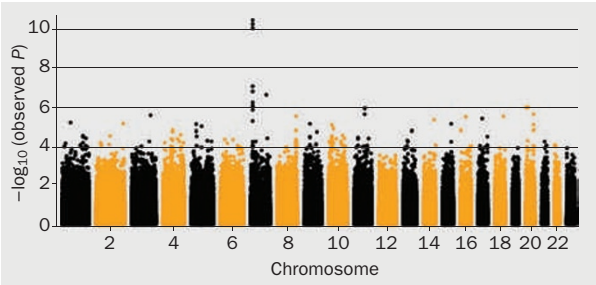
DEMENTIA

TMEM106B is a susceptibility locus for FTLD

A genome-wide association study has identified variants in chromosomal region 7p21 that are associated with the risk of developing a common form of frontotemporal lobar degeneration (FTLD). "up to 30–50% of patients with FTLD may have a family history of similar disease, but only a subset have a known Mendelian cause, so additional genetic risk factors are felt to play an important role," explains lead author Vivianna Van Deerlin from the University of Pennsylvania School of Medicine, Philadelphia.

Given that FTLD is a clinically and pathologically heterogeneous condition, the researchers decided to focus their attention on one particular subtype—FTLD with TAR DNA-binding protein (TDP-43) inclusions (FTLD-TDP). The study population consisted of 515 individuals who had received a clinical diagnosis of dementia and were confirmed to have either TDP-34 pathology at autopsy or a pathogenic mutation in the progranulin (*GRN*) gene, both of which are indicators of FTLD-TDP. The control group contained 2,509 individuals without FTLD-TDP. A small replication study was performed with a further 89 cases and 553 controls.

The genome-wide association study revealed a strong association between FTLD-TDP and several single nucleotide polymorphisms (SNPs) that mapped in the region of the *TMEM106B* gene on chromosome 7p21. *TMEM106B* encodes a 274 amino acid transmembrane protein, the function of which is currently unknown. After the data were subjected to a Bonferroni correction, genome-wide significance was reached for three of the SNPs—rs6966915, rs1020004 and rs1990622. The researchers noted that the rs1020004 genotype in correlated with disease severity: AA homozygotes showed shorter disease durations (signifying more-severe disease) than did GG homozygotes.



Manhattan plot showing region of genome-wide significant association on chromosome 7. Permission obtained from Nature Publishing Group © Van Deerlin, V. M. *et al. Nat. Genet.* **42**, 234–239 (2010).

> "...the SNPs we identified seemed to influence the gene's expression as well as disease state..."

The next challenge will be to determine the physiological role of *TMEM106B* and the relationship between this gene and the etiology of FTLD. "Interestingly, the SNPs we identified seemed to influence the gene's expression as well as disease state," says Van Deerlin. "Our goal now is to fit *TMEM106B* into the puzzle of FTLD. Given the major interest in this area, it is highly likely that TMEM106B will go from an unnamed protein to a named protein with an important role in the pathophysiological pathway of FTLD."

Senior author John Trojanowski predicts swift progress in elucidating the events that underlie the FTLD-TDP disease process: "one can be cautiously optimistic that what took 20 years to accomplish to advance understanding of tau-mediated neurogeneration in Alzheimer disease and FTLD-tau could be compressed into 4–5 years for TDP-43 proteinopathies, so that the likelihood of finding better diagnostics and disease-modifying therapies will be greatly accelerated."

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