

Genetic and Proteogenomic Insights into Sex-Biased Causal Genes and Drug Targets in Alzheimer's Disease

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INTRODUCTION

Sex differences in Alzheimer's disease (AD) are pervasive, reflected in the higher prevalence and incidence in women [1], as well as distinct biological pathways that contribute to sex differences in brain aging, clinicopathologic trajectories, and disease resilience [2-5]. Initial work further indicates genetic sex dimorphism in AD [6-7], but large-scale sex-stratified genetic studies are still missing and limited integration with functional genomics analyses has precluded critical insight into sex-specific disease mechanisms and risk genes.

Aim: Elucidate sex differences in AD and identify sex-biased, potentially druggable AD genes by:

1. Conducting the largest sex-stratified genome-wide association study (GWAS) of AD.
2. Performing sex-stratified proteome-wide association studies (PWAS) of AD by directly integrating GWAS with large-scale proteogenomics data in brain and CSF.
3. Prioritizing sex-biased, potentially druggable AD genes through multi-omics functional follow-up and computational drug repurposing analyses.

METHODS

Sex-stratified AD GWAS and sex heterogeneity analyses were conducted in European ancestry individuals using a 3-stage design, followed by fixed-effects meta-analysis using GWAMA (Fig. 1A). Models adjusted for age, APOE*4 and APOE*2 dosage, genetic principal components, technical covariates, and genetic relationship matrices (implemented in LMM-BOLT or Regenie). Genome-wide significant hits within each sex were filtered to those showing FDR.P_{sex-het} < 0.1; significant signals with FDR.P_{sex-het} < 0.05, were further attributed Tier 1 statistical support.

PWAS were performed via FUSION, by combining sex-stratified AD GWAS with sex-matched and non-sex-stratified proteogenomics weights from brain [8] and CSF [9] (Fig. 2A). Brain proteomic profiling used isobaric tandem mass tag (TMT) peptide labelling with liquid chromatography-mass spectrometry (TMT-MS). In CSF, proteins were profiled using the SOMAscan 7K platform.

Additional multi-omics approaches, including quantitative trait locus (QTL) summary-based Mendelian randomization (SMR) and colocalization, were utilized to further prioritize sex-biased genes.

Pathway, cell-type, and computational drug repurposing enrichment analyses were performed using sex-biased prioritized genes.

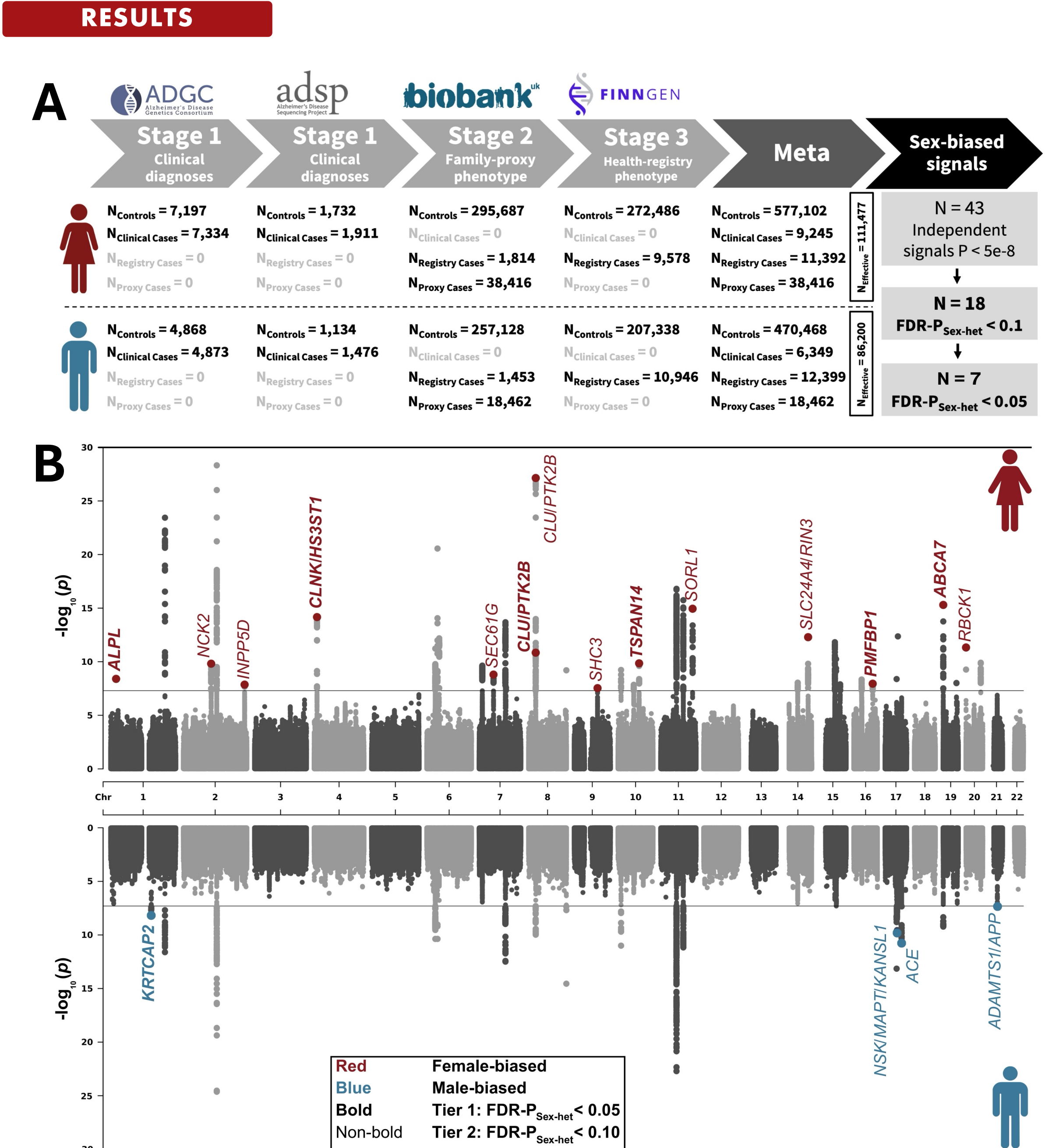


Figure 1. Sex-stratified genome-wide association study of Alzheimer's disease. A) Overview of study design and sample size. To increase specificity to AD, the meta-analyses were intersected to variants with association results in Stage 1 (clinically confirmed cases and controls, with a subset of pathology verified individuals). Sex-biased signals were identified among genome-wide significant loci (P < 5 × 10⁻⁸) that additionally passed FDR.P_{sex-het} < 0.1 (Tier 2), yielding 18 signals, with 7 passing FDR.P_{sex-het} < 0.05 (Tier 1). B) Miami plot for the GWAS meta-analyses; top, women; bottom, men. The solid horizontal lines indicate genome-wide significance; plots are truncated at P < 1 × 10⁻³⁰. Loci are colored by direction (red, female-biased; blue, male-biased), with bold annotations denoting Tier 1 support. Lead variants for independent loci are annotated with their nearest protein-coding gene (Ensembl v47) or known AD risk locus.

CONCLUSION

This integrative, sex-aware multi-omics framework reveals substantial asymmetry in the genetic and molecular architecture of AD, with female-biased signals converging on astrocyte-expressed genes, sex hormone interactions, and potential repurposable drugs. These findings highlight sex as a meaningful biological variable of AD heterogeneity, providing a foundation for sex-informed target discovery and precision medicine strategies.

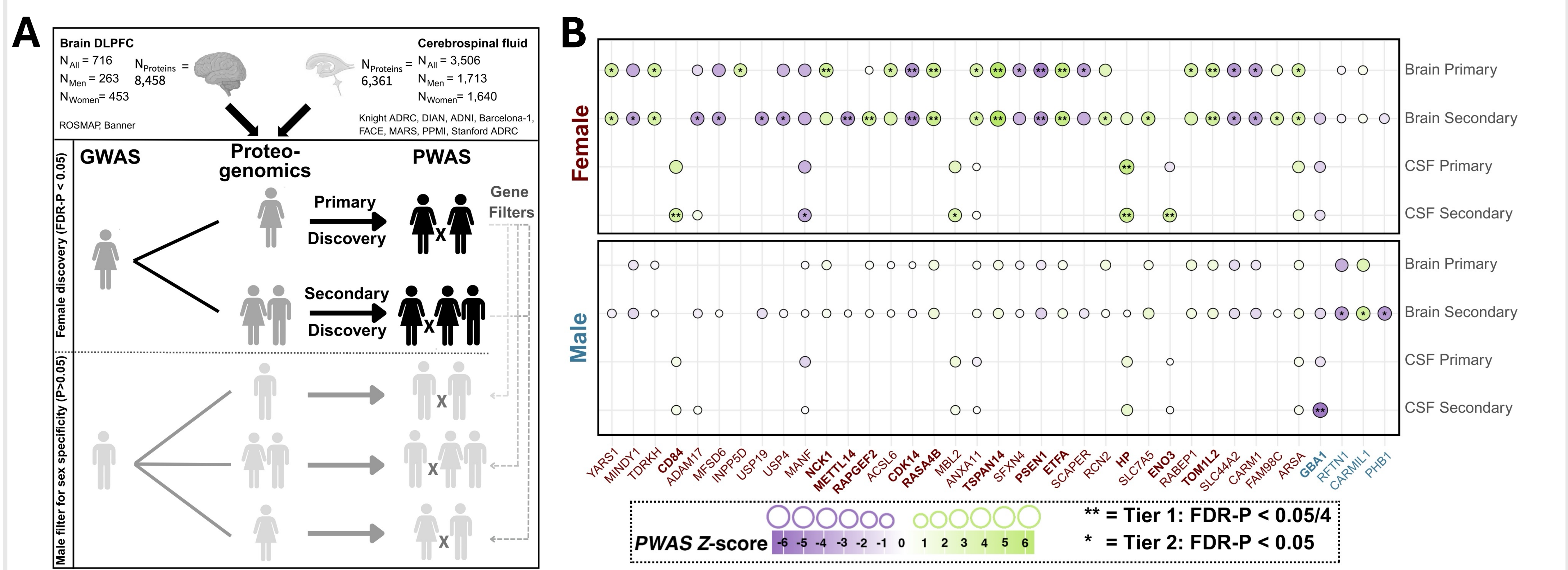


Figure 2. Sex-stratified proteome-wide association studies of Alzheimer's disease in brain and CSF. A) Overview of the sex-stratified PWAS design. In the primary discovery, the female-specific AD GWAS was integrated with female-stratified proteogenomic weights to perform a fully sex-matched PWAS. In the secondary discovery, non-sex-stratified proteogenomic weights were leveraged to identify subthreshold signals in the sex-stratified AD GWAS. To ensure sex-specificity, all discoveries were filtered to exclude proteins with nominally significant associations in the opposite sex (P > 0.05 filter). The design is mirrored for male-specific discoveries. B) Dot plot presenting PWAS Z-scores for sex-specific gene-AD association tests across brain and CSF, stratified by discovery type (primary and secondary) and sex. Color intensity reflects Z-score magnitude; asterisks denote Tier 1 (FDR.P < 0.05/4) and Tier 2 (FDR.P < 0.05) support.

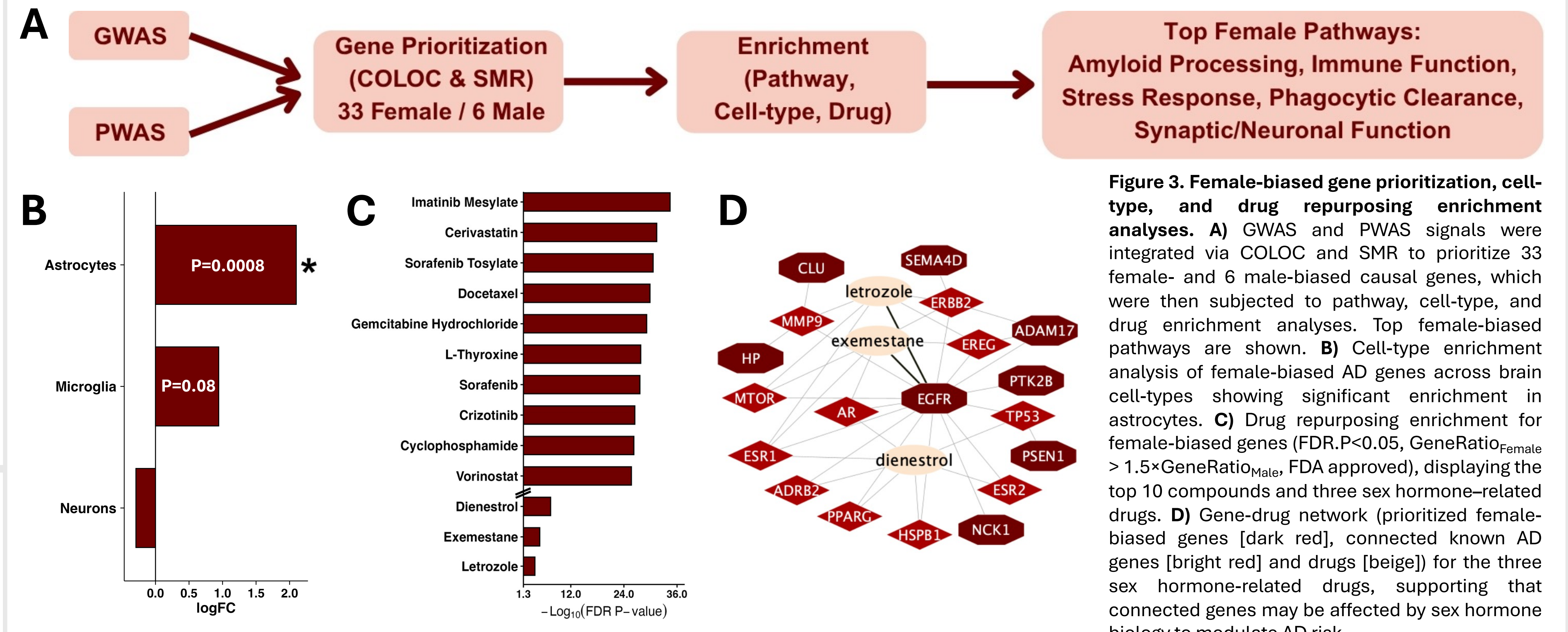


Figure 3. Female-biased gene prioritization, cell-type, and drug repurposing enrichment analyses. A) GWAS and PWAS signals were integrated via COLOC and SMR to prioritize 33 female- and 6 male-biased causal genes, which were then subjected to pathway, cell-type, and drug enrichment analyses. Top female-biased pathways are shown. B) Cell-type enrichment analysis of female-biased AD genes across brain cell-types showing significant enrichment in astrocytes. C) Drug repurposing enrichment for female-biased genes (FDR.P < 0.05, GeneRatio_{Female} > 1.5 × GeneRatio_{Male}, FDA approved), displaying the top 10 compounds and three sex hormone-related drugs. D) Gene-drug network (prioritized female-biased genes [dark red], connected known AD genes [bright red] and drugs [beige]) for the three sex hormone-related drugs, supporting that connected genes may be affected by sex hormone biology to modulate AD risk.