Quantitative susceptibility mapping in genetic FTD

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Introduction

- Early brain changes (grey- and white-matter) are detectable before symptom onset in genetic FTD (Rohrer et al., 2015, Cash et al., 2017, Bouzigues et al., 2026).
- QSM is an imaging tool that quantifies tissue magnetic susceptibility, which is influenced by iron, myelin, microstructural organisation, and tissue composition (Ma et al., 2025).
- In other neurodegenerative diseases like Alzheimer's and Parkinson's disease, QSM has quantified changes in subcortical regions like the caudate and substantia nigra, respectively (Ravanfar et al., 2021).
- However, unlike in other neurodegenerative diseases, magnetic susceptibility changes remain poorly characterised in FTD.
- Aim: To characterise tissue susceptibility differences between controls, asymptomatic and symptomatic mutation carriers in the GENFI cohorts.

Results

- No significant QSM differences were observed between disease stages in any ROIs.
- R2* was significantly reduced across disease stages in the bilateral insula, anterior frontal, superior temporal, caudal middle frontal, and posterior cingulate regions.
- Insular (*p=0.03*) and anterior frontal (*p=0.01*) R2* reductions were detectable in asymptomatic carriers compared to controls (uncorrected), highlighting potential early changes in susceptibility.
- Symptomatic carriers showed further R2* reductions in the insula (*p=0.008*), superior temporal (*p=0.01*), caudal middle frontal (*p=0.005*), and posterior cingulate (*p=0.049*) regions compared with asymptomatic carriers (uncorrected).

Methods

The study included non-carrier controls, asymptomatic carriers (8 C9orf72, 10 GRN, 11 MAPT), and symptomatic carriers (10 C9orf72, 3 GRN, 8 MAPT) from the GENFI cohort. CDR+NACC FTLD-NM = 0 for asymptomatic carriers and +1 for symptomatic carriers

Participants underwent MRI, including T1-weighted and multi-echo gradient-echo imaging for QSM and R2* mapping. Image pre-processing and ROI extraction were completed as described in *Figure 1*.

*Table 1. Sample demographics; continuous variables presented as mean ± SD; * denotes significant difference from controls*

	Non-carrier	Asymptomatic carrier	Symptomatic carrier
N	30	29	21
Age, years	52.6 ± 11.6	49.1 ± 9.8	61.9 ± 6.7*
Sex, F:M	16:14	15:14	10:11
Education, years	14.8 ± 3.2	14.6 ± 3.2	12.6 ± 3.4

We selected 13 cortical and subcortical ROIs based on previous research: the insula, nucleus accumbens, caudate, globus pallidus, putamen, thalamus, caudal middle frontal, posterior cingulate, precuneus, anterior frontal, superior frontal, superior temporal, and temporal pole regions.

Mean QSM and R2* values were calculated for the ROIs, and averaged across hemispheres. For each bilateral ROI, QSM and R2* were modelled separately with linear regression, adjusting for age and sex.

Overall group effects were assessed using ANOVA. Post-hoc pairwise comparisons were performed to identify specific group differences. Uncorrected p-values are reported for this preliminary sample subset.

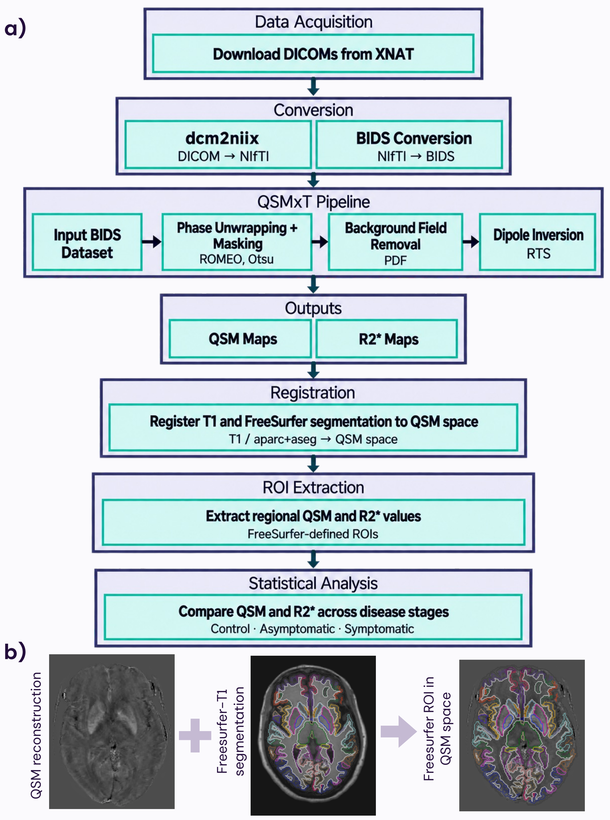

Figure 1a) and b) Flowcharts depicting QSM analysis methodology.

Significant reduction in R2* for asymptomatic carriers vs controls

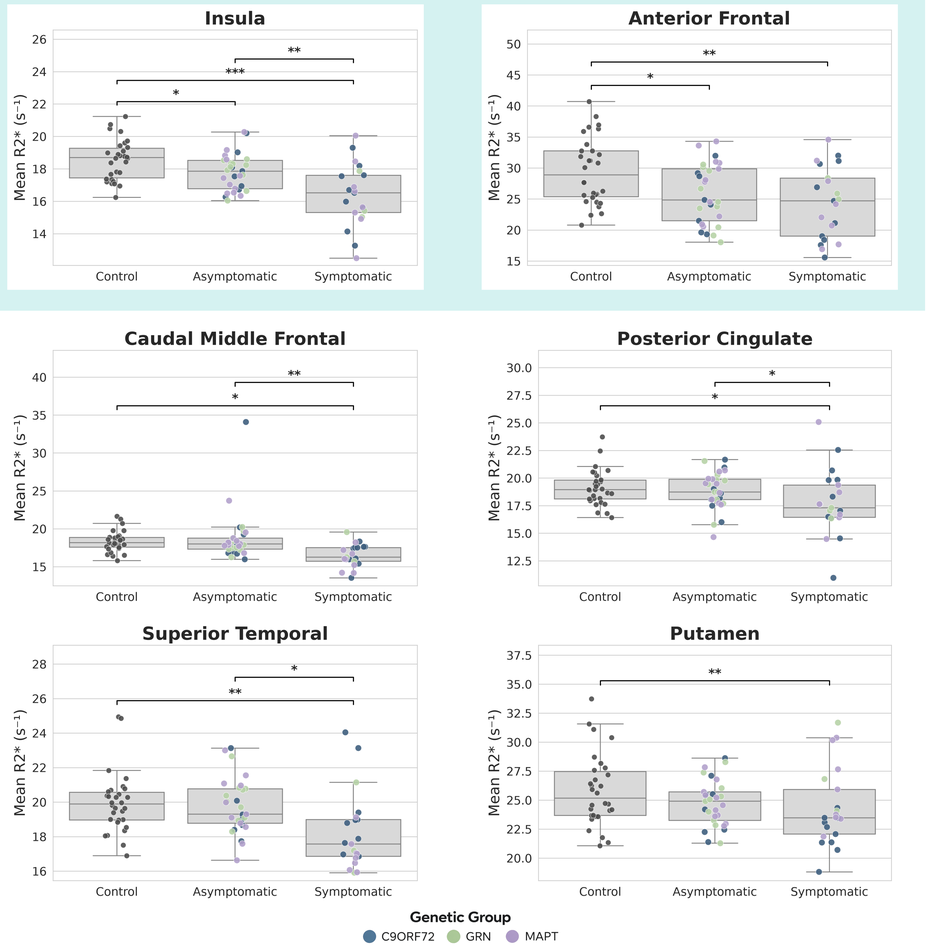

Figure 2) Mean bilateral R2* values across control, asymptomatic (CDR+NACC FTLD-NM global = 0), and symptomatic (CDR+NACC FTLD-NM global = 1+) groups in selected regions. Significant (uncorrected) pairwise comparisons are denoted as *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Conclusions

These results highlight changes in microscopic magnetic relaxation, but no detectable change in the average susceptibility. Changes in R2* but not QSM could reflect alterations in tissue microstructure and/or myelin, rather than susceptibility changes driven solely by iron accumulation.

More work will be needed to identify which specific microstructural/tissue-composition alterations are occurring. We also aim to explore gene-specific patterns and the relationship between QSM, R2* and clinical severity in the wider GENFI cohort.

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