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BIOMARKERS

POSTER PRESENTATIONS

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Neuroimaging / Optimal neuroimaging measures for tracking disease progression

Modelling the cascade of biomarker changes in progranulin-related frontotemporal dementia

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Abstract

Background: Progranulin related frontotemporal dementia (FTD-*GRN*) is a fast progressive disorder, in which pathophysiological changes precede overt clinical symptoms in only a short time period. Modelling the cascade of multimodal biomarker changes aids in understanding the etiology of this disease, enables monitoring of individual mutation carriers, and would give input for disease-modifying treatments. In this cross-sectional study, we estimated the temporal cascade of biomarker changes for FTD-*GRN*, in a data-driven way.

Method: We included 56 presymptomatic and 35 symptomatic *GRN* mutation carriers, and 35 healthy non-carriers. Of the symptomatic subjects, 17 had behavioural variant FTD (bvFTD), 16 presented as non-fluent variant primary progressive aphasia (nfvPPA). The selected biomarkers for establishing the cascade of changes were neurofilament light chain, regional grey matter volumes, fractional anisotropy of white matter tracts, and cognitive domains. We used a data-driven analysis called discriminative event-based modelling (Venkatraghavan, NeuroImage, 2019) with a novel modification to its Gaussian Mixture Model (GMM) called Siamese GMM, to estimate the cascade of biomarker changes for FTD-*GRN*. Using cross-validation, we estimated disease severities of individual mutation carriers in the test set based on their progression along the biomarker cascade established on the training set.

Result: Neurofilament light chain and white matter tracts were the earliest biomarkers to become abnormal in FTD-*GRN* mutation carriers. Attention and executive functioning were also affected early on in the disease process. Based on the estimated individual disease severities, presymptomatic mutation carriers could be distinguished from symptomatic mutation carriers with a sensitivity of 95% and specificity of 100% in the

cross-validation experiment. There was a high correlation (r=0.94, p<0.001) between estimated disease severity and years since symptom onset in nfvPPA, but not in bvFTD (r=0.33, p=0.46).

Conclusion: In this study, we unravelled the temporal cascade of multimodal biomarker changes for FTD-*GRN*. Our results suggest that axonal degeneration is one of the first disease events in FTD-*GRN*, which calls for designing disease modifying treatments that strengthens the axons. We also demonstrated a good delineation between symptomatic and presymptomatic carriers using the estimated disease severities, which suggest that our model could enable monitoring of individual mutation carriers.

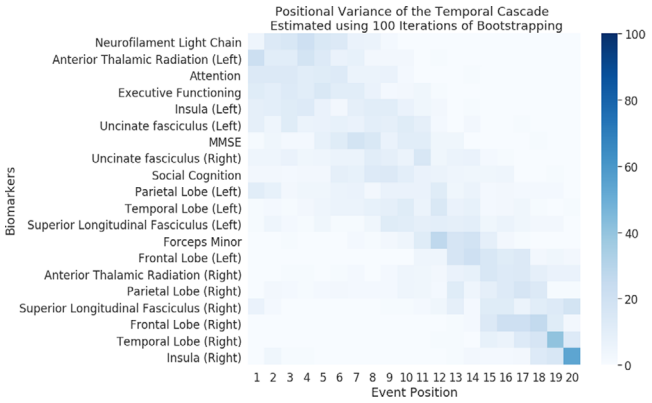

FIGURE 1

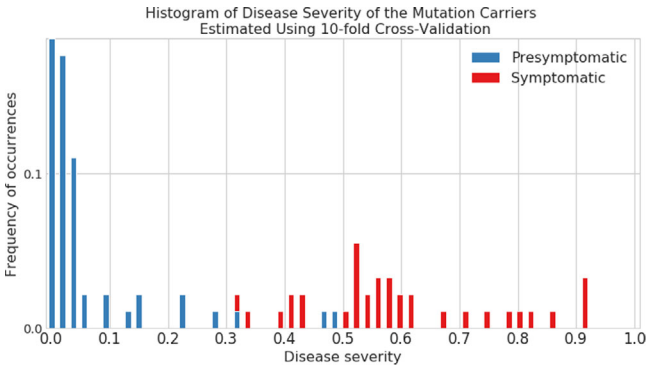

FIGURE 2