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NEUROIMAGING

TMEM106B modulates disease severity in genetic frontotemporal dementia phenoconverters

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Abstract

Background: A common variant within TMEM106B is associated with risk for Frontotemporal Lobar Degeneration-Tar DNA binding Protein-43 (FTLD-TDP). A recent study has shown that the minor allele G of TMEM106B-rs1990622 confers protection against FTLD-TDP in symptomatic mutation carriers through reductions in NfL serum levels, brain atrophy, and cognitive decline. It is unknown whether this protective effect is present in phenoconverters of the disease.

Method: We included 518 participants from the GENetic Frontotemporal dementia Initiative (GENFI), which recruits genetic FTD cases and their family members, both carriers and non-carriers of FTD mutations. Of these, 21 were phenoconverters,

209 were non-carrier controls, 70 were presymptomatic and 45 symptomatic C9orf72 carriers, 92 presymptomatic and 29 symptomatic GRN carriers, and 39 presymptomatic and 13 symptomatic MAPT carriers. Effects of interaction between TMEM106B-rs1990622 and phenoconverter status were examined using mixed effects models, with a random effects structure featuring subjects nested within families and fixed effects for age at baseline and sex. Serum neurofilament light chain (NfL) was measured using the Simoa platform. Cognitive assessment included the Mini-Mental State Examination (MMSE), tests of attention, processing speed, executive function, and language, as well as the Cambridge Behavioural Inventory (CBI), with mixed effects also including years of education as a covariate. Brain volumetry was assessed using T1-weighted MRI and these mixed effect models also included additional covariates of total intracranial volume and scanner site.

Result: In phenoconverters, each copy of the protective allele G was associated with a significant reduction in the rate of serum NfL accumulation (-5.33 pg/mL/year; $p = 7.79 \times 10^{-9}$). Structural imaging analyses revealed decreased rates of atrophy in fronto-orbital regions and the insular cortex among protective allele carriers. Cognitive trajectories showed significantly slower decline across multiple domains including general cognition (MMSE; $p = 0.003$), attention and processing speed ($p = 2.2 \times 10^{-4}$), executive function ($p = 2.6 \times 10^{-7}$), language ($p = 2.9 \times 10^{-3}$), and behavioural symptoms as measured by CBI ($p = 9.5 \times 10^{-3}$).

Conclusion: The TMEM106B-rs1990622 protective variant significantly modulates disease progression in genetic FTD phenoconverters across multiple markers, suggesting its potential as a therapeutic target.