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Epigenome-wide association studies identify differentially methylated loci across frontotemporal lobar degeneration subgroups

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State of the art: Frontotemporal dementia (FTD) is the second most common form of early onset dementia. FTD encompasses distinct clinical syndromes characterized by behavioural and language problems, and overlaps with motor neuron disease/amyotrophic lateral sclerosis as well as with atypical parkinsonian disorders, including progressive supranuclear palsy. Frontotemporal lobar degeneration (FTLD) is the umbrella term describing the neuropathology of the FTD spectrum. The three major FTLD subgroups are characterised by specific proteinaceous inclusions: FTLD-TDP, FTLD-tau, and FTLD-FUS. Although alterations in DNA methylation have consistently been associated with neurodegenerative diseases, including Alzheimer's disease, little is known for FTLD and its heterogeneous subgroups and subtypes. The main goal of this study was to investigate DNA methylation changes in FTLD-TDP and FTLD-tau. **Methodology:** We used frontal cortex genome-wide DNA methylation profiles from three FTLD cohorts (144 FTLD and 93 controls), generated using Illumina 450K or EPIC arrays. We performed epigenome-wide association studies followed by meta-analysis to identify differential methylated loci across FTLD subgroups. We also used weighted gene correlation network analysis to identify DNA methylation signatures associated with FTLD. **Results:** A meta-analysis of the three cohorts revealed differentially methylated loci across FTLD subgroups, including hypomethylation in a gene not previously linked to FTLD, which is involved in stress granules. Co-methylation network analysis revealed several DNA signatures associated with the FTLD risk, and with specific FTLD subtypes and traits (e.g. disease onset). **Conclusion:** Our data implicates novel FTLD-associated loci and supports a role for DNA methylation in the pathogenesis of FTLD.

Conflicts of interest

N/A