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GENETICS

Sex-stratified GWAS meta-analyses reveal novel sex-specific association with CSF biomarkers of Alzheimer's Disease

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Abstract

Background: Cerebrospinal fluid (CSF) biomarkers, including amyloid-β 42 (Aβ42), have emerged as essential endophenotypes in genome-wide association studies (GWAS) of Alzheimer's disease (AD), advancing our understanding of AD biological processes beyond traditional case-control studies. Using the largest sample size to date (N = 18,491), we aim to elucidate sex-specific associations with AD pathology by performing sex-stratified GWAS of three well-established CSF endophenotypes, Aβ42, Tau, and phosphorylated tau (pTau181).

Method: We conducted meta-analyses of sex-stratified GWAS for each CSF biomarker, leveraging 22 US and European cohorts with available raw CSF and genotype data (N = 6,785; 51.84% male; age=68), along with summary statistics from six external

cohorts (N = 11,706; 45.27% male; age=69). Consistent quality control was applied prior to genetic analyses, including z-score standardization on raw CSF biomarker values in internal cohorts. The GWAS adjusted for age, ten principal components of genetic ancestry, and cohort-array combination as applicable. We defined a sex-specific effect as a variant association that reached genome-wide significance in one sex and had non-overlapping 95% confidence intervals of the effect estimates between sexes.

Result: We identified seven genome-wide significant loci, including four previously reported loci and three novel female-specific associations, including one for Aβ42 (rs372578, p(Females)=1.86E-08, b(F)=-0.09, p(Males)=0.78), Figure 1), one for Tau (rs1582763, p(F)=5.56E-09, b(F)=-0.09, p(M)=0.05, Figure 2), and one for pTau181 (rs6434518, p(F)=2.95E-08, b(F)= 0.17, p(M)=0.80, Figure 3). The lead Aβ42 variant, rs372578, is an eQTL for *BMP6* (p = 8.00E-04, http://www.braineac.org), which encodes a TGF-beta ligand involved in iron homeostasis and bone/fat development. Increased expression of *BMP6* is linked to hippocampal neurogenesis defects in AD patients and APP-transgenic mice. The lead Tau variant, rs1582763, is in the *MS4* locus, an established genetic risk factor for AD with some evidence of female-specificity, and has been linked to soluble *TREM2* level regulation in CSF. Finally, the top pTau181 variant, rs6434518, is an eQTL for immune response genes *STAT4*, *STAT1* (p = 2.40E-02), and *MYO1B* (p = 2.60E-02) involved in lipid metabolism and proteostasis.

Conclusion: Our results highlight significant female-specific genetic associations across CSF biomarkers, underscoring the importance of sex-specific genetic analyses in deepening understanding of AD genetic architecture.

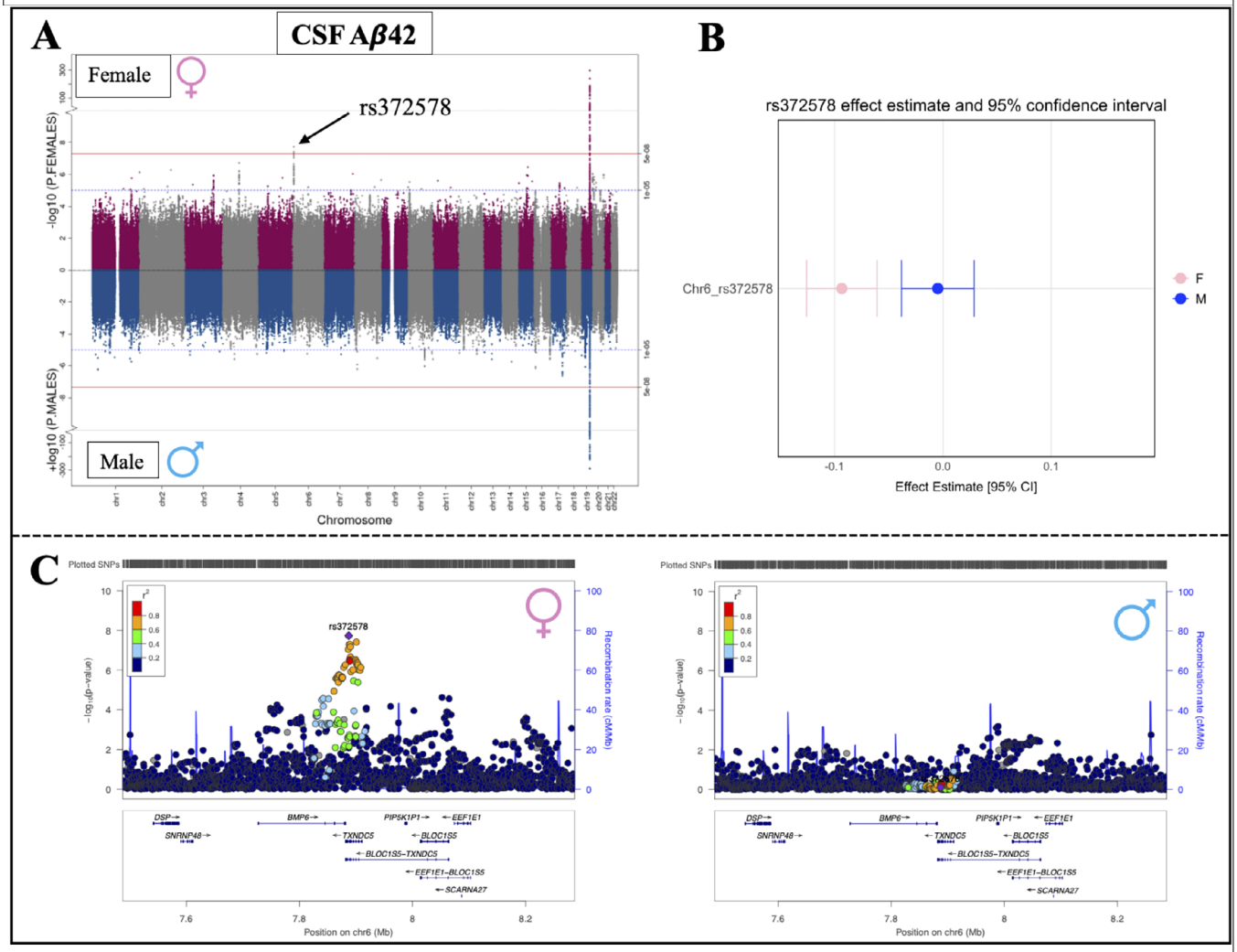

Fig 1. Minor allele of female-specific genome-wide significant locus on chromosome 6 (rs372578) associated with CSF Aβ42 levels. (A) Miami plot with female variant associations on the top in pink and male variant associations on the bottom in blue. (B) Forest plot of rs372578 by sex, including meta-analysis estimates and 95% CI. (C) Locus Zoom plots displaying the genomic region surrounding the chromosome 6 locus by sex, with female on the left and male on the right.

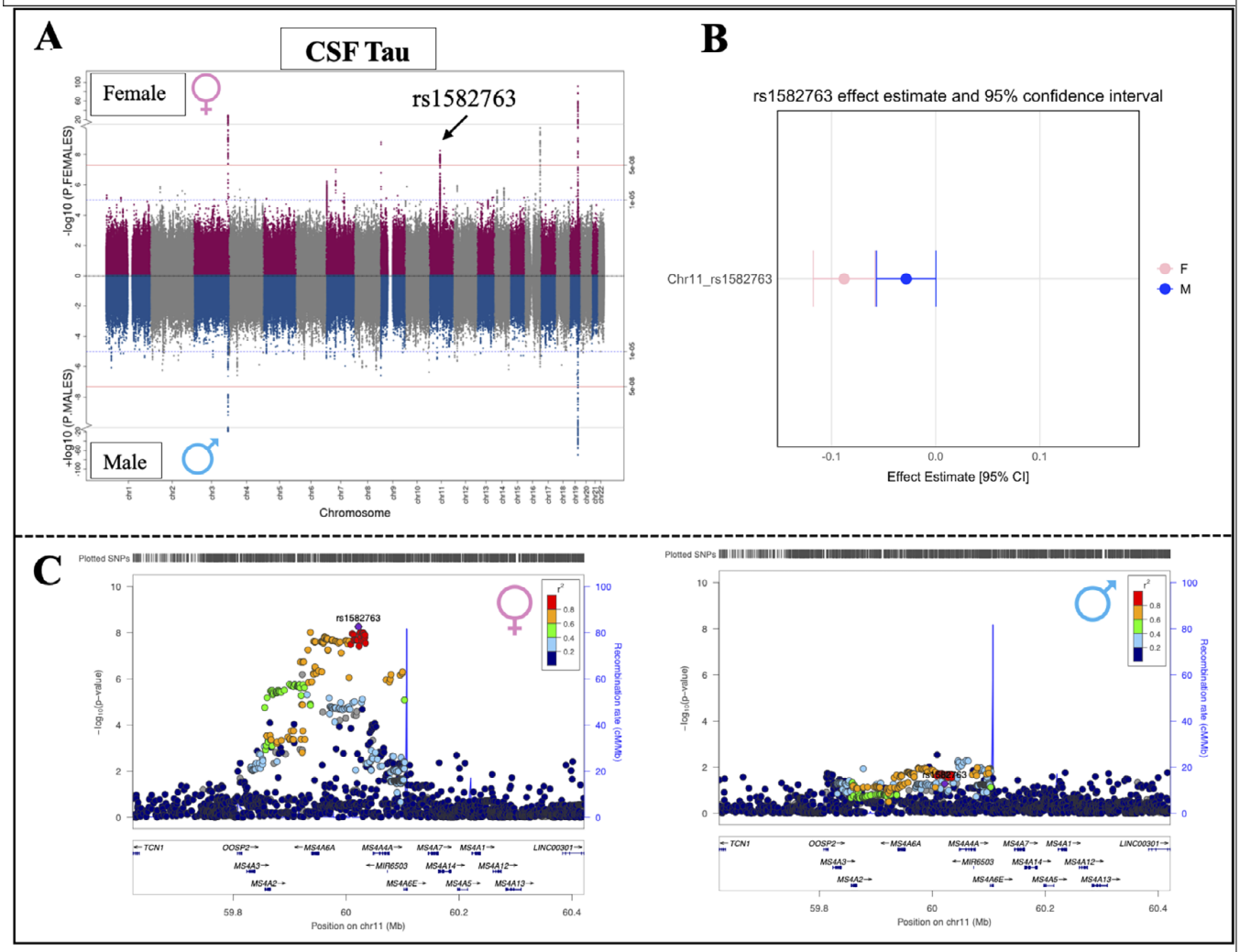

Fig 2. Minor allele of female-specific genome-wide significant locus on chromosome 11 (rs1582763) associated with CSF Tau levels. (A) Miami plot with female variant associations on the top in pink and male variant associations on the bottom in blue. (B) Forest plot of rs1582763 by sex, including meta-analysis estimates and 95% CI. (C) Locus Zoom plots displaying the genomic region surrounding the chromosome 11 locus by sex, with female on the left and male on the right.

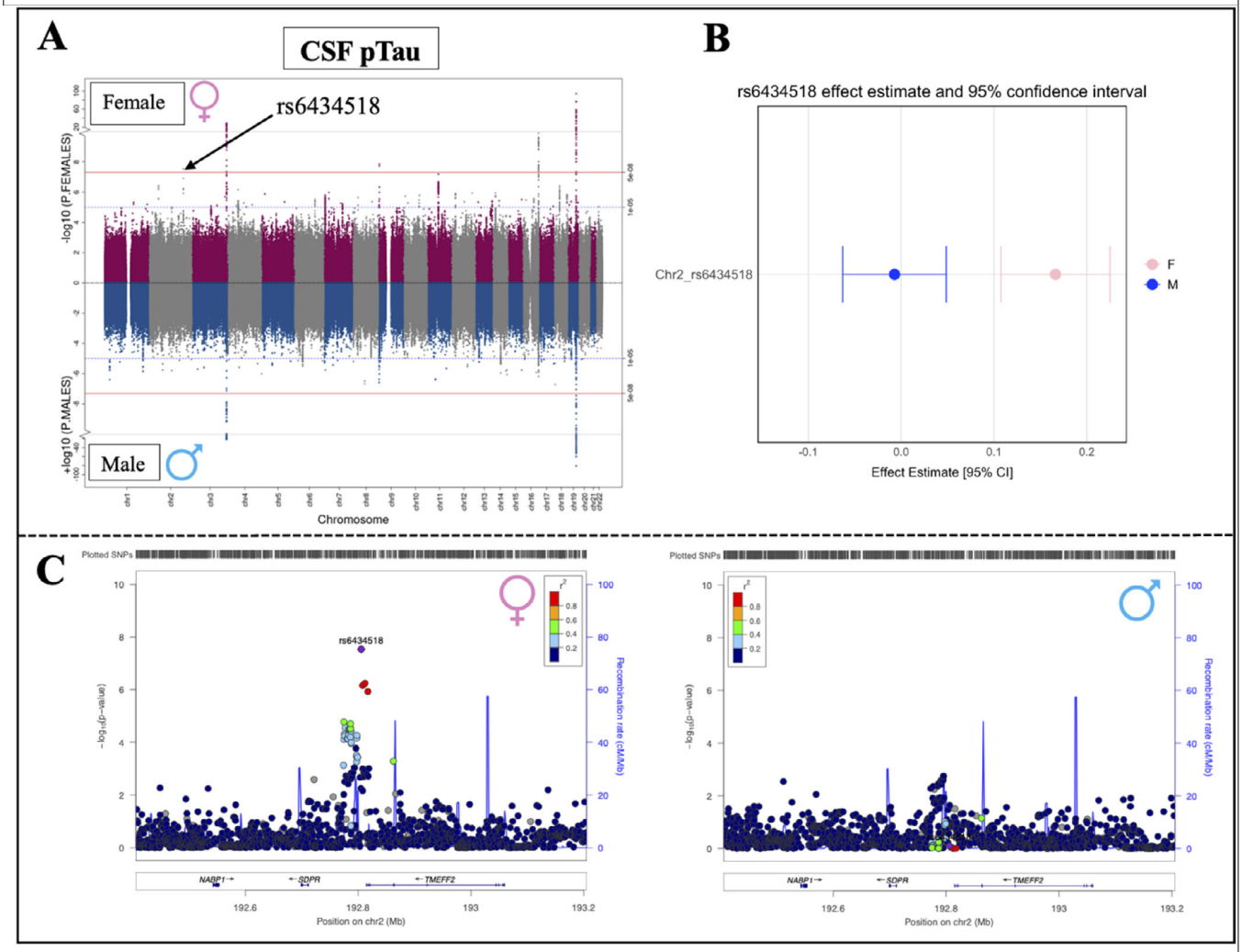

Fig 3. Minor allele of female-specific genome-wide significant locus on chromosome 2 (rs6434518) associated with CSF pTau181 levels. (A) Miami plot with female variant associations on the top in pink and male variant associations on the bottom in blue. (B) Forest plot of rs6434518 by sex, including meta-analysis estimates and 95% CI. (C) Locus Zoom plots displaying the genomic region surrounding the chromosome 2 locus by sex, with female on the left and male on the right.