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Saturday

Rare variant burden contributes to frontal and temporal lobe volumes in genetic frontotemporal dementia: Results from GENFI

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State of the art: Frontotemporal dementia (FTD) is a neurodegenerative condition characterized by heterogeneous clinical, pathological and genetic features. Mutations in three genes account for the majority of autosomal dominant FTD: GRN, MAPT, and C9orf72. We tested whether gene-based aggregate burden of genome-wide rare/uncommon variants contribute to variation in frontal and temporal lobe volumes in the GENetic Frontotemporal dementia Initiative (GENFI), after controlling for effects of autosomal dominant mutations.
Methodology: GENFI recruits known carriers of the three FTD mutation subgroups and their family members. We included 520 participants with genotype (Neurochip; imputed against TOPMed), and T1w-MRI brain volumetric data. Gene-based burden tests were used to examine the association of rare/uncommon variants (maf<0.05) with total, left and right frontal and temporal volumes, controlling for age, total intracranial volume, mutation status, population stratification, and family membership (kinship matrix).
Results: Of the 520 participants, 310 were mutation carriers (symptomatic=85). 6,149,807 SNPs in 28,307 genes were tested (significance threshold: 0.05/28,307= 1.7 x 10-6). Aggregate rare-variant burden in SNORD115-7 (15q11.2; p=3.3X10-6) was associated with a lower right frontal volume, and MIR4741 (18q11.2; p=4.9x10-8) and SNORD77 (1q25.1; p= 4.89x10-8) was associated with a lower left temporal volume. Rare variant burden in ENOX1 (13q14.11; p=1.52 x 10-6) was associated with higher total and right frontal volumes, and B3GALT1 (2q24.3; p=4.89x10-8) was associated with higher left temporal volume.
Conclusion: Identification of deleterious or protective rare/uncommon variants contributing to disease phenotypes may help find the missing heritability in genetic FTD. Replication of results followed by functional studies are needed.

Conflicts of interest

N/A