Subtype and stage inference identifies distinct atrophy patterns in genetic frontotemporal dementia that MAP onto specific *MAPT* mutations

Alexandra L. Young, Martina Bocchetta, David M Cash, Rhian S Convery, Katrina M Moore, Mollie R Neason, David L Thomas, John C. van Swieten, Barbara Borroni, Raquel Sanchez-Valle, Fermin Moreno, Robert Laforce Jr., Caroline Graff, Matthis Synofzik, Daniela Galimberti, James B Rowe, Mario Masellis, Carmela Tartaglia, Elizabeth Finger, Rik Vandenberghe, Alexandre Mendonca, Fabrizio Tagliavini, Isabel Santana, Simon Ducharme, Christopher Butler, Alexander Gerhard, Johannes Levin, Adrian Danek, Markus Otto, Giovanni B Frisoni, Roberta Ghidoni, Sandro Sorbi, Steven CR Williams, Daniel C. Alexander, Jonathan D Rohrer, Genetic FTD Initiative (GENFI)

Background
Mutations in the MAPT gene are known to cause frontotemporal dementia (FTD), but there is heterogeneity in FTD phenotype across individuals. Here we used an unsupervised learning algorithm – Subtype and Stage Inference (SuStaIn) – to relate phenotypic heterogeneity to specific mutations in the MAPT gene.
Method
SuStaIn evaluates the optimal grouping of individuals into disease subtypes, where each subtype consists of a sequence (set of stages) in which biomarkers transition between different z-scores. We applied SuStaIn to cross-sectional regional brain volumes extracted from T1-weighted MRI data from MAPT carriers in the GENFI study to find the best stratification of the data into subtypes, and the temporal progression of each subtype. We used data from 82 MAPT carriers (57 presymptomatic and 25 symptomatic) to identify subtypes and data from a control group of 300 non-carriers to derive z-scores. We subtyped and staged individuals at up to five annual follow-up visits to assess the consistency of the subtypes longitudinally. We compared the specific mutations and clinical and neuropsychological test scores of individuals assigned to each subtype.
Result
SuStaIn identified two groups of MAPT carriers with distinct atrophy patterns (Figure 1), which we termed a 'temporal' subtype and a 'frontotemporal' subtype. The subtype assignments were consistent at follow-up visits (Table 1): there were no individuals that changed from the temporal to the frontotemporal subtype or vice-versa. Subtype assignment was strongly associated with IVS10+16, R406W and P301L mutations (Table 2): there was a one-to-one mapping between IVS10+16 and R406W mutations and the temporal subtype, and a near one-to-one mapping between P301L mutations and the frontotemporal subtype. The temporal subtype was associated with memory problems, whereas the frontotemporal subtype was associated with worse performance on tests of attention and visuospatial skills (Table 3).
Conclusion
Our results demonstrate the utility of SuStaIn for identifying disease subgroups and associating imaging patterns with genetics and cognition. We show that different MAPT mutations give rise to distinct atrophy patterns and clinical syndromes, providing insights into the underlying disease biology, and potential utility for patient stratification.