Symptom Onset in Genetic Frontotemporal Dementia

Katrina M Dick, Corey T McMillan, John van Swieten, Alexander Gerhard, Isabelle Le Ber, Giovanni Frisoni, Bradford C Dickerson, Caroline Graff, Nupur Ghoshal, Barbara Borroni, Daniela Galimberti, Ian Mackenzie, Matthis Synofzik, Raquel Sanchez-Valle, Isabel Santana, Fermin Moreno, Johannes Levin, James B Rowe, Alexandre Mendonça, Mario Masellis, Philippe Couratier, Edward D Huey, Sandro Sorbi, Robert Laforce Jr, Rik Vandenberghe, Chiadi U Onyike, Emily Rogalski, Simon Ducharme, Sokratis G Papageorgiou, Adeline Ng Su Lyn, Fabrizio Tagliavini, Christopher R Butler, Elizabeth Finger, Murray Grossman, Olivier Martinaud, Markus Otto, Erik D Roberson, Jennifer M Nicholas, John R Hodges, Adam Boxer, Howard J Rosen, Bradley F Boeve, Jonathan D Rohrer on behalf of the Frontotemporal dementia Prevention Initiative (FPI)

Background

Genetic frontotemporal dementia (FTD) is caused by mutations in three main genes: C9orf72, progranulin (GRN) and microtubule-associated protein tau (MAPT). Little is currently known about the factors that influence age at symptom onset in FTD. This study aimed to investigate this through data collected from multiple families through the Frontotemporal dementia Prevention Initiative, a group connecting research centres within four large studies: GENFI, ARTFL, LEFFTDS and DINAD.

Materials and Methods

We collected data from 3020 individuals from 1269 families including age at symptom onset (AAO), age at death (AAD) and clinical diagnosis: 1248 C9orf72 (624 families), 706 MAPT (221 families: 63 different mutations, most commonly P301L), and 1059 GRN (421 families: 120 different mutations, most commonly T272fs). We assessed several factors influencing AAO, including parental AAO and AAO by mutation type and family.

Results

The mean age at symptom onset was 58.6 (standard deviation 9.9) in C9orf72, 50.4 (9.6) in MAPT, and 61.4 (8.9) in GRN (Figure 1). We assessed the correlation of individual AAO with parental AAO and mean AAO within the family. The strongest correlation between individual AAO and both parental AAO (r = 0.55, p<0.001) (Fig.4) and mean AAO in the family (r = 0.67, p <0.001) (Fig. 5) was seen in MAPT. In C9orf72, there was a significant correlation between individual AAO and both parental AAO (r = 0.34, p<0.001) (Fig. 6) and mean AAO in the family (r = 0.48, p <0.001) (Fig. 7) but to a lesser extent than MAPT. The lowest correlation was in the GRN group for both individual AAO and parental AAO (r = 0.19, p=0.001) (Fig.2) and mean family AAO (r=0.30, p<0.001) (Fig. 3) although these are both significant.

Conclusion

In a preliminary analysis we show that a significant proportion of the observed variance in age at symptom onset in genetic FTD can be explained by family history but is variable by mutation type. In our final analysis we plan to develop a model for predicting age at symptom onset in different FTD mutations. Such findings will be essential in analysing data in presymptomatic cohorts when estimating time to symptom onset, and will hopefully provide empirical support for the use of such predictive models in clinical trials.

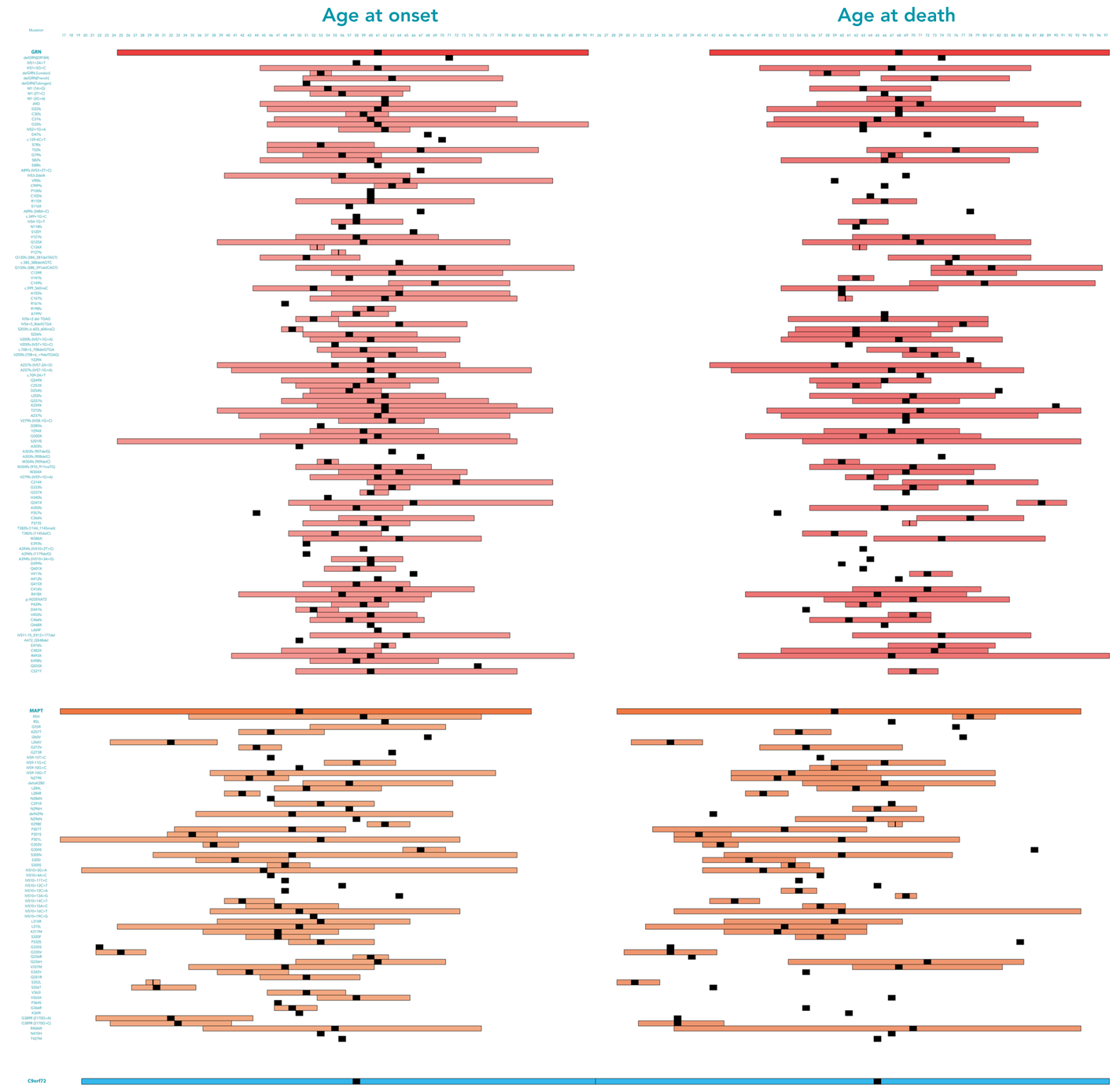

Figure 1: Mean and range of ages of onset and death in individual genetic mutations across GRN, MAPT and C9orf72

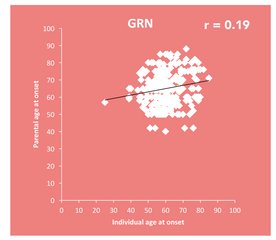

Figure 2

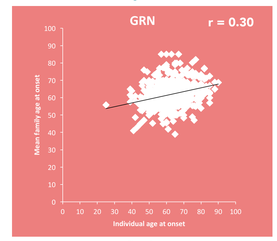

Figure 3

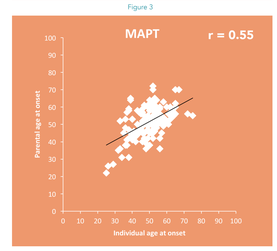

Figure 4

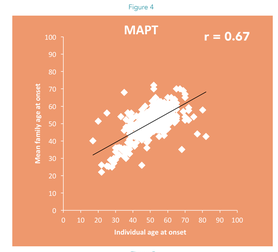

Figure 5

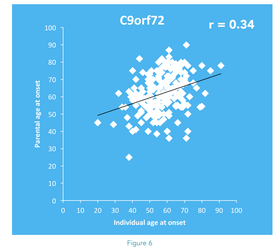

Figure 6

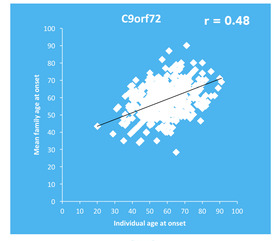

Figure 7

Figures 2, 4, 6: Scatter plots showing the relationship between individual age of onset and mean family age of onset in the three mutation groups
Figures 3, 5, 7: Scatter plots showing the relationship between individual age of onset and parental age of onset in the three mutation groups

KMD is supported by an Alzheimer's Society PhD Studentship. JDR is an MRC Clinician Scientist and has received funding from the NIHR Rare Diseases Translational Research Collaboration.