

Brain Age Gap Estimate As A Predictor Of Symptom Onset In Genetic Frontotemporal Dementia

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Key Message

MRI-based Brain Age Gap Estimate predicts progression in C9orf72 genetic FTD only

Introduction

Genetic frontotemporal dementia (g-FTD) is a young onset dementia caused by mutations in C9orf72, GRN, and MAPT genes. These cases provide an opportunity to detect pathological changes during the presymptomatic stage¹. In C9orf72 neuroimaging reveals early diffuse changes whereas GRN and MAPT show more focal patterns. However, no biomarkers are sensitive enough to detect proximity to symptom onset at an individual level. We explored whether a machine learning derived biomarker for brain age could be predictive of time to symptom onset. This robust measure has been associated various conditions but has not been explored in g-FTD².

Methods

- Study population: 866 participants from the GENetic FTD Initiative (GENFI), a global multi-centre study of g-FTD.
- Carriers (n=647) and non-carriers (n=239) were categorised by NACC-CDR+FTLD-NM-GLOBAL scores (Table):
 - Stable: score remained 0, 0.5, or >0.5 across all visits,
 - Progressor: score increased across visits, or
 - Mixed if score fluctuated across visits.
- Brain age analyses were conducted using brainageR v 2.1².
- Brain age gap estimate (BAGE) was calculated as “brain predicted age - chronological age”.
- Correlation analyses were conducted for BAGE and age and estimated year of symptom onset (EYO) by progression group and genetic group (Figure 1).
- Two BAGE groups (above and below the median) were included in survival analyses (Cox proportional hazards and Kaplan Meier) for each genetic group (Figure 2).

Tables and Figures

Table Study Demographics

Variable	Non-Carrier Stable/Baseline <1	Stable/Baseline 0	Stable/Baseline 0.5	Stable/Baseline 1+	Progressor 0.5	Progressor 1+	Mixed	ANOVA/KW/Chi-sq
Age (years) median [IQR]	42.1 [15.5]	43.5 [15.3]	46.6 [21.4]	62.6 [11.4]	44.8 [22.8]	52.2 [18.5]	46.4 [16.5]	
Education (years) median [IQR]	15.0 [3.5]	15.0 [3.0]	16.0 [4.0]	12.5 [5.0]	15.0 [5.0]	13.5 [5.3]	15.0 [4.0]	
NACC-CDR+FTLD-NM-SB (at baseline visit) median [IQR]	0.0 [0.0]	0.0 [0.0]	1.0 [1.0]	11.0 [12.9]	0.0 [0.0]	0.5 [2.1]	0.0 [1.0]	Kruskal-Wallis: chi2=676.43 (p<0.01**)
Estimated years to onset median [IQR] missing = 3	-17.3 [19.5] n=238	-17.2 [15.8] n=210	-13.7 [18.6]	3.90 [7.04]	-13.5 [20.8]	-1.26 [10.8]	-9.17 [16.2] n=108	
Brain Age Gap Estimate median [IQR]	-1.70 [8.52]	0.21 [9.64]	2.57 [12.06]	9.83 [10.92]	0.69 [12.37]	4.15 [11.69]	-0.88 [10.92]	Kruskal-Wallis: chi2=149.57 (p<0.01**)
Genetic Group C9ORF72 / GRN / MAPT	93 (38.9%) / 99 (41.4%) / 47 (19.7%)	92 (43.6%) / 92 (43.6%) / 27 (12.8%)	35 (48.6%) / 24 (33.3%) / 13 (18.1%)	91 (56.2%) / 49 (30.2%) / 22 (13.6%)	26 (45.6%) / 24 (42.1%) / 7 (12.3%)	9 (25.0%) / 15 (41.7%) / 12 (33.3%)	37 (33.9%) / 48 (44.0%) / 24 (22.0%)	Chi2=31.07 (p<0.01**)
Sex M / F	134 (56.1%) / 105 (43.9%)	129 (61.1%) / 82 (38.9%)	38 (52.8%) / 34 (47.2%)	62 (38.3%) / 100 (61.7%)	38 (66.7%) / 19 (33.3%)	24 (66.7%) / 12 (33.3%)	61 (56.0%) / 48 (44.0%)	Chi2=26.91 (p<0.01**)
Total N	239	211	72	162	57	36	109	

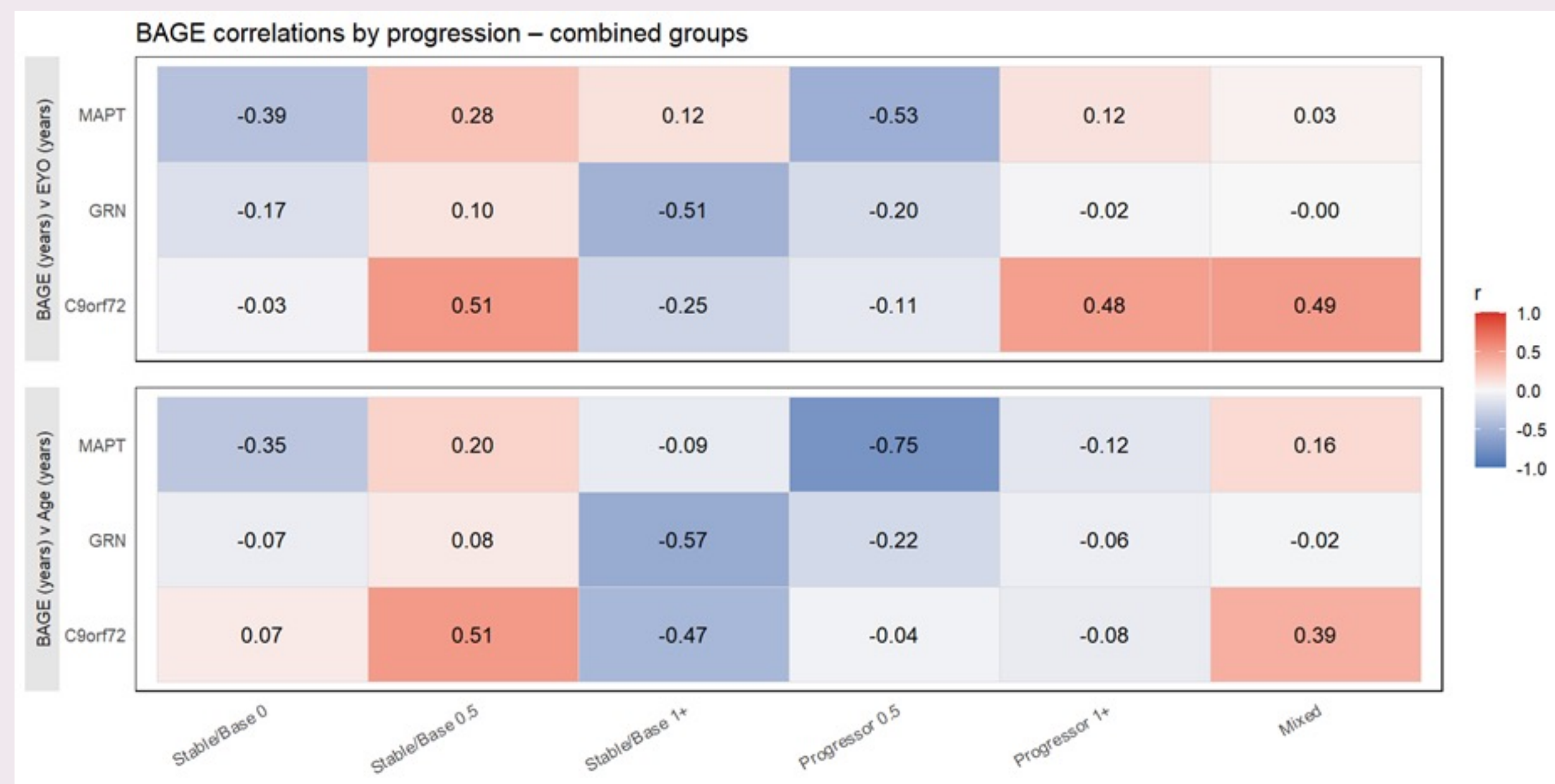


Figure 1 BAGE correlations by genetic group and progression

Results

Brain age gap estimates (BAGE) differed across groups, with Stable/Baseline 1+ showing the highest BAGE (9.83 years) while non-carriers showed the lowest BAGE (-1.70). In C9orf72, BAGE correlated positively with EYO in Stable/Base 0.5, Progressor 1+, and Mixed groups. Cox proportional hazards was significant for C9orf72 genetic group (p<0.05), but not for GRN (p=0.35) or MAPT (p=0.21).

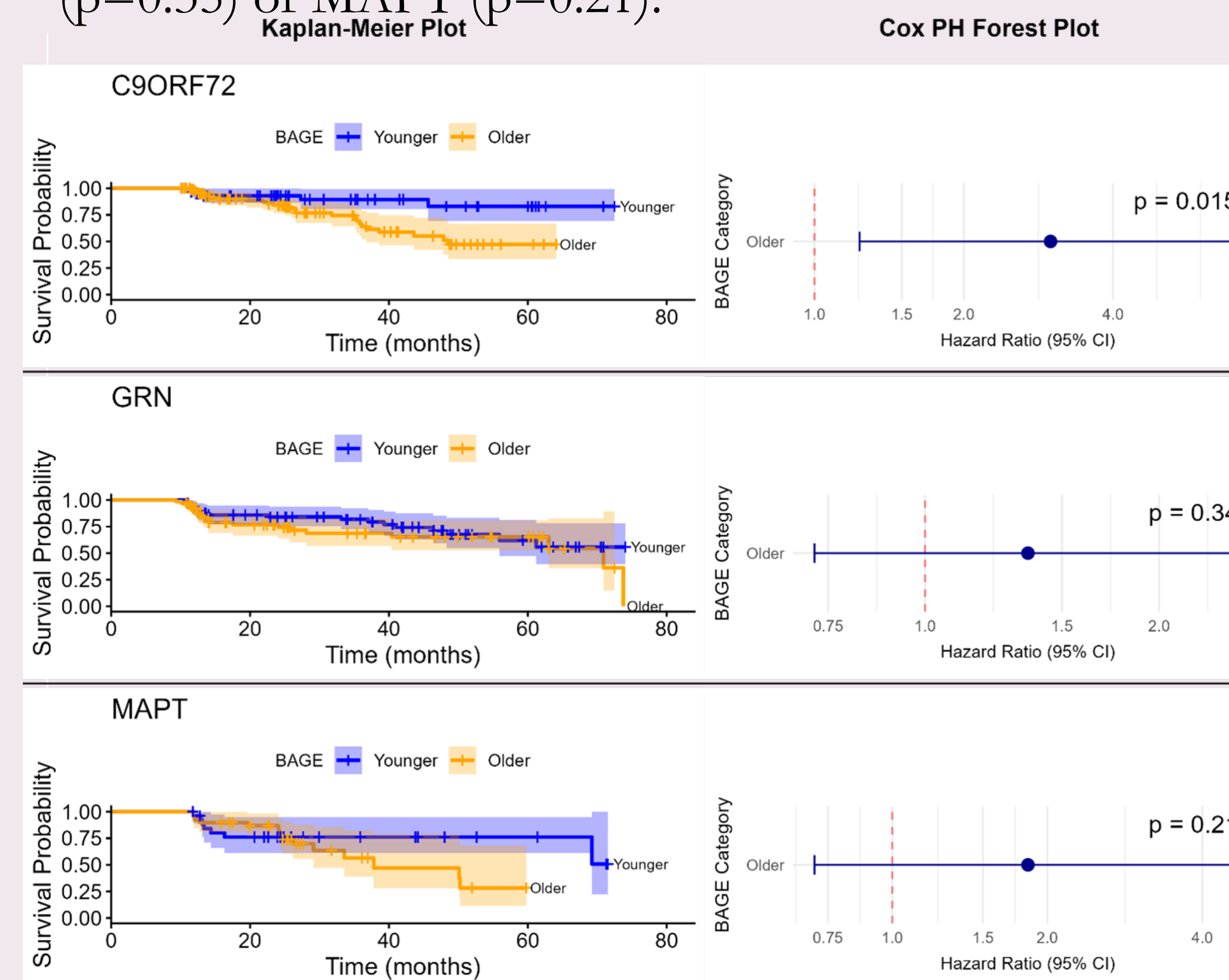


Figure 2 Survival curves and hazard ratio estimates of BAGE

Conclusions

BAGE derived is predictive of onset for presymptomatic C9orf72 carriers only. For presymptomatic GRN and MAPT carriers, this whole brain analysis appears to be missing more focal atrophy. We suggest that measures that account for localised regional atrophy may be more predictive in these groups.

References

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