

Sex-based Clinical and Proteomic Patterns in autopsy-confirmed Lewy body disease



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BACKGROUND

- Lewy body disease (LBD) is clinically heterogeneous, spanning cognitive, motor, and neuropsychiatric features
- Sex differences are seen in prevalence, phenotype, biomarkers, and outcomes, but their biological correlates are not well defined
- Prior work shows sex-specific associations in AD proteomics
- Despite known sex differences across domains, plasma proteomic signatures in LBD remain uncharacterized

METHODS

- Participants:** Autopsy-confirmed LBD cases (n=186) and controls (n=99) from the BBDP with complete clinicopathologic characterization and plasma proteomics available.
- Clinical & neuropathologic measures:** Demographics; cognitive (MMSE, CDR, CDR-SB) and motor (UPDRS-III) status closest to death and blood draw; Lewy body stage and density; AD co-pathology.
- Plasma proteomics:** 126 proteins quantified via multiplex NULISA platform (Alamar Biosciences); NPQ values used for analyses.
- Statistics:** Unadjusted sex differences examined using Wilcoxon rank-sum tests. Significant proteins (FDR q<0.05) were further evaluated using multivariable linear regression adjusting for age, education, disease severity (CDR-SB), AD co-pathology, and blood draw-to-autopsy interval.

FINDINGS

Table 1. Demographic and clinical characteristics by sex in an autopsy-confirmed LBD cohort.

Characteristic	Women (n = 66)	Men (n = 120)	P value
Sex distribution, n (%)	66 (35.4)	120 (64.5)	<0.001*
Age at death, years	86.9 (8.8)	83.4 (7.4)	0.06
Age at blood draw, years	84.0 (9.2)	81.1 (7.2)	0.043*
Education, years	14.3 (2.5)	16.0 (3.1)	<0.001*
MMSE closest to blood draw	23.1 (7.4)	24.3 (12.4)	NS
UPDRS-III closest to blood draw	12.9 (15.0)	19.4 (17.8)	0.023*
CDR closest blood draw	0.8 (0.9)	1.0 (0.9)	NS
CDR-Sum of Boxes closest to blood draw	4.7 (5.7)	5.9 (5.4)	0.048*
Last MMSE	20.7 (8.7)	20.4 (7.7)	NS
Last UPDRS-III	27.7 (20.3)	25.9 (21.3)	NS
Dementia prevalence (y, %)	56.1	66.7	NS
USSLB stage	2.8 (0.9)	3.0 (0.9)	NS
Total Lewy body density	19.5 (12.6)	22.6 (11.3)	NS

Table 2. Adjusted associations between sex and plasma proteins in LBD (female vs. male).

Protein	Direction	Adjusted β (F vs M)	95% CI	Adjusted p
CCL22	F > M	0.3621	0.1051–0.6191	0.0061
NPTX1	F > M	0.2429	0.0722–0.4136	0.0056
APOE	F > M	0.4393	0.2349–0.6437	<0.0001
ICAM1	F > M	0.1051	–0.0502–0.2605	0.1830
BACE1	F > M	0.1407	0.0223–0.2591	0.0202

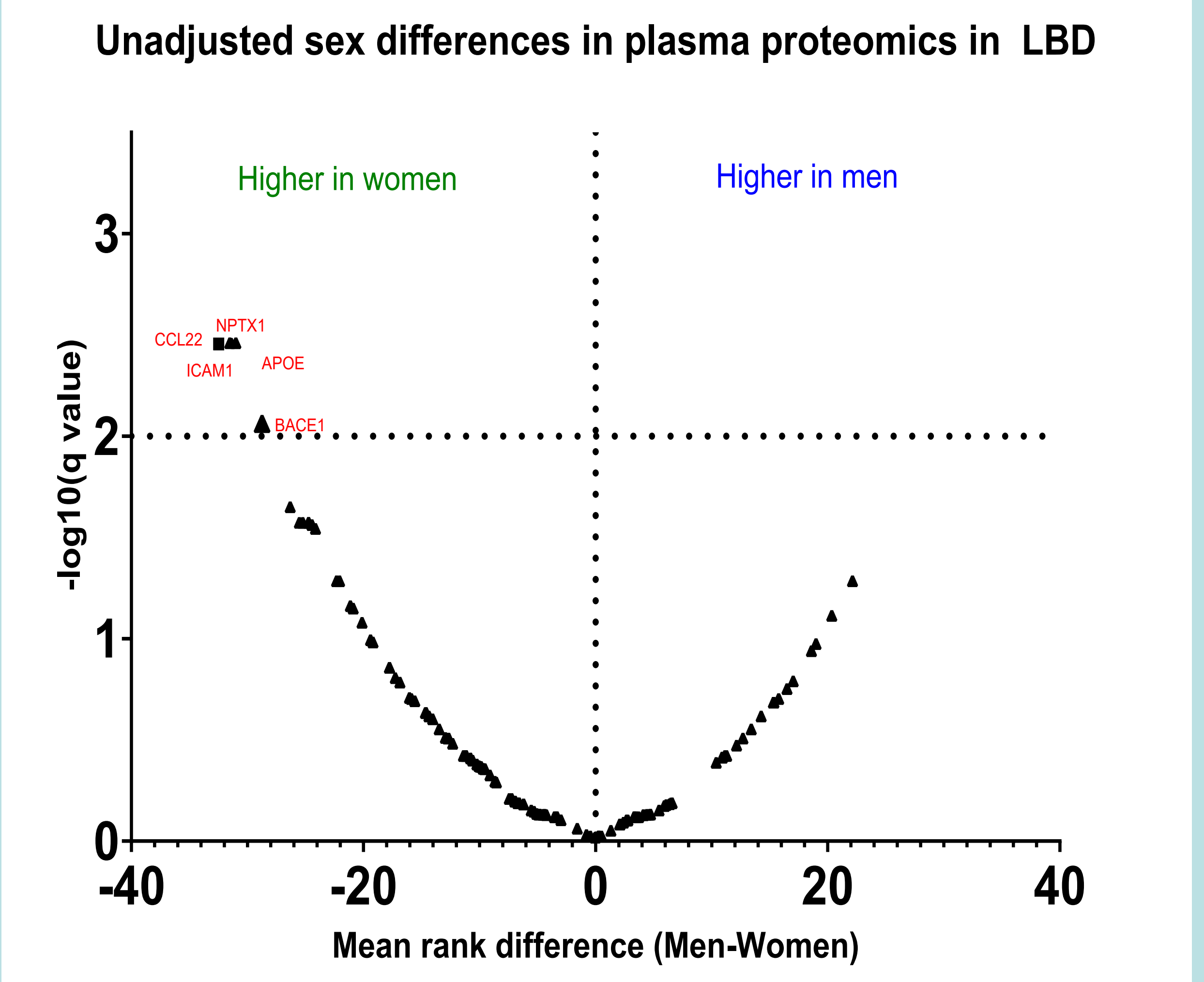


Figure 1. Sex differences in plasma proteomics in LBD (unadjusted). Volcano plot of mean rank differences (men – women) versus $-\log_{10}$ q-value. Five proteins were significantly elevated in women (q < 0.01, dotted line): NPTX1, CCL22, APOE, ICAM1, and BACE1. No proteins reached significance in men.

INTERPRETATION

- The cohort was largely characterized by **mild dementia (mean CDR–SB of ~4.5–5.5)** at the time closest to plasma collection.
- In a well-characterized autopsy cohort, sex differences in plasma proteomic profiles were observed in Lewy body disease.
- Several proteins showed sex-biased abundance in LBD in unadjusted discovery analyses.
- Proteins implicated span pathways relevant to **neurodegeneration, inflammation, and co-pathology**, highlighting biologic heterogeneity by sex.
- Comparable analyses in controls showed absent sex-based proteomic differences.

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