Predicting Age of Symptom Onset in Genetic **Frontotemporal Dementia**

Background – what is FTD?

Frontotemporal dementia is the second most common form of dementia in people under 65. Today the only known risk factors for FTD are genetic and around a $\frac{1}{3}$ of FTD is inherited. There are three main genes that cause familial FTD: C9orf72, Progranulin (GRN) and MAPT. For many of those affected the question on their mind is 'when am I going to develop symptoms'. At present little is known about the factors influencing the age at symptom onset in FTD. This study aimed to investigate these factors by collecting data from individuals across the world in all three gene categories.

Materials and methods – what we did

Data was collected from multiple families across the world through the Frontotemporal Dementia Prevention Initiative and in reviewing 307 peer reviewed journal articles relating to genetic FTD. The combined dataset contains 3315 individuals from 1418 families. 1370 C9orf72 (703 families), 791 MAPT (254 families), and 1154 GRN (461 families). We assessed several factors influencing age of onset (AAO), including parental AAO and AAO by mutation type and family.

Results – what we found

The mean age at symptom onset was youngest in MAPT at 50.4 years (10.0), followed by C9orf72 at 58.4 years (9.8) and the oldest was GRN at 61.4 years (8.9). We were interested in the relationship between an individuals AAO, the parental AAO and mean AAO in 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 – why is this research important? We show that a significant proportion of the variants in age at symptom onset in genetic FTD can be explained by family history, but that this is variable by genetic mutation type.

This research is important as it is the first study in the world enabling us to predict when an individual may develop symptoms in genetic FTD. These findings will be essential in analysing data in presymptomatic cohorts when estimating time to symptom onset, and will hopefully inform pharmaceutical companies at what age they should begin to enrol patients into clinical trials.



Figure 1: Geographic variability of the three FTD genes across the world 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



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C9orf72

Figure 6



