Tracing Biomarker Trajectories Through Parkinson's Disease from Cross-sectional Data in the UK Biobank

Evan Boyle, Ludmila Volobouevа, Katrina Paumier, William Hagstrom, Ferhan Qureshi, David Brazel
Octave Bioscience, Inc, Menlo Park, CA, USA

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Introduction

Background: Parkinson's disease (PD) can disrupt a wide range of physiological processes, including inflammation, digestion, hormone signaling, and cognition. Multiple groups have spotlighted protein biomarkers for early detection of PD but data comparing early- and late-stage changes are lacking. Whether blood biomarker signals persist throughout disease progression has consequences for both disease detection and monitoring.

Objectives

1. To enumerate blood-based molecular biomarker changes relative to the emergence of clinical signs in PD.
2. To propose mechanisms underlying biomarker signals observed across PD cohorts.

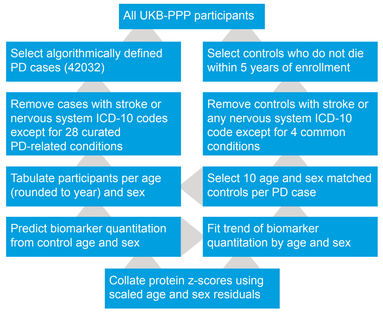

Figure 1: Flow chart for ascertaining 602 UK Biobank Pharma Proteomics Project participants with PD and 6,026 matched controls and computing protein z-scores from matched control data

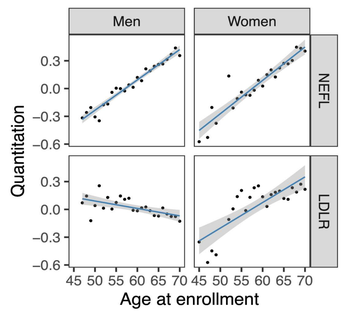

Figure 2: Visualization of diverging age and sex trends for two proteins: neurofilament light polypeptide (NEFL) and low-density lipoprotein receptor (LDLR). Quantitation is in relative $\log_2$ units (NPX). Observations are binned by age rounded to year.

Methods

602 confirmed PD patients and 6,026 age- and sex-matched neurologically healthy controls (NHCs) with proteomic profiling were ascertained in the UK Biobank Pharma Proteomics Project (UKB-PPP). Parkinson's protein abundances were standardized to z-scores relative to NHCs using age, sex, and average protein abundance. We performed Mann-Whitney U tests for cases both before and after diagnosis vs NHCs, Cox proportional hazard modeling for survival and reverse time survival analyses, and Pearson correlation for protein abundance vs time relative to the PD algorithmically determined diagnosis date. Similar analyses were performed in Parkinson's Progression Markers Initiative (PPMI) cases stratified by initiation of dopaminergic medication plus association with MDS-UPDRS scores using generalized least squares regression. Protein trajectories for each were visualized as moving window averages.

Findings

- **Late PD biomarkers** | The greatest changes in plasma protein signal occurred years after diagnosis: see DDC, PRL, LEG1, and BCHE.
- **Early PD biomarkers** | A small number of proteins changed early in disease before attenuating after diagnosis: see BAG3, DPEP1, DCTPP1, and B3GNT7.
- **Stable PD biomarkers** | Several proteins changed years before diagnosis and persisted after initiating dopaminergic therapy: see HPGDS, PEPD, and PPME1

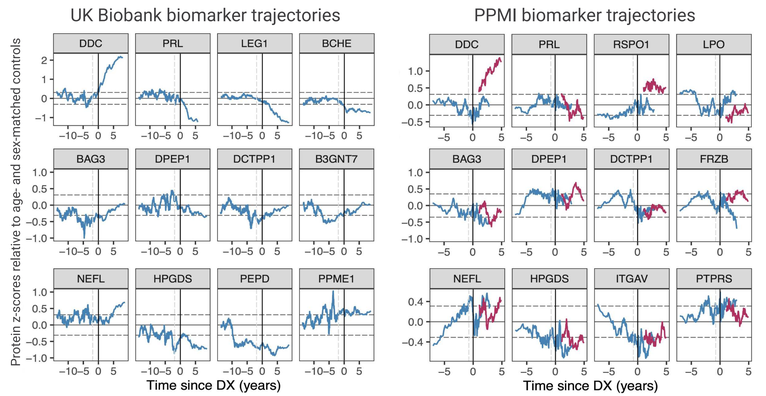

Figure 3: Biomarker trajectories in UK Biobank Explore 3072 and PPMI Explore 1536 Olink data. In PPMI trajectories, participants are stratified into unmedicated (blue) and medicated (maroon) groups. Dashed horizontal lines are 95% confidence intervals for a standard normal window mean (40 individuals in UKB and 30 in PPMI). Not all proteins assayed in the UKB-PPP were available in the PPMI dataset.

- **UKB hit biomarkers (left)** | Most PD biomarkers were hits in only one association. Pre diagnostic risk markers had the greatest sample size and yield.
- **PPMI hit biomarkers (right)** | Biomarkers best tracked with disease duration followed by MDS-UPDRS part total score.

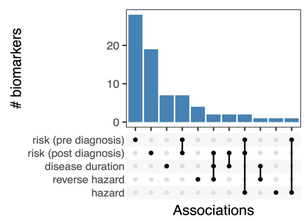

Figure 4: Upset plot of the yield of hit biomarkers across all tested associations in the UK Biobank dataset.

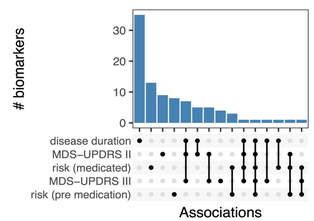

Figure 5: Upset plot of the yield of hit biomarkers across all tested associations in the PPMI dataset

Interpretation

- Dopamine decarboxylase (DDC) appears to respond to levodopa administration
- Prolactin (PRL) appears to respond to dopamine agonist administration.
- Some neuroendocrine biomarkers visible late in disease (GHRL, ERBB3, EGFR) are not detected before clinical diagnosis.
- Inflammatory and neuromuscular proteins that differ early in disease such as AHNAK, integrin alpha-V (ITGAV), hematopoietic prostaglandin D synthase (HPGDS), and neurofilament light polypeptide (NEFL) usually persist later in disease
- Candidate early detection biomarkers seldom change monotonically across full disease duration and do not track MDS-UPDRS subtotals.

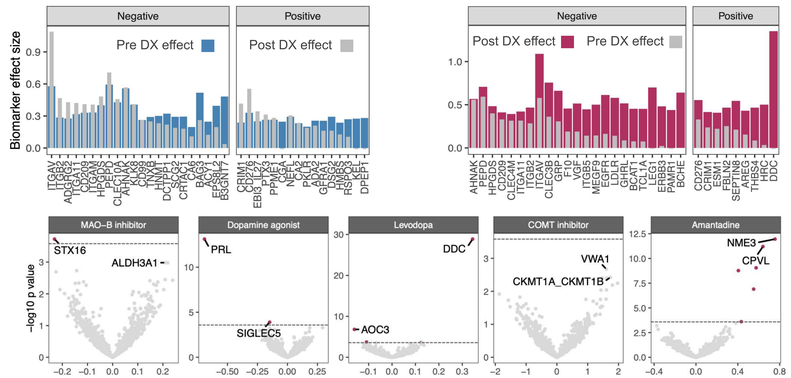

Figure 6: UKB PD biomarkers discovered in cases before (upper left, in blue) or after (upper right, in maroon) algorithmically determined PD diagnosis date. The effect size in the complementary analysis is shown in gray bars. PPMI medication dosage volcano plots (below) showing biomarker associations with log LEDD or COMT use

Conclusions

We confirm that blood biomarker signals appear seven or more years in advance of the emergence of clinical signs. Candidate biomarkers for PD exhibit diverse trajectories, and biomarkers linked to the same physiological process often share similar trajectories. Proteomic changes due to common Parkinson's medications are substantial and most likely overshadow molecular disease progression signal. We conclude that successful monitoring of PD patient physiology with blood-based biomarkers should be contextualized with disease duration, matched control ranges, and medications employed by the patient to improve reliability of biomarker-derived insights.

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References: Sun BB, Chiou J, Traylor M, Benner C, Hsu YH, Richardson TG, Surendran P, Mahajan A, Robins C, Vasquez-Grinnell SG, Hou L. Plasma proteomic associations with genetics and health in the UK Biobank. Nature. 2023 Oct 12;622(7982):329-38.
Rutledge J, Lehallier B, Zarifkar P, Losada PM, Shahid-Besanti M, Western D, Gorijala P, Ryman S, Yutsis M, Deutsch GK, Mormino E. Comprehensive proteomics of CSF, plasma, and urine identify DDC and other biomarkers of early Parkinson's disease. Acta neuropathologica. 2024 Jun;147(1):52.

Correspondence: eboyle@octavebio.com