NEURODEGENERATIVE DISEASE

Frontotemporal dementia risk variant accelerates cognitive decline in Parkinson disease

> The presence of the FTD risk variant was associated with faster cognitive decline

Genetic variants that increase the risk of frontotemporal dementia (FTD) are also associated with faster rates of cognitive decline in Parkinson disease (PD), according to a new study published in *Annals of Neurology*. The findings suggest that similar therapeutic strategies could be adopted to treat the cognitive elements of both diseases.

Common variants near the *TMEM106B* gene, which encodes the lysosomal protein transmembrane protein 106B (TMEM106B), are associated with an increased risk of developing FTD, although the effects of genetic variation at this locus on the disease course of FTD have not yet been established. *TMEM106B* genotype also influences the risk of cognitive symptoms in amyotrophic lateral sclerosis (ALS) and of developing TAR DNA-binding protein 43 (TDP43) pathology in Alzheimer disease (AD), observations that have led to the suggestion that it could play a broader role in neurodegenerative processes.

TMEM106B variants that are associated with an increased risk of FTD lead to high TMEM106B protein levels, resulting in abnormal lysosomal phenotypes. "Lysosomal function is probably important not only in FTD but in many neurodegenerative diseases that have the common feature of misfolded proteins," explains Alice Chen-Plotkin, who led the new study. "We looked across multiple different neurodegenerative diseases to see if variants in *TMEM106B* modified the course of disease."

In the new study, Chen-Plotkin and her team measured cognitive ability with the Mini-Mental State Examination (MMSE) in a cohort of individuals already enrolled in research studies at the University of Pennsylvania, USA. The cohort included a total of 867 individuals with FTD, PD, AD or mild cognitive impairment (MCI) and 137 healthy controls. They monitored the members of this cohort for a median of 3 years (maximum 10 years) and repeated the MMSE annually during this period. The team combined this long-term cognitive assessment with genotyping for a *TMEM106B* variant that has previously been associated with an increased risk of FTD.

The presence of the FTD risk variant was associated with faster cognitive decline in the patients with PD as well as in the patients with FTD, but not in the patients with AD or MCI. Cognitive decline was not seen in healthy controls during the study period. In a surprise for the team, the biggest effect of *TMEM106B* genotype was on PD, and this effect was specific to the cognitive aspect of PD — the rate of change in motor function was not associated with *TMEM106B* genotype.

Chen-Plotkin and her team then carried out a similar longitudinal study using a different cognitive test, the Mattis Dementia Rating Scale-2 (DRS-2), in which individual cognitive domains are scored. The cohort for this study was composed of 128 individuals with PD who were enrolled in studies at the University of Pennsylvania, including some individuals who took part in the initial MMSE study. The same association of *TMEM106B* genotype with cognitive decline was present in individuals with PD regardless of the test used, and the attention, conceptualization and memory domains were affected.

Last, the team sought to replicate their findings in a broader, international cohort, which included 371 patients with PD from 11 countries. In this cohort, they studied a different FTD risk variant of *TMEM106B* and found that this variant was also associated with faster rates of cognitive decline.

Whereas TDP43 proteinopathy is a key feature of FTD, ALS and AD, this pathology is not common in PD, so the new results suggest that TMEM106B influences diseases via TDP43-dependent and TDP43-independent mechanisms. "Increasingly, lysosomal function (or dysfunction) has been shown to be important in the development of PD, so this suggests that the effects of TMEM106B on the lysosomes may play a role in how PD progresses," notes Chen-Plotkin. "It also suggests that targeting TMEM106B may be therapeutically helpful not only in FTD but in PD as well."

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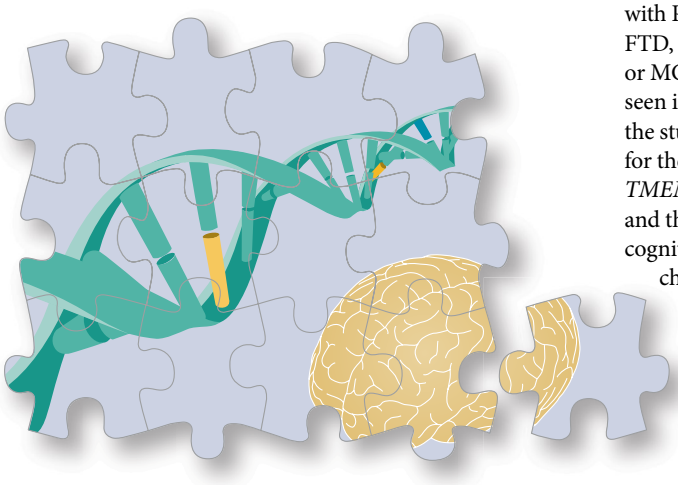

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ORIGINAL ARTICLE Tropea, T. F. et al. TMEM106B effect on cognition in Parkinson's disease and frontotemporal dementia. *Ann. Neurol.* https://doi.org/10.1002/ana.25486 (2019)
FURTHER READING Aarsland, D. et al. Cognitive decline in Parkinson disease. *Nat. Rev. Neurol.* **13**, 217–231 (2017)