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INTRODUCTION

Background: Sex influences susceptibility, progression, and clinical presentation of neurodegenerative diseases¹, but the contribution of sex-specific inflammatory biology remains incompletely understood. While previous studies have reported sex differences in blood and cerebrospinal fluid (CSF) inflammatory biomarkers, these have largely been limited to individual diseases²⁻⁸. **Objective:** To systematically evaluate a large panel of CSF inflammatory biomarkers across neurodegenerative diseases to identify shared sex-dependent inflammatory mechanisms.

METHODS

Participants: Neurodegenerative disease (ND) participants (n = 200; 115F, 85M) and healthy controls (HC; n = 55; 28F, 27M) were analyzed separately. **Protein Quantification:** CSF inflammatory proteins (737 measured; 371 retained after quality control, preprocessing, and exclusion of assays with high MissingFreq) were quantified using Olink Explore Inflammation panels I and II (PEA technology), with expression reported as normalized protein expression (NPX, log₂ scale). **Statistical Analysis:** Linear regression assessed sex differences in biomarker levels, adjusting for age, assay plate, and diagnosis. Multiple testing was controlled using the Benjamini–Hochberg procedure.

Demographics of Subjects for Sex-Specific Biomarker Analysis				
Diagnosis	Sex M (n)	Mean Age SD	Sex F (n)	Mean Age SD
FTLD-Tau-related-syndromes	24	63.5 (13.4)	23	63.4 (14.1)
FTLD-TDP43-related-syndromes	29	59 (9.3)	34	59.1 (6.9)
Alzheimer's Disease (AD)	32	68.5 (8.6)	58	65.9 (9.2)
Healthy Controls (HC)	27	57.6 (13.3)	28	52.6 (14.9)

Stratified for FTLD-TDP43 and FTLD-Tau				
1. FTLD-Tau n total = 47	Sex M (n)	Mean Age SD	Sex F (n)	Mean Age SD
1.1 Genetically Confirmed (MAPT)	9	50.4 (8.6)	11	53 (10.7)
1.2 Pathologically Confirmed (Post-mortem)	4	71.2 (4.2)	4	79 (6.3)
1.3 Clinical Dx suggestive of Tau pathology (total)	11	71.3 (9.5)	8	69.9 (7.2)
1.3.1 Subtypes				
PSP	11		8	
2. FTLD-TDP43 n total = 63				
2.1 Genetically Confirmed (c9orf72; GRN)	18	57.2 (8)	30	58.3 (6.8)
2.2 Pathologically Confirmed	3	68.2 (9.5)	1	73.9 (0)
2.3 Clinical Dx suggestive of TDP43 pathology (total)	8	58.6 (9.4)	3	60.9 (3.2)
2.3.1 Subtypes				
ALS	1		0	
FTD-ALS	4		2	
svPPA	3		1	

Table 1: Participant demographics by diagnostic group. Demographics characteristics of study participants stratified by diagnostic category.

RESULTS

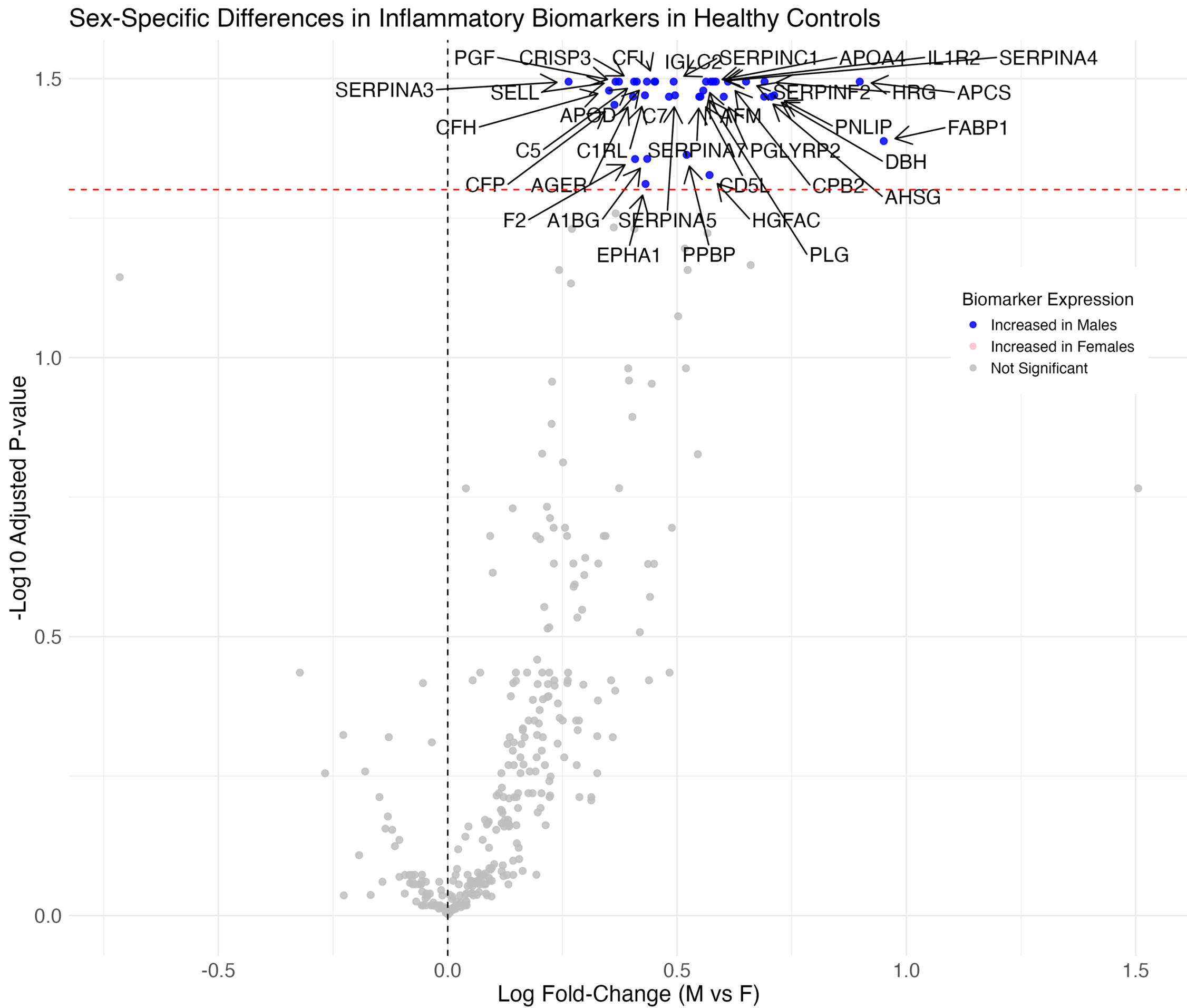


FIGURE 1. (A) Volcano plot showing differential expression of inflammatory biomarkers between males and females in HC. Positive log fold change values indicating higher expression in males and negative values indicating higher expression in females. The horizontal red dotted line indicates the statistical significance threshold (–log₁₀ adjusted p-value).

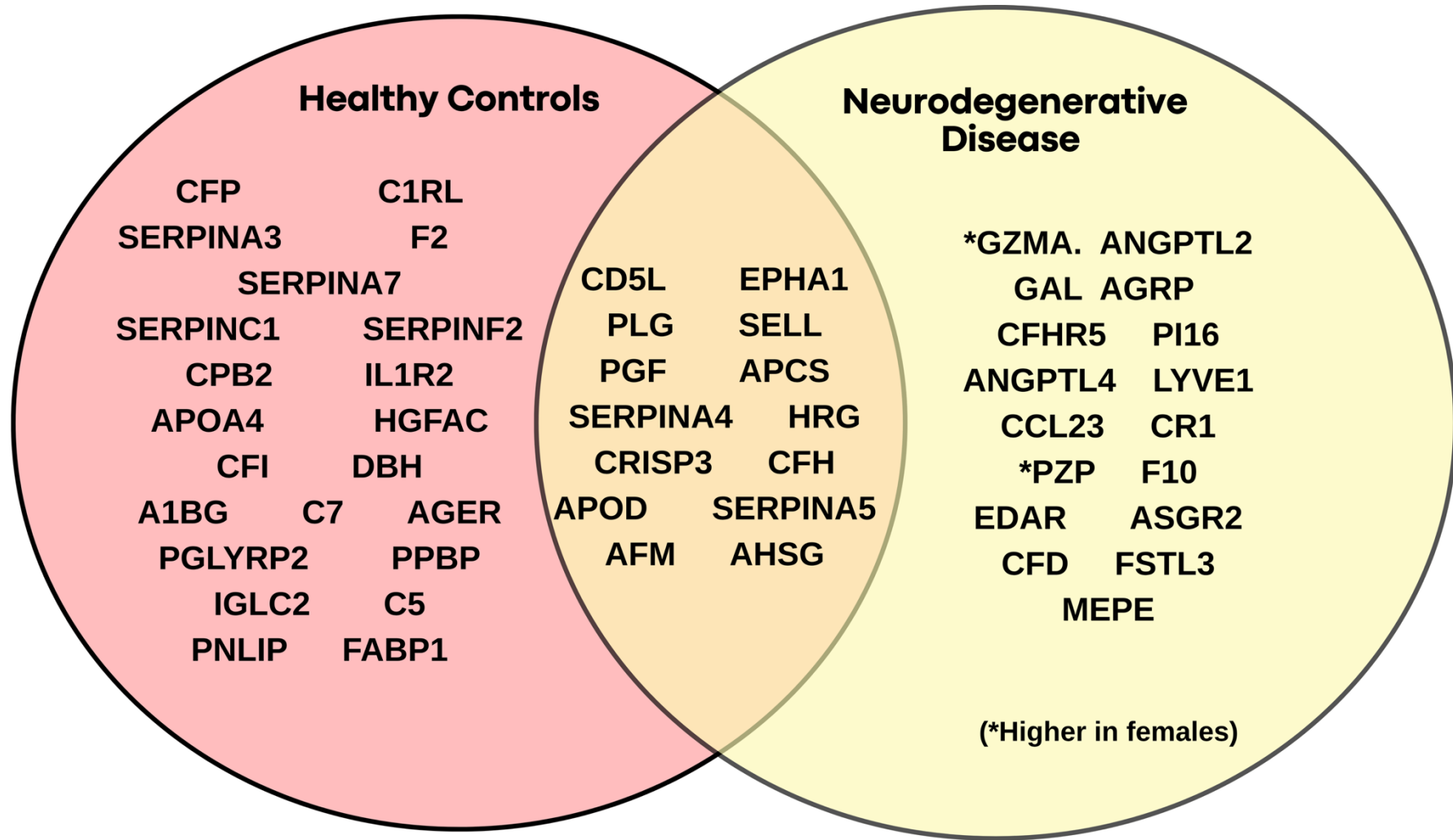


FIGURE 2. Venn diagram illustrating the overlap between HC and ND biomarkers. Of 31 sex-stratified biomarkers in ND, 14 overlapped with HC. The resulting 17 disease-specific biomarkers (15 elevated in males, 2 in females: GZMA and PZP) represent sex-specific inflammatory biomarkers.

KEY CONCLUSIONS

Sex differences in CSF inflammatory biomarkers were identified across neurodegenerative diseases and HC, with a greater proportion of biomarkers elevated in males. These findings suggest sex-dependent inflammatory signatures that may contribute to disease mechanisms, influence disease progression, and inform precision medicine approaches. **Next Steps:** We will examine associations between sex-related inflammatory biomarkers and neurodegeneration (NfL), clinical severity (CDR-SB), and disease progression in males and females.

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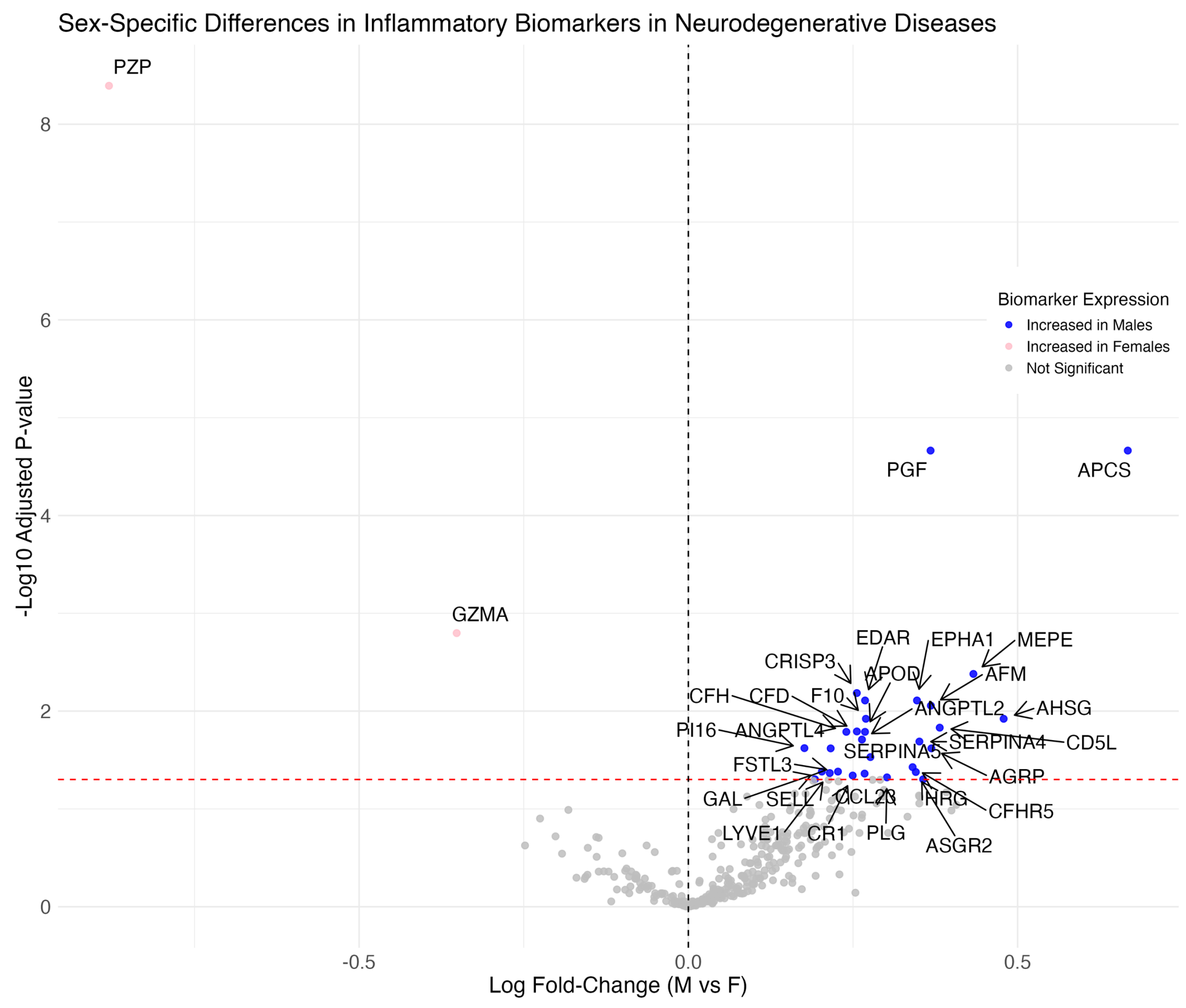


FIGURE 1. (B) Volcano plot showing differential expression of inflammatory biomarkers between males and females in ND cohort.

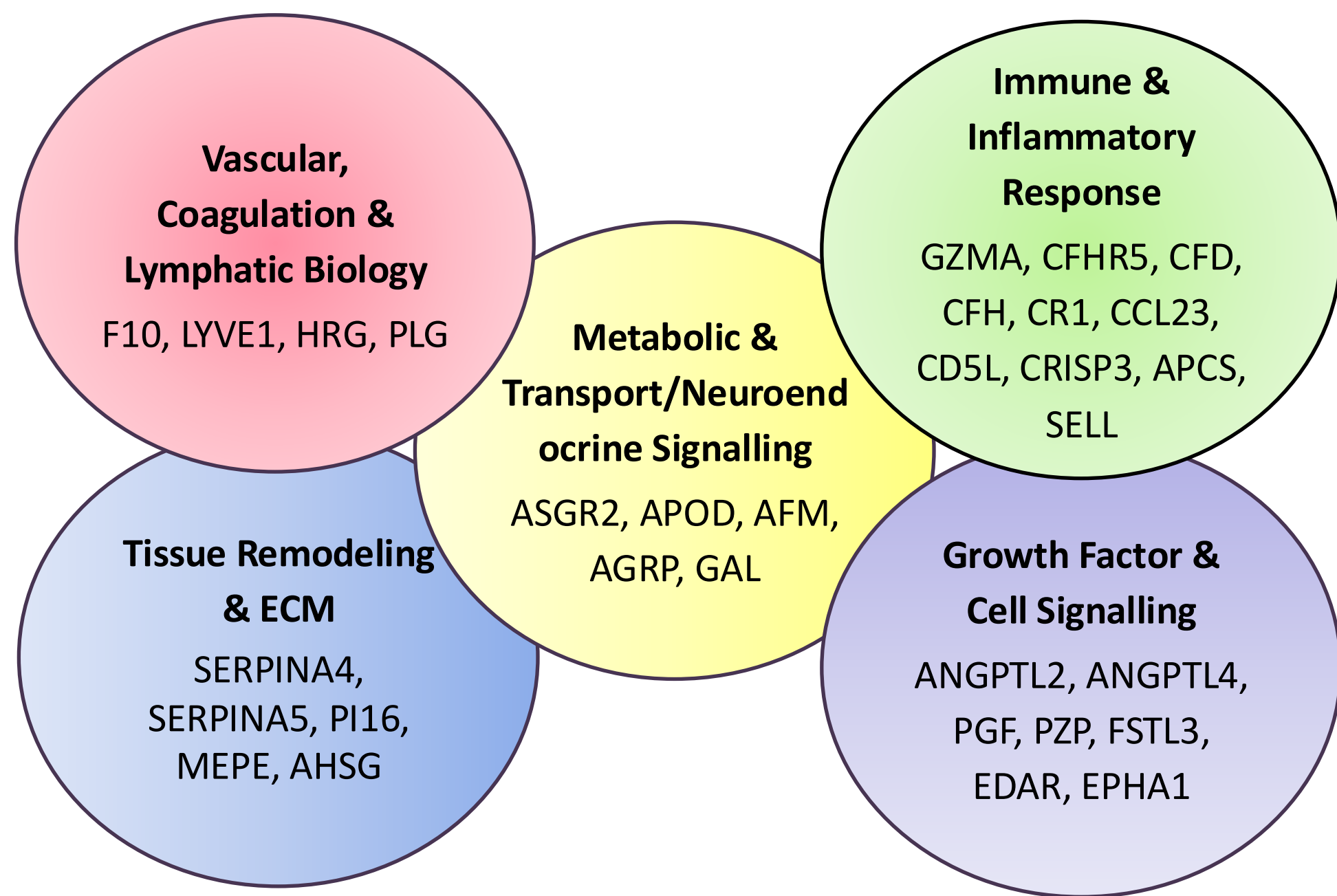


FIGURE 3. Functional classification of sex-associated inflammatory biomarkers identified by Olink Proximity Extension Assay (PEA). Significant biomarkers were grouped according to their primary biological functions using annotations from Olink and UniProt.

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