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GENETICS

Fine-mapping of the TMEM106B locus reveals four haplotypes that are differentially associated with risk for neurodegeneration

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Abstract

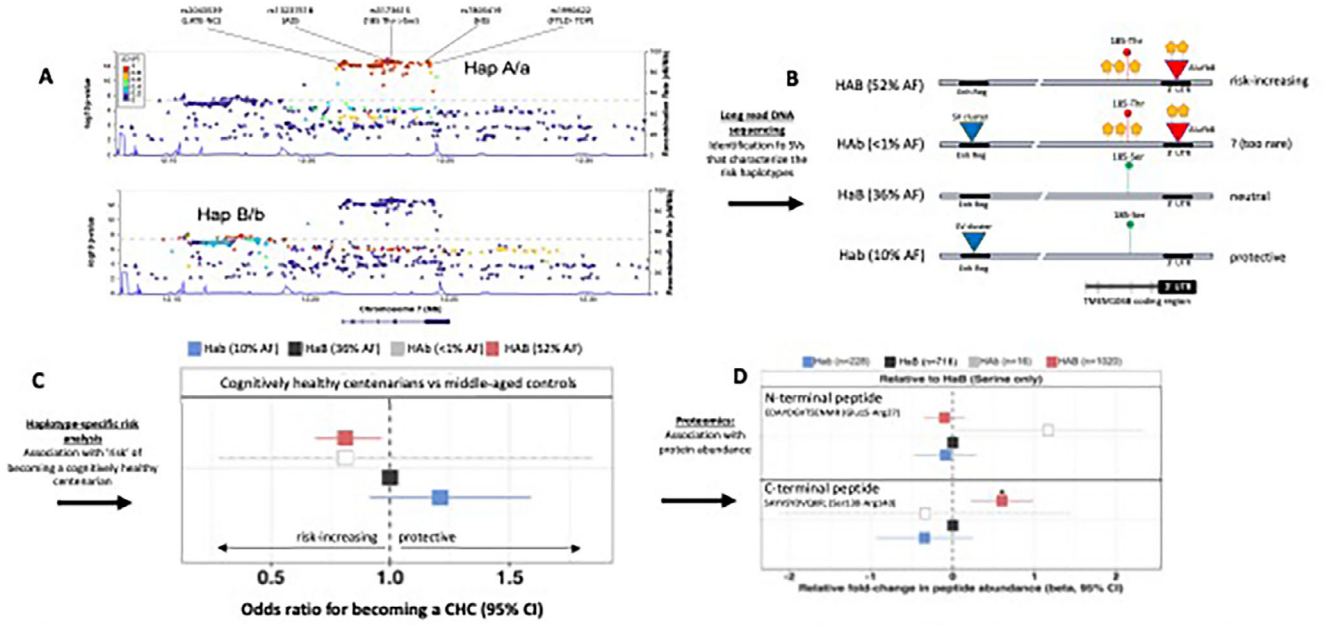
Background: Genome-wide association studies (GWAS) linked *TMEM106B* variants to susceptibility for neurodegenerative diseases, but the causal genetic elements remain unclear.

Method: We used genotyping data from 5,792 Alzheimer disease cases and controls, and applied COJO to identify haplotypes in the TMEM106B locus that independently associated with AD. Then, we used long-read sequencing data from 513 individuals to annotate these haplotypes with structural variations that map into them.

Results: Analysis of the genotyping data revealed that the *TMEM106B* locus consists of four major haplotypes: HA/Ha (covering the coding region), and HB/Hb (covering the upstream regulatory region). These combine into four combinations with varying population-frequencies: *HAB* (57%), *HaB* (34%), *Hab* (9%), and *HAb* (<1%). Long-read sequencing of 513 individuals showed that *HA* haplotypes (marked by 185-Threonine) carry unique methylated CpG sites and an AluYb8-retrotransposon in the 3' UTR, while the *Ha* haplotypes are marked by the 185-Serine allele. *Hb* haplotypes carry several structural variants (SVs) in nearby distal enhancers, including a 19 Kbp rearrangement, absent in all other haplotypes. Joint association models revealed that the *HAB* combination (AluYb8+185-Threonine) is risk-increasing, while *Hab* (SVs+185-Serine) confers the protective effect. *HaB* (185-Serine only) is neutral, while *HAb* was too rare to assess. Relative to middle-aged non-demented controls, cognitively healthy centenarians were more enriched with *Hab* (OR=1.49, padj=2.18×10-2) than with *HaB* (OR=1.23, padj=5.06×10-2). Proteomic analysis of temporal cortex tissues (n = 182) indicated that relative to the neutral *HaB* combination, the protective *Hab*

is associated with 1.1-fold *lower* TMEM106B C-terminal peptide abundance, while the risk-increasing *HAB* is associated with 1.16-fold *higher* abundance.

Conclusion: Our data indicates that the genetic structure underlying the association of the *TMEM106B* locus with neurodegenerative diseases is driven by the effect of multiple haplotypes.



The TMEM106B GWAS locus deconvolutes into multiple haplotypes, each with a unique effect on AD risk. A. Identification of 'independent' haplotypes using AD GWAS data. Top panel: Locus plot depicting haplotype HA/a: a ~50kb LD-block that associates with AD, covering the coding TMEM106B region and the sentinal GWAS SNPs. Bottom panel: Haplotype HB/b, a ~150kb LD block that associates with AD independently from HA/a. **B.** Long-read sequencing indicated that HA was characterized by a Thr-residue at position 185, and characterized by an AluYb8 retrotransposon (red) in the 3' UTR accompanied with unique methylated CpGs (yellow). Ha is marked by the 185-Ser, and divided into HaB and Hab, where Hab is characterized by a cluster of SVs in the enhancer region upstream of TMEM106B (blue). **C.** The 'risk' for becoming a cognitively healthy centenarian (CHC) differed per haplotype. **D.** Using available proteomics data from the centenarian temporal cortex, we determined the haplotype-specific effect on TMEM106B C-terminal and N-terminal protein abundance