

Investigation of common structural variations reveals new susceptibility loci of Alzheimer’s disease

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Abstract

Objectives: Genetic studies have identified numerous single-nucleotide polymorphisms (SNPs) associated with Alzheimer’s disease (AD). However, the association between AD and structural variations (SVs) remains largely unknown. We aimed to identify novel AD-risk loci through a genome-wide association study of SVs and investigate the genome-wide contribution of SVs to AD risk.

Methods: We identified 44,122 high-confidence SVs using the long-read sequencing data of 11 Chinese genomes. We then genotyped these SVs using 35X short-read sequencing in Chinese AD cohorts, obtaining high-quality genotypes for 17,294 SVs for association analysis.

Results: We showed that the polygenic effects of common SVs account for additional AD risk beyond that explained by common SNPs. Notably, we identified a common SV in the FAM193B locus that is associated with AD risk with genome-wide significance ($P = 5.5 \times 10^{-13}$), revealing a new susceptibility locus of AD. Moreover, we showed that this SV acts as a causal variant by upregulating FAM193B expression and mediating the pleiotropic association between brain FAM193B expression and AD risk.

Conclusions: This study reveals a significant contribution of common SVs to AD heritability and identifies a new AD risk SV in the FAM193B locus, highlighting the importance of integrating SVs into genetic studies of AD.

Results

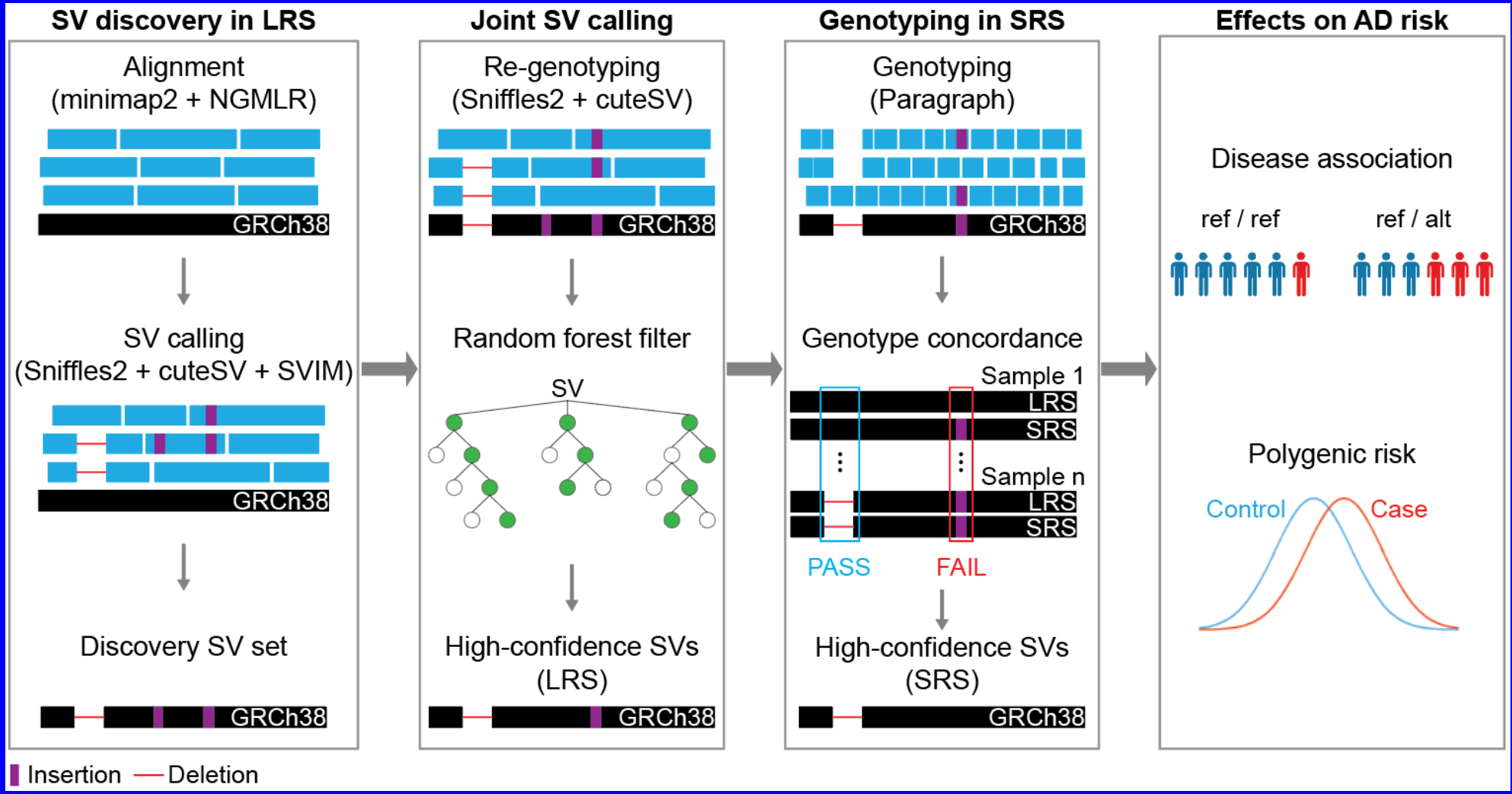


Fig. 1. Analytical workflow of SV discovery, joint SV calling, SV genotyping, and AD association analysis of SVs.

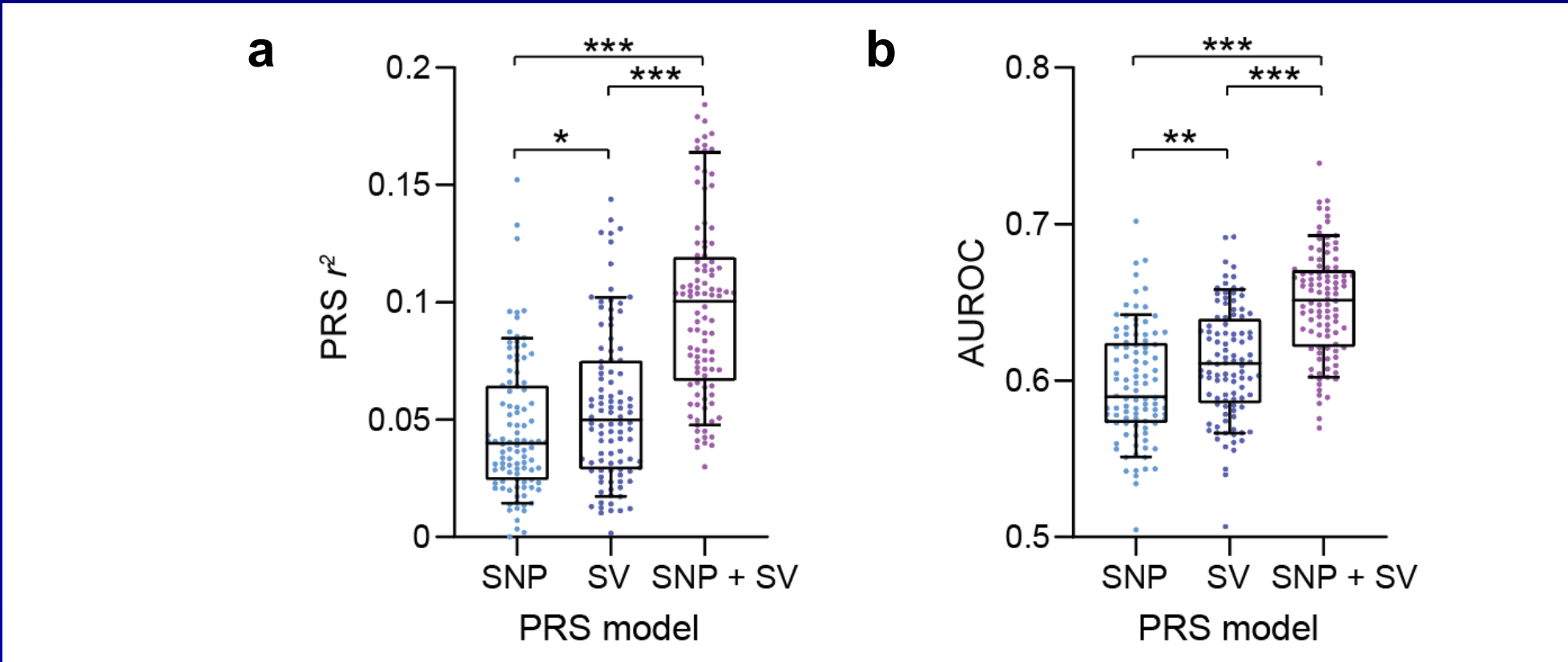


Fig. 2. Polygenic effects of common structural variations on AD. (a) Correlations between AD and PRS calculated using SNPs, SVs, and both SNPs and SVs (“SNP + SV”). r^2 , Nagelkerke’s pseudo r^2 ; (b) Areas under the receiver operating characteristic curve (AUROCs) showing the performance of distinguishing patients with AD from NCs using PRS models based on SNP, SV, and SNP + SV. ** $P < 0.01$, *** $P < 0.001$; paired 2-tailed Mann–Whitney U-test; 10 times repeated 10-fold cross validation.

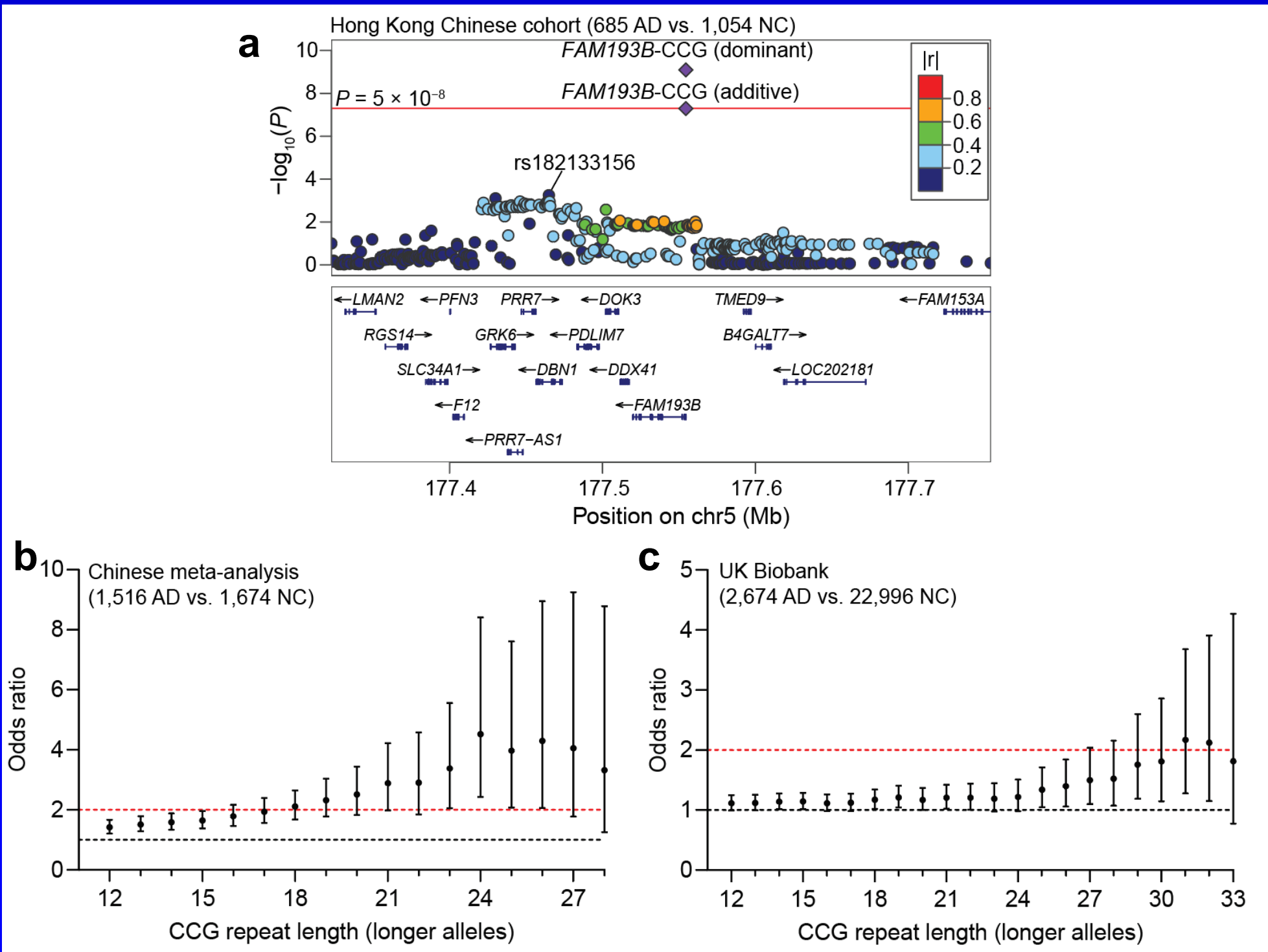


Fig. 3. Identification of a common AD risk CCG repeat in the FAM193B locus. (a) Associations between genetic variants in the FAM193B locus and AD. (b-c) Dosage effects of the FAM193B-CCG repeat in Chinese (b) and European (c) population.

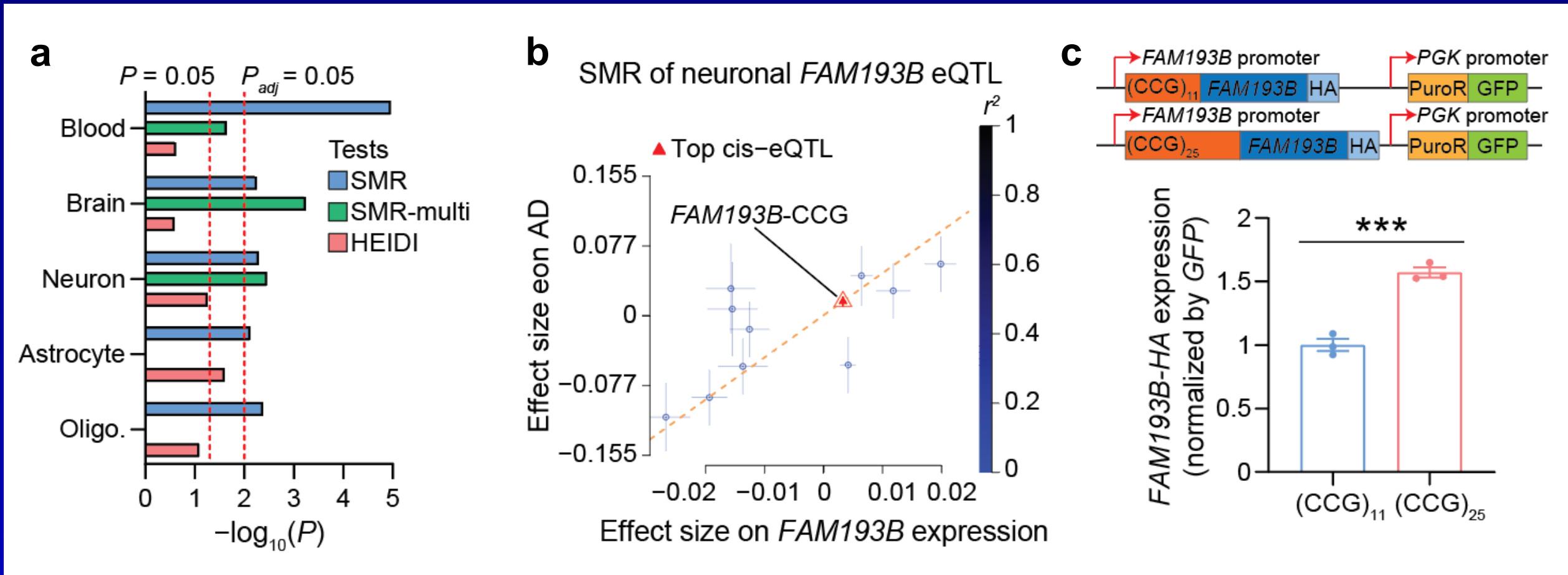


Fig. 4. The FAM193B-CCG repeat mediates the pleiotropic association between FAM193B expression and AD. (a) Summary data-based Mendelian randomization (SMR) analysis of the causal effect of the FAM193B-CCG repeat on FAM193B expression and AD. HEIDI, heterogeneity in dependent instruments. (b) Multi-variant SMR plots showing the pleiotropic association between FAM193B expression in neurons and AD. The top cis-expression quantitative trait locus (eQTL) is colored red, while the colors of other dots represent their linkage disequilibrium (r^2) with the top cis-eQTL. The brain eQTL summary statistics were obtained from Cui et al.² and Klein et al.³. (c) Expression levels of FAM193B-HA mRNA driven by FAM193B promoters containing 11 or 25 CCG repeats in HEK293T cells

Conclusion

1. Common SVs account for additional heritability beyond that explained by common SNPs
2. The FAM193B-CCG repeat is a novel AD risk genetic factor
3. The FAM193B-CCG repeat is a causal variant mediating the pleiotropic association between brain FAM193B expression and AD risk.

References

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2. Cui, Y. et al. *Nature Genetics* 57, 369–378 (2025)
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