p-007

Thursday

Modules of genotypic variance reflect anatomic heterogeneity across the FTD-ALS spectrum

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State of the art TAR DNA-binding protein (TDP-43) proteinopathies yield a variety of neurodegenerative conditions including frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS). However, the contribution of both shared and disparate single nucleotide polymorphisms (SNPs) to phenotypic presentations is unclear. We hypothesize that disparate genetic variation may contribute to our understanding of phenotypic heterogeneity, including the anatomic distribution of atrophy across brain networks.

Methodology We used weighted correlation analysis of GWAS summary statistics for FTLD-TDP and ALS to identify data-driven modules of highly correlated SNPs. Module SNPs were used to construct polygenic risk scores (PRS). PRS were tested for association with age-, sex-, and intracranial volume-adjusted T1-weighted MRI volumes in somatomotor and salience network regions derived from the Schaefer 100x7 parcellation in sporadic and familial FTLD-TDP (n=49), ALS (n=101), and FTD-ALS (n=31) cases.

Results We identified 493,591 SNPs commonly genotyped across FTLD-TDP and ALS, and the top 1% of these were selected for analysis. We identified modules associated with risk for either ALS (M1, containing 1,907 SNPs) or FTLD-TDP (M2, containing 1,727 SNPs). A PRS was calculated for M1-ALS and M2-FTLD-TDP for each individual. In individuals with FTD-ALS, higher M2-FTLD-TDP PRS, compared to M1-ALS PRS, was associated with lower adjusted volumes in salience regions, compared to somatomotor regions.

Conclusion Examining genotypes revealed modules of correlated SNPs across the FTD-ALS spectrum which relate to relative regional atrophy patterns. We suggest that genotypic variation across TDP-43 proteinopathies may contribute to individual-level presentations of these syndromes.

Conflicts of interest

N/A