

Genetic link between asymmetry and handedness genes and agrammatic primary progressive aphasia: a mendelian randomization approach

Malik Nassan, Ignazio Piras, Emily Rogalski, Changiz Geula, Hassan Dashti, M-Marsel Mesulam, Richa Saxena, Matt Huentelman

Introduction: Primary progressive aphasia (PPA) main subtypes are logogenic, semantic, and agrammatic. The risk factors to developing PPA are largely unknown. We sought to assess if dyslexia, left handedness, or brain asymmetry might be risk factors of PPA through mendelian randomization (MR) approach.

Methods: Significant single nucleotide polymorphisms (SNPs) from genome-wide-association-studies (GWAS) were used as proxies for the exposures: 42 SNPs for dyslexia, and 48 SNPs for left-handedness; of which 18/48 SNPs with correlated cortical asymmetry. GWAS summary statistics for the outcomes were obtained for semantic PPA and agrammatic PPA. The logopenic variant was approximated by proxy through the rubric of 'clinically diagnosed AD with salient language impairment' but without formal PPA diagnosis. Alzheimer's and Frontotemporal dementia were also included as outcomes. MR analyses were performed.

Results: The genetic proxy of cortical asymmetry in left-handedness was significantly associated with the diagnosis of FTD (beta= 1.67, P=0.03) which was driven specifically by agrammatic PPA (beta= 4.3 P= 0.007). None of the other exposures were significantly associated with the outcomes (P>0.05). Brain asymmetry (regardless of handedness) was not tested due to lack of genome-wide-significant SNPs in the largest asymmetry GWAS.

Conclusion: Our results suggest an association between cortical asymmetry genes, and agrammatic PPA. Whether the additional association with atypical-handedness is necessary remains to be determined, but is unlikely given the absence of association between left handedness and PPA. Interestingly, the genes of the cortical asymmetry are implicated in microtubule-related proteins and Tau pathways (*TUBA1B*, *WASF3*, *TUBB*, and *MAPT*).

Conflicts of interest

nothing to disclose