# Early changes in heart rate variability in asymptomatic FTD mutation carriers.

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## Background

Autonomic function, controlled by the autonomic nervous system, regulates involuntary body processes such as heart rate and pain perception. In frontotemporal dementia (FTD), autonomic function is impaired, but its measurement in this population is limited (Hazelton et al., 2023). Heart rate variability (HRV), the variation between successive heartbeats, is a proxy for autonomic function: higher HRV reflects greater parasympathetic activity and cardiovascular health, while lower HRV indicates reduced fitness and recovery. The Genetic FTD Initiative (GENFI) has spearheaded the use of digital health technologies (DHTs), such as smart watches like Fitbit, for remote monitoring and the early identification of FTD symptoms.

## Methods

Participants attended their GENFI research visit at UCL and completed the Clinical Dementia Rating Scale plus Frontotemporal Lobar Degeneration Clinical Dementia Rating Scale and National Alzheimer's Coordinating Centre Behaviour and Language Domains (CDR + NACC FTLD), as well as the extended version incorporating neuropsychiatric and motor components (CDR+NACC-FTLD-NM) during their clinical examination. After the visit, a Fitbit Charge 6 was provided for for 28 days, and worn when asleep and awake.

Resting HRV was measured through average root mean square of successive differences (RMSSD), per person over 30-days. Mutation carriers were classified based on CDR+NACC-FTLD-NM stages: asymptomatic (0; n = 18, mean age = 37.2 , SD = 11.5 ), prodromal (0.5; n = 44, mean age = 46.8, SD = 10.1), and symptomatic (>0.5; n = 7, mean age = 64.1, SD = 5.93). Differences in average RMSSD between these groups and 30 mutation-negative controls (mean age = 50, SD = 12.7) were analysed using a linear regression model, adjusting for age.

| Genetic status | *N* | Age (*SD*) | Sex in % Female |
|---|---|---|---|
| **Non-carriers** | 30 | 50 (12.7) | 50.0 |
| **Mutation carriers** | | | |
| *Asymptomatic (CDR = 0)* | 18 | 37.2 (11.5) | 44.4 |
| *Prodromal (CDR = 0.5)* | 44 | 36.8 (10.1) | 54.6 |
| *Symptomatic (CDR ≥1)* | 7 | 64.1 (5.9) | 57.1 |
| **Total** | 99 | 47.0 | 51.5 |

**Table 1.** Participant demographics


## Results

### Early changes in HRV in asymptomatic mutation carriers

Asymptomatic mutation carriers had greater HRV with significantly higher RMSSD scores (mean = 45.3, SD = 11.4), compared to mutation negative controls (mean = 29.9, SD = 16.5, $p < .001$). No significant differences were found between controls and prodromal mutation carriers (mean = 31.1, SD = 10.8, $p = 0.93$) or between controls and symptomatic mutation carriers (mean = 19.1, SD = 6.11, $p = 0.22$), although there was a trend to a lower RMSSD in the latter group.

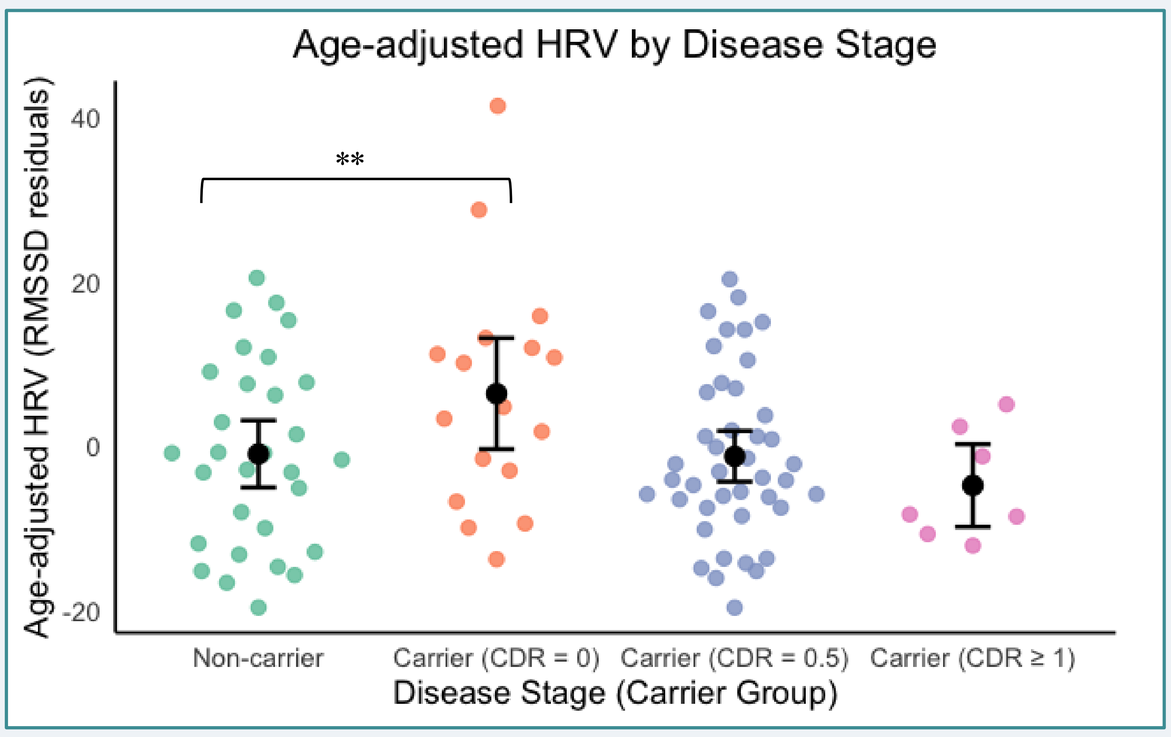


**Figure 1**. Age-Adjusted Heart Rate Variability (RMSSD) Across FTD Stages by FTLD-CDR-NM Score. My

### Changes in HRV by group and stage

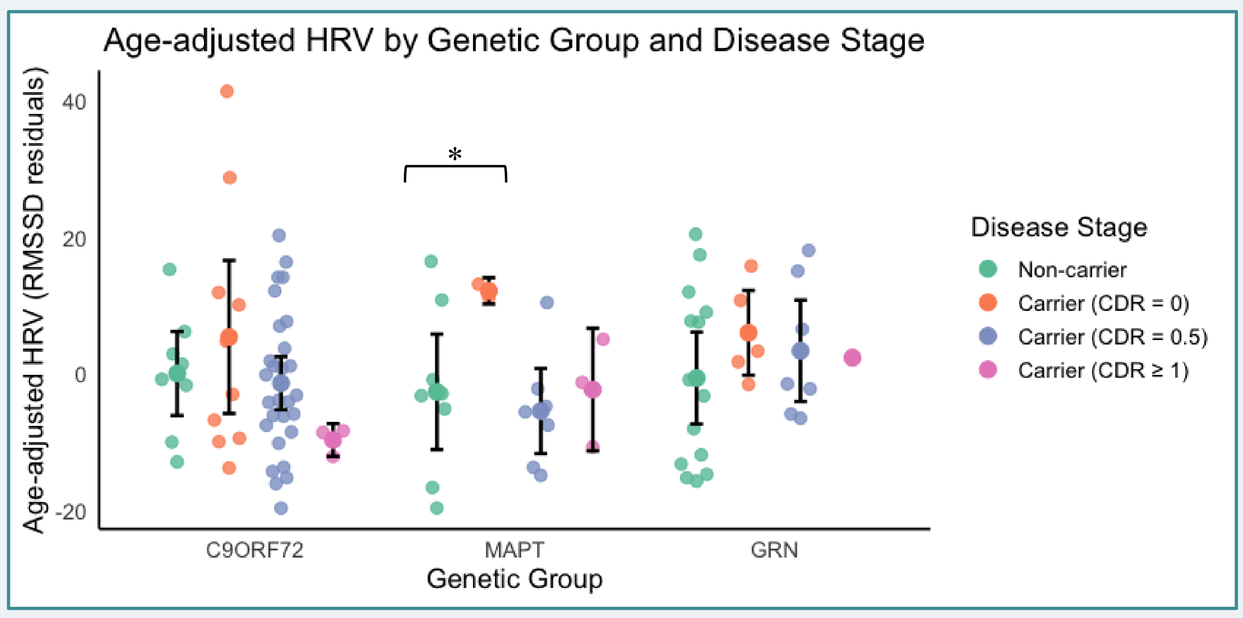


**Figure 2**. Age-Adjusted Heart Rate Variability (RMSSD) Across Genetic Mutations (C9orf72, MAPT, GRN) split by FTD Stages by FTLD-CDR-NM Score.

**In the C9orf72 group** (n = 51), HRV decreased across disease stages. Although differences between non-carriers and carriers did not reach statistical significance, there is an observed trend of declining HRV as disease severity increases.

**In the MAPT group** (n = 21), asymptomatic carriers (CDR=0) demonstrated significantly higher HRV (mean = 61.9, SD = 12.4, p = 0.041) compared to non-carriers (mean = 33.0, SD = 11.1). No additional significant differences were observed across disease stages. Notably, HRV appeared to increase in later stages, although this subgroup (CDR ≥1) was small (n = 3), limiting interpretation.

**In the GRN group** (n = 27), HRV patterns were similar to those observed in C9orf72, with reduced HRV across stages. However, none of these differences reached statistical significance relative to non-carriers.

## Future direction

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Oura Rings (4th Generation) have been incorporated into all UCL GENFI research visits, and are worn by participants, alongside the Fitbit Charge 6, for 28 days following each visit.

The data collected, including HRV, body temperature, sleep, and activity, will be used to detect early physiological changes. Data will also be compared to Fitbit data to identify which device is most effective for identifying early physiological markers of familial FTD.

## Conclusion

We found increased HRV at the asymptomatic stage (CDR = 0) compared to controls, while HRV declines in later stages, suggesting progressive parasympathetic dysfunction. Although the small sample size may be limiting the ability to detect changes, these findings support DHTs as potential biomarkers for tracking physiological changes across FTD stages, while facilitating remote, unsupervised monitoring before and after symptom onset. Future work will continue to validate digital wearables for detecting physiological changes in the GENFI study.

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