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Progression of MRI and neuropsychiatric changes in predementia frontotemporal dementia mutation carriers with TMEM106B genetic variants

State-of-the-art:

The TMEM106B risk-allele is associated with an earlier age of FTD onset and a higher burden of FLAIR-MRI white-matter hyperintensities (WMH) in symptomatic GRN mutation carriers. As higher WMH burden is associated with neuropsychiatric symptoms (NPS), those carrying the risk-allele may also experience NPS worsening. We hypothesized that risk-allele carrying FTD mutation carriers have higher rates of WMH accumulation and NPS progression from the predementia stages.

Methodology:

We compared the predementia (CDR-plus-NACC-FTLD global 0 and 0.5) progression rates of WMH total volume (normalized to intracranial volume) and NPI-Q (Neuropsychiatric Inventory-Questionnaire) total scores among FTD mutation carriers and noncarriers who carry the TMEM106B risk-allele (A/A) or carry one protective allele (A/G). We included three mutation carrier groups (GRN+;C9orf72+;MAPT+). We used a mixed-effects model (reference: Noncarriers(A/G)).

Results:

WMH: (N=42 GRN+; 84 C9orf72+; 59 MAPT+; 167 Noncarriers). Longitudinally, GRN+(A/A) (p=0.003) had higher rates of WMH accumulation compared to Noncarriers(A/G). Rates of WMH accumulation in GRN+(A/G), C9orf72+(A/A), C9orf72+(A/G), MAPT+(A/A), and MAPT+(A/G) were similar to Noncarriers(A/G).

NPI-Q: (N=41 GRN+; 74 C9orf72+; 51 MAPT+; 150 Noncarriers). Longitudinally, GRN+(A/A) (p=0.002), C9orf72+(A/A) (p=0.04), and MAPT+(A/G) (p=0.005) showed higher rates of NPI-Q increases compared to Noncarriers(A/G). Rates of NPI-Q increases in GRN+(A/G), C9orf72+(A/G), and MAPT+(A/A) groups were similar to Noncarriers(A/G).

Conclusion:

TMEM106B risk-allele may interact with GRN mutation and cause accelerated white-matter changes that may be associated with NPS worsening. Further studies are warranted to identify potential correlates of NPS changes in other mutation carriers. Our findings may reflect pro-inflammatory environment and WM injury associated with TMEM106B risk-variants.