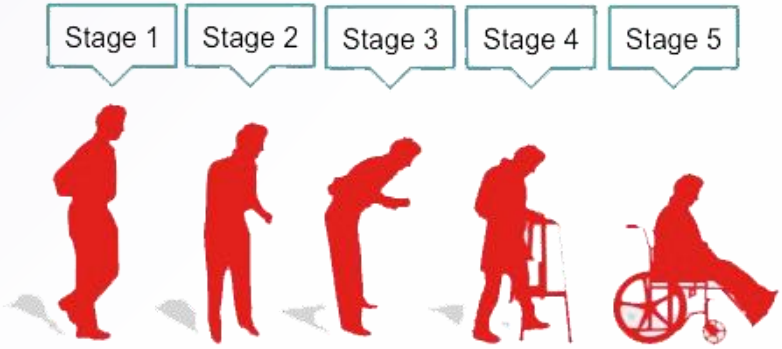


c) ROC curve by cross-validation



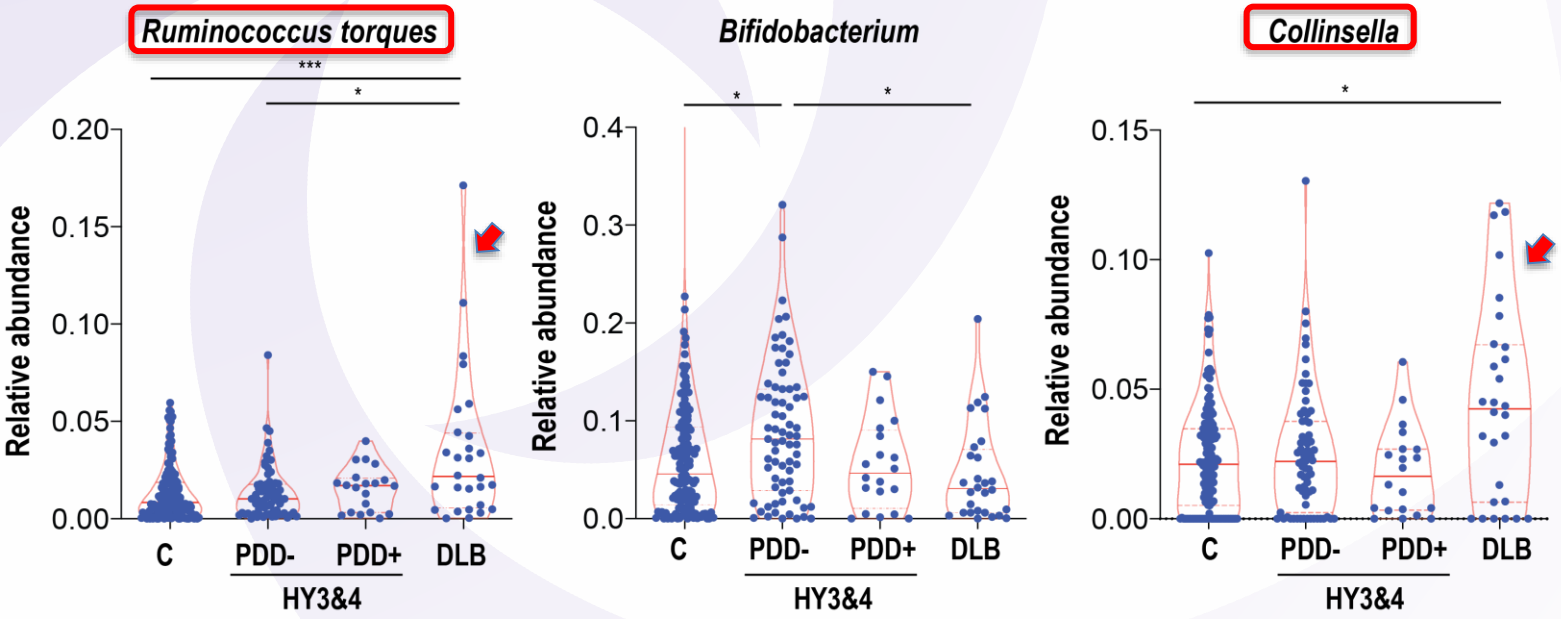
PCoA (center of gravity and SEM)

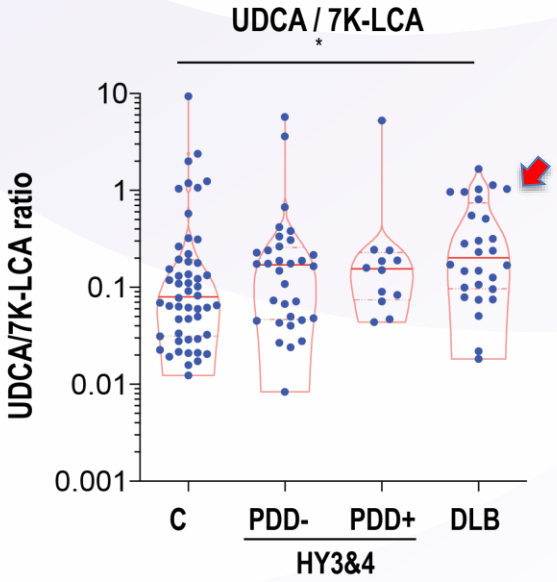


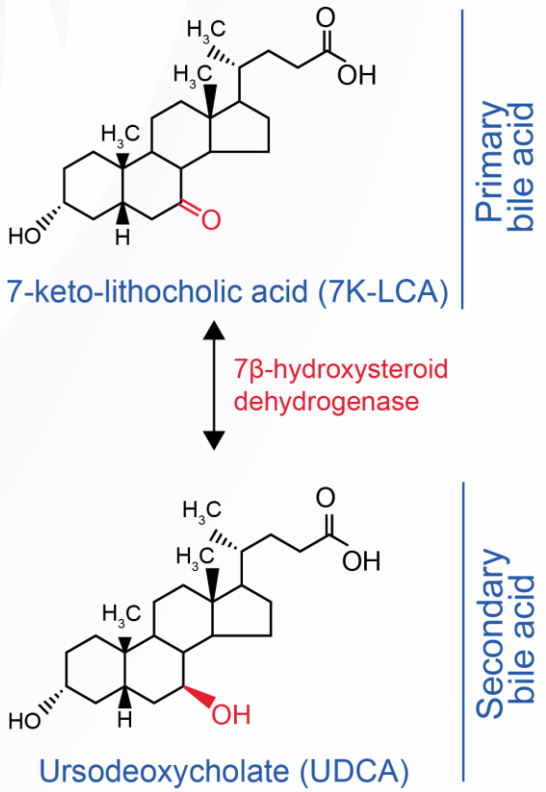


Hoehn & Yahr (HY) stages

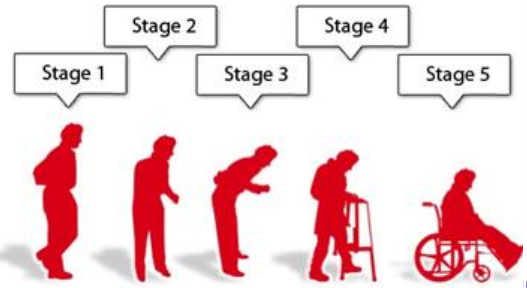
- ***Ruminococcus torques*** **and** ***Collinsella*** **are major secondary bile acids-producing bacteria**
- **Intestinal ursodeoxycholate (UDCA) / 7-keto-litocholate (7K-LCA) was high in DLB**







Hoehn & Yahr stages 1-5



Secondary bile acid-producing genera

Gut-Brain axis in Parkinson's disease (PD), idiopathic REM sleep behavior disorder (iRBD), and dementia with Lewy bodies (DLB)

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1. *Akkermansia*↑ (PD, iRBD, DLB)

Mucin↓ → Intestinal permeability↑ → Abnormal aggregation of α-synuclein fibrils in intestinal neural plexus ↑

2. Short-chain fatty acids (SCFA)-producing bacteria↓ (PD, DLB)

SCFA↓ → Vagal GPR41 stimulation↓ → GLP-1↓ → Microglial activation↑

3. Secondary bile acids-producing bacteria↓ (DLB)

Secondary bile acids↓ → Neuroinflammation in substantia nigra↓

a. UDCA suppresses pro-inflammatory cytokines (*Mol Neurobiol*, 56: 267, 2019, *PLoS One*, 12: e0180673, 2017).
b. UDCA have anti-oxidant and anti-apoptotic effects (*Oncol Rep*, 38: 3632, 2017, *Biochem Pharmacol*, 64: 1661, 2002).
c. UDCA have mitochondrial protective effects in mouse models of Alzheimer's disease (*Neurobiol Dis*, 50: 21, 2013, *Mol Neurobiol*, 45: 440, 2012).
d. UDCA is effective in mouse models of PD (*Neurosci Lett*, 741: 135493, 2021, *Neurology*, 85: 846, 2015).
e. Substantia nigra is more vulnerable to neuroinflammation than neocortex or hippocampus (*J Neuroinflammation*, 18: 225, 2021).
f. The onset of DLB and PDD is more than 10 years later than that of PD (*Mol Neurodegener*, 14: 5, 2019).

UDCA, ursodeoxycholate