

# Differential early subcortical involvement in genetic frontotemporal dementia within the GENFI cohort

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## Background

Studies have previously shown evidence for presymptomatic cortical atrophy in genetic frontotemporal dementia (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. We aimed to examine the specific pattern of subcortical changes (including specific subregions), to determine which areas were impaired across the different disease stages of genetic FTD.

## Methods

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 (NC) (Table). Cortical and subcortical volumes of interest were generated using automated parcellation methods on volumetric 3T 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).

## Results

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 (Figure). In the *C9orf72* group 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 the *MAPT* group 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%).

|         | NC      | <i>C9orf72</i> |         |        | <i>MAPT</i> |         |         | <i>GRN</i> |         |        |
|---------|---------|----------------|---------|--------|-------------|---------|---------|------------|---------|--------|
| CDR     | --      | 0              | 0.5     | ≥1     | 0           | 0.5     | ≥1      | 0          | 0.5     | ≥1     |
| n       | 298     | 107            | 32      | 63     | 47          | 13      | 20      | 125        | 30      | 43     |
| Age yrs | 46 (13) | 44 (12)        | 49 (12) | 63 (9) | 39 (11)     | 47 (12) | 58 (10) | 46 (12)    | 52 (13) | 64 (8) |
| Male %  | 42%     | 41%            | 38%     | 65%    | 43%         | 41%     | 65%     | 34%        | 50%     | 49%    |

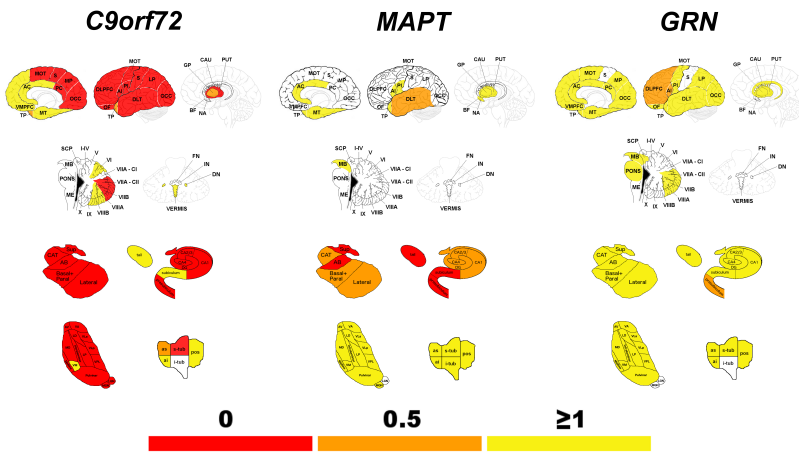


Figure: Sequential pattern of neuroanatomical involvement in *C9orf72*, *MAPT* and *GRN*. The colour map indicates the stage defined by CDR®+NACC FTLD global scores when the specific region becomes involved, as significantly smaller than controls.

## Conclusions

*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.

