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Genetic overlap between cortical brain morphometry and frontotemporal dementia risk

Santiago Díaz-Torres, Natalia Ogonowski, Luis M. García-Marín, Claudia Durán-Aniotz, Jennifer S. Yokoyama, Miguel E. Renteria

Background: Frontotemporal dementia (FTD) has a complex genetic aetiology, with mutations in several genes associated with the disease. However, the precise mechanisms underlying the selective vulnerability of neurons in the frontal and temporal regions remain unknown.

Methods: We leveraged summary statistics from genome-wide association studies (GWASs) and used LD-score regression to estimate pairwise genetic correlations between FTD and cortical and subcortical brain imaging phenotypes. Then, we conducted GWAS pairwise to identify genomic loci with shared signals between FTD and strongly-correlated brain measures. Finally, we performed functional annotation and summary-based-data Mendelian randomisation for eQTL data for genes within overlapping genomic loci of interest.

Results: Genetic correlations between FTD and neuroimaging traits were high but not statistically significant, likely due to the relatively low sample size of the FTD GWAS. Five strongly-correlated regions (rg > 0.45) were identified, and a region in chromosome 17 was aetiologically shared between FTD and the right inferior parietal surface area and the right medial orbitofrontal cortical thickness. Functional annotation identified eight protein-coding genes and NSF gene expression as shared between FTD and phenotypic variation in the two brain regions.

Conclusions: Our results highlight the molecular and genetic overlap between FTD risk and brain morphology, particularly the right inferior parietal surface area and right medial orbitofrontal cortical thickness. They also implicate NSF gene expression in the aetiology of FTD.

Conflicts of interest

Nothing to declare