Sex-specific Transcriptomic, Proteomic Differences across Multiple Alzheimer's Disease Cohorts

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Introduction

In most regions worldwide, Alzheimer's disease (AD) has been shown to disproportionally affect women. The goal of this study is to better understand potential contributing or mediating factors to these sex-specific differences using data from three independent cohorts.

Material and Methods

Prefrontal cortex RNA samples obtained from the Netherlands Brain Bank (NBB)[1] were analyzed using Illumina bead chips arrays to identify genes differentially expressed between the sexes. These results were validated in the dorsolateral prefrontal cortices of an independent cohort from the Harvard Brain Tissue Resource Center (HBTRC) using a custom expression profiling array[2]. Proteomic validation of the identified gene of interest was performed using Mount Sinai Brain Bank (MSBB)[3] frontal pole brain specimens where both tandem mass tag (TMT) and label-free quantification LC-MS/MS were performed.

Results

In the NBB gene expression dataset, only eight DEGs were identified in male vs. female AD patients which did not also show a significant sex-specific difference in the controls. In the HBTRC transcriptomic dataset, 24 such DEGs were found. The overlap between the identified DEGs from both these datasets consisted of only one differentially expressed gene, CD99 (Figure 1). In both transcriptomic datasets, the controls showed sex-specific differences in CD99, but did not reach statistical significance (Figure 2).

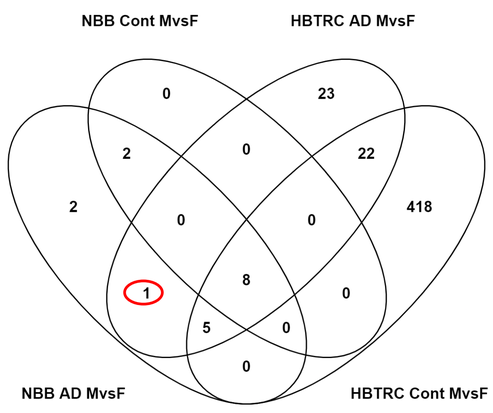

Figure 1. Venn diagram of DEGs comparing AD and controls, male vs. female in the transcriptomic datasets of Netherlands Brain Bank (NBB) and Harvard Brain Tissue Resource Center (HBTRC)

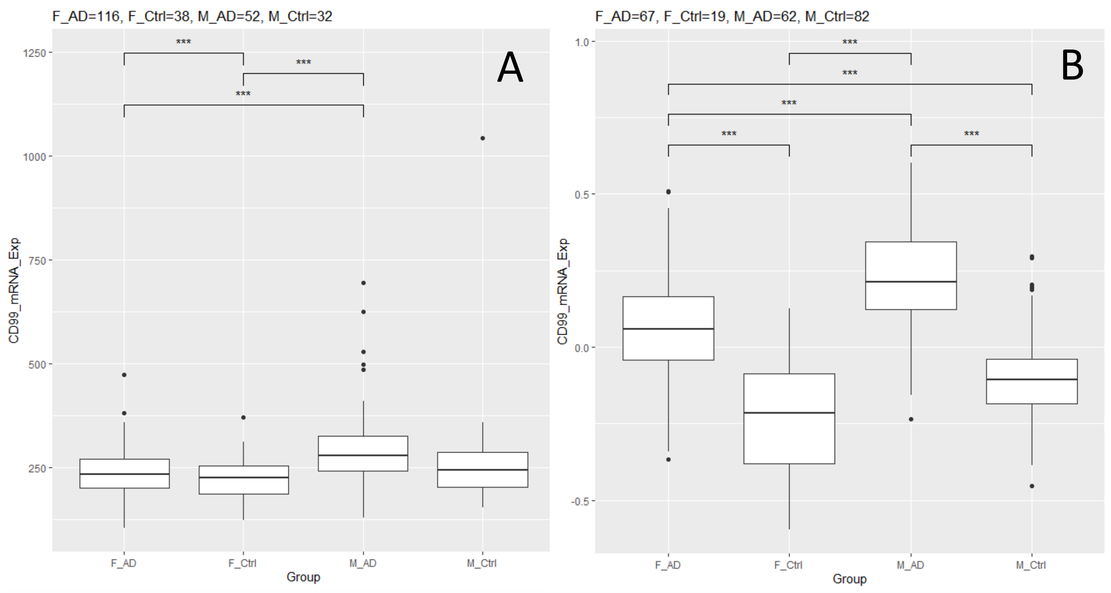

Figure 2. (A) NBB Illumina bead chip array results for CD99, for AD females (F_AD), control females (F_Ctrl), AD males (M_AD), male controls (M_Ctrl). The number of individuals in each group are indicated above each plot. Significant adjusted p-values (Benjamini-Hochberg procedure) are indicated (<0.5=*, <0.1=**, <0.001 = ***). (B) HBTRC custom expression profiling array results for CD99.

Proteomic validation of transcriptomic results showed significant sex-specific differences in both AD and controls, as well as between them. We found significant increased expression of CD99 in females and males with AD, but with males showing higher expression levels than females (Figure 3).

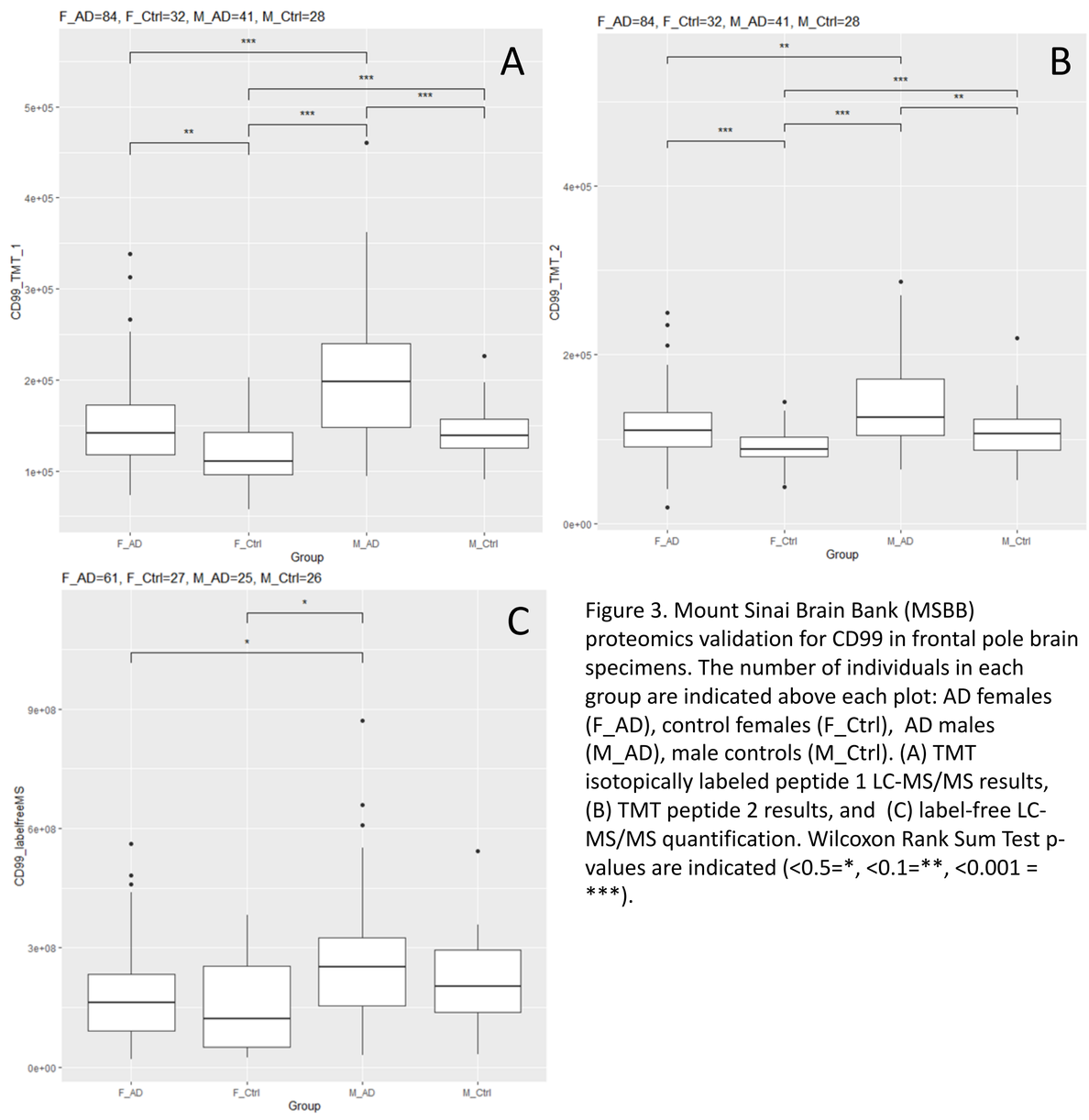

Figure 3. Mount Sinai Brain Bank (MSBB) proteomics validation for CD99 in frontal pole brain specimens. The number of individuals in each group are indicated above each plot: AD females (F_AD), control females (F_Ctrl), AD males (M_AD), male controls (M_Ctrl). (A) TMT isotopically labeled peptide 1 LC-MS/MS results, (B) TMT peptide 2 results, and (C) label-free LC-MS/MS quantification. Wilcoxon Rank Sum Test p-values are indicated (<0.5=*, <0.1=**, <0.001 = ***).

Conclusions

CD99 is significantly differentially expressed between men and women and upregulated in AD. CD99 is a cell-surface protein that does not belong on any known protein superfamilies. It has unique features and only partially understood mechanisms of action. It is involved in many relevant biological processes, including leukocyte diapedesis (transendothelial migration) which is a tightly regulated process, and exacerbated T-cell infiltration into the brain has been described in relation to AD. Further experiments need to be conducted to determine if the described sex-specific differences contribute to the increased pathogenic burden in AD in women.

References

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3. Wang et al., "The Mount Sinai cohort of large-scale genomic, transcriptomic and proteomic data in Alzheimer's disease", *Scientific Data*, 2018, doi: 10.1038/sdata.2018.185. Data was obtained from the AD Knowledge Portal.