"Skin α-Synuclein Aggregation Seeding Activity as a Novel Biomarker for Parkinson Disease"

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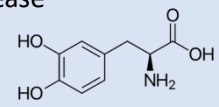
Parkinson's Disease (PD) Background

- Second most common neurodegenerative disease[1]
- Characterized by symptoms such as[6]
  - Shaking or tremors at rest
  - Bradykinesia (slowness of movement)
  - Muscle stiffness
  - Cognitive changes such as dementia, depression, and/or anxiety
- No existing cure
- Existing treatments target symptoms, not the source of disease



L-dopa structure

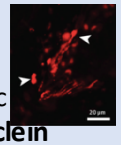
Diagnosis

Current diagnostic techniques are lacking. By the time of diagnosis a large amount of dopaminergic neurons have already died. Therefore, development of early diagnostic techniques are critical for early distribution of treatment.

α-synuclein

α-synuclein: a small, insoluble protein, composed of 140 amino acids and encoded by the SNCA gene[2]

- Normal role: involved with vesicle tracking, vesicle docking, and neurotransmitter release, however still uncertain
- PD brains are have abnormal α-synuclein behavior… which is why PD is classified as a synucleinopathy
  - ➢ Lewy Bodies: clumps of α-synuclein and other proteins that aggregate in regions of the brain
  - ➢ Oligomerization of α-synuclein is hypothesized to be toxic



- Autopsies show neuronal death (specifically in dopaminergic neurons) that could be **linked** to the aggregation of **α-synuclein**
  - Neuronal death in basal ganglia region of brain
- Immunohistochemistry and immunofluorescence has detected a-synuclein in peripheral tissues…. however inaccurate for diagnosis

Found that misfolded a-synuclein exhibits "prion-like aggregation seeding ability", meaning that it will trigger other proteins to also misfold, and the clumps of abnormal proteins will proliferate. This is a possible explanation for how neuronal death spreads through the brain

Article Goal:

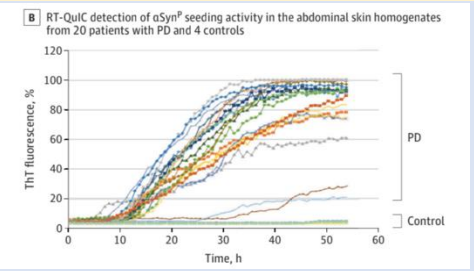
Assess α-synuclein presence in peripheral skin tissue as a contender for a synucleinopathic disease biomarker. This could be beneficial because….

- Could show confirmation of PD *before* the disease progresses far and symptoms show
- Would be a minimally invasive technique, as peripheral tissue is easier to access than the brain
- Would provide a way to monitor changes induced by therapies that target α-synuclein (which currently exist!)

Experimental Information

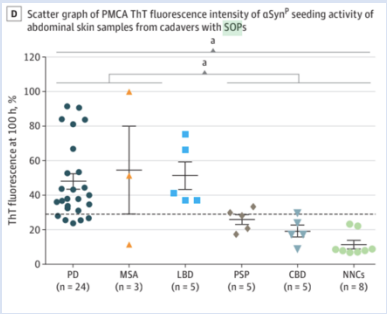
- Skin samples from 130 autopsies
  - Cadavers had a variety of neurodegenerative diseases: PD, Lewy body dementia, multiple system atrophy, and tauopathic diseases, along with controls
  - Diagnosis was confirmed by neuropathological tissue exams
- Skin samples from 41 biopsies
  - Diagnosed PD patients and controls only
  - Obtained from leg or posterior cervical region of neck

1. First confirmed presence of a-syn by IHC and IF
2. Used real-time quaking-induced conversion (RT-QuIC)
   - The presence of an abnormal a-syn protein prion protein will form aggregates known as amyloids that fluoresce
3. Used protein misfolding cyclic amplification (PMCA assays)
   - A technique conceptually similar to PCR that involves leaving prion with normal protein, so that the normal protein is converted. Ultrasound then breaks up protein so to repeat



RT-QuIC & PMCA Assay:

- Increased levels of fluorescence for synucleopathies compared to control



"To our knowledge, this study has demonstrated for the first time that skin a-synuclein has aggregation seeding activity that was significantly higher in individuals with PD and other synucleopathies than in those with tauopathies and NNCs"

Limitations

- Compared to PD and "normal" cases, not enough non-PD synonucleopathies examined
- More skin biopsies would be helpful
- (!)Remember, diagnosis of PD from clinical symptoms is not precise, so the separation of PD s non-PD may not be reliable
  - Follow up with autopsies

Sources

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