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Radiogenomics of C9orf72 expansion carriers reveals global transposable element de-repression and enables prediction of thalamic atrophy and clinical impairment

State of the art

Hexanucleotide repeat expansion (HRE) within C9orf72 is the most common genetic cause of frontotemporal dementia (FTD). Thalamic atrophy occurs in both sporadic and familial FTD but is thought to distinctly affect HRE carriers with FTD (C9-FTD). Separately, emerging evidence suggests widespread de-repression of transposable elements (TEs) in the brain in several neurodegenerative diseases, including C9-FTD. Whether TE activation can be measured in peripheral blood and how the reduction in peripheral C9orf72 expression observed in HRE carriers relates to atrophy and clinical impairment remain unknown.

Methodology

We used the Freesurfer pipeline and its extensions to assess the effects of C9orf72 HRE and diagnosis on atrophy of thalamic nuclei (N=78). We also generated a novel, whole-blood RNA-seq dataset to determine the relationships between C9orf72 expression, TE activation, thalamic atrophy, and clinical severity (N=114).

Results

We confirm global thalamic atrophy and reduced peripheral C9orf72 expression in HRE carriers. Moreover, we identify disproportionate atrophy of the right mediodorsal lateral nucleus in HRE carriers and show that C9orf72 expression associates with clinical severity, independent of thalamic atrophy. Strikingly, we find global peripheral activation of TEs, including the human endogenous LINE-1 element, L1HS. L1HS levels associate with atrophy of multiple pulvinar nuclei, a thalamic region implicated in C9-FTD.

Conclusion

Integration of peripheral transcriptomic and neuroimaging data from HRE carriers reveals atrophy of specific thalamic nuclei; shows that C9orf72 levels relate to clinical severity; and identifies marked de-repression of L1HS, levels of which predict atrophy of FTD-relevant thalamic nuclei.