Genetic Frontotemporal dementia

Etiology

Approximately a third of frontotemporal dementia (FTD) is genetic with mutations in three genes accounting for most of the inheritance: C9orf72, GRN, and MAPT. Impaired synaptic health is a common mechanism in all three genetic variants, so developing fluid biomarkers of this process could be useful as a readout of cellular dysfunction within therapeutic trials.

Differential synaptic dysfunction is seen in the genetic forms of frontotemporal dementia, with abnormalities in multiple measures in those with MAPT mutations, but only changes in neuronal pentraxins within the GRN and C9orf72 mutation groups. Such markers may be useful in future trials as measures of synaptic dysfunction, but further work is needed to understand how these markers change throughout the course of the disease [1)].

Clinical features

Reduced empathy is a common symptom in frontotemporal dementia (FTD). Although empathy deficits have been extensively researched in sporadic cases, few studies have explored the differences in familial forms of FTD.

Empathy was examined using a modified version of the Interpersonal Reactivity Index (mIRI) in 676 participants from the Genetic FTD Initiative: 216 mutation-negative controls, 192 C9orf72 expansion carriers, 193 GRN mutation carriers and 75 MAPT mutation carriers. Using global scores from the CDR® plus NACC FTLD, mutation carriers were divided into three groups, asymptomatic (0), very mildly symptomatic/prodromal (.5), or fully symptomatic (1 or more). The mIRI Total score, as well as the subscores of Empathic Concern (EC) and Perspective Taking (PT) were assessed. Linear regression models with bootstrapping were used to assess empathy ratings across genetic groups, as well as across phenotypes in the symptomatic carriers. Neural correlates of empathy deficits were examined using a voxel-based morphometry (VBM) analysis.

All fully symptomatic groups scored lower on the mIRI Total, EC, and PT when compared to controls and their asymptomatic or prodromal counterparts (all $p < .001$). Prodromal C9orf72 expansion carriers also scored significantly lower than controls on the mIRI Total score ($p = .046$). In the phenotype analysis, all groups (behavioural variant FTD, primary progressive aphasia and FTD with amyotrophic lateral sclerosis) scored significantly lower than controls (all $p < .007$). VBM revealed an overlapping neural correlate of the mIRI Total score across genetic groups in the orbitofrontal lobe but with additional involvement in the temporal lobe, insula and basal ganglia in both the GRN and MAPT groups, and uniquely more posterior regions such as the parietal lobe and thalamus in the GRN group, and medial temporal structures in the MAPT group.

Significant empathy deficits present in genetic FTD, particularly in symptomatic individuals and those with a bvFTD phenotype, while prodromal deficits are only seen using the mIRI in C9orf72 expansion carriers [2)]

Studies have previously shown evidence for presymptomatic cortical atrophy in genetic FTD. Whilst initial investigations have also identified early deep grey matter volume loss, little is known about the extent of subcortical involvement, particularly within subregions, and how this differs between genetic groups.

480 mutation carriers from the Genetic FTD Initiative (GENFI) were included (198 GRN, 202 C9orf72, 80 MAPT), together with 298 non-carrier cognitively normal controls. Cortical and subcortical volumes of interest were generated using automated parcellation methods on volumetric 3 T T1-weighted MRI scans. Mutation carriers were divided into three disease stages based on their global CDR® plus NACC FTLD score: asymptomatic (0), possibly or mildly symptomatic (0.5) and fully symptomatic (1 or more).

In all three groups, subcortical involvement was seen at the CDR 0.5 stage prior to phenoconversion, whereas in the C9orf72 and MAPT mutation carriers there was also involvement at the CDR 0 stage. In the C9orf72 expansion carriers the earliest volume changes were in thalamic subnuclei (particularly pulvinar and lateral geniculate, 9-10%) cerebellum (lobules VIIa-Crus II and VIIIb, 2-3%), hippocampus (particularly presubiculum and CA1, 2-3%), amygdala (all subregions, 2-6%) and hypothalamus (superior tuberal region, 1%). In MAPT mutation carriers changes were seen at CDR 0 in the hippocampus (subiculum, presubiculum and tail, 3-4%) and amygdala (accessory basal and superficial nuclei, 2-4%). GRN mutation carriers showed subcortical differences at CDR 0.5 in the presubiculum of the hippocampus (8%).

C9orf72 expansion carriers show the earliest and most widespread changes including the thalamus, basal ganglia and medial temporal lobe. By investigating individual subregions, changes can also be seen at CDR 0 in MAPT mutation carriers within the limbic system. Our results suggest that subcortical brain volumes may be used as markers of neurodegeneration even prior to the onset of prodromal symptoms [3].

1)
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3)
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