

# Locus Coeruleus Changes in Familial Alzheimer's Disease and Its Clinical Correlates: Insights from the PICOGEN Barcelona Cohort

Isabel Martín-Sobrino<sup>1\*</sup>, Beatriz Bosch<sup>1,2\*</sup>, Marta Peña-González<sup>3</sup>, Agnès Pérez-Millan<sup>1,2,4</sup>, Núria Guillén<sup>1,2</sup>, Adrià Tort-Merino<sup>1,2</sup>, Clàudia Morante-Serra<sup>1</sup>, Guadalupe Fernández-Villullas<sup>1,2</sup>, Josep Maria Augé<sup>1\*</sup>, Albert Lladó<sup>1,2</sup>, Emma Muñoz-Moreno<sup>3</sup>, Lea T Grinberg<sup>5</sup>, Raquel Sánchez-Valle<sup>1,2\*</sup>, Neus Falgàs<sup>1,2\*</sup>

<sup>1</sup>Alzheimer's disease and other cognitive disorders Group. Service of Neurology, Hospital Clínic de Barcelona. Fundació Recerca Clínic Barcelona-IDIBAPS.

<sup>2</sup>Centro de Investigación Biomédica en Red en Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain

<sup>3</sup>Magnetic Resonance Imaging Core Facility, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Catalonia, Spain

<sup>4</sup>eHealth Center, Faculty of Computer Science, Multimedia and Telecommunications, Universitat Oberta de Catalunya, 08016 Barcelona, Spain

<sup>5</sup>Department of Neuroscience, Mayo Clinic, Jacksonville, Florida, USA. Department of Laboratory Medicine and Pathology, Mayo Clinic, Jacksonville, Florida, USA



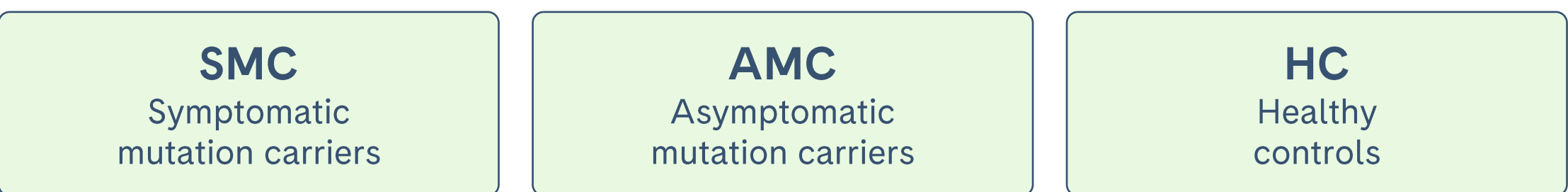
## BACKGROUND

Previous research has demonstrated that **tau pathology accumulates early in Alzheimer's disease (AD), particularly in the locus coeruleus (LC)** (Braak stage 0). The LC's early involvement **contributes to the onset of neuropsychiatric symptoms** and sleep disturbances in sporadic AD. Although **a few MRI studies have reported early changes in LC integrity in autosomal dominant AD (ADAD)**, the clinical implications of these changes remain poorly understood. **Our study aims to investigate the clinical impact of LC degeneration in both asymptomatic (AMC) and symptomatic mutation carriers (SMC)** within the PICOGEN Clínic Barcelona Cohort, focusing on its potential role in cognitive and neuropsychiatric symptoms.

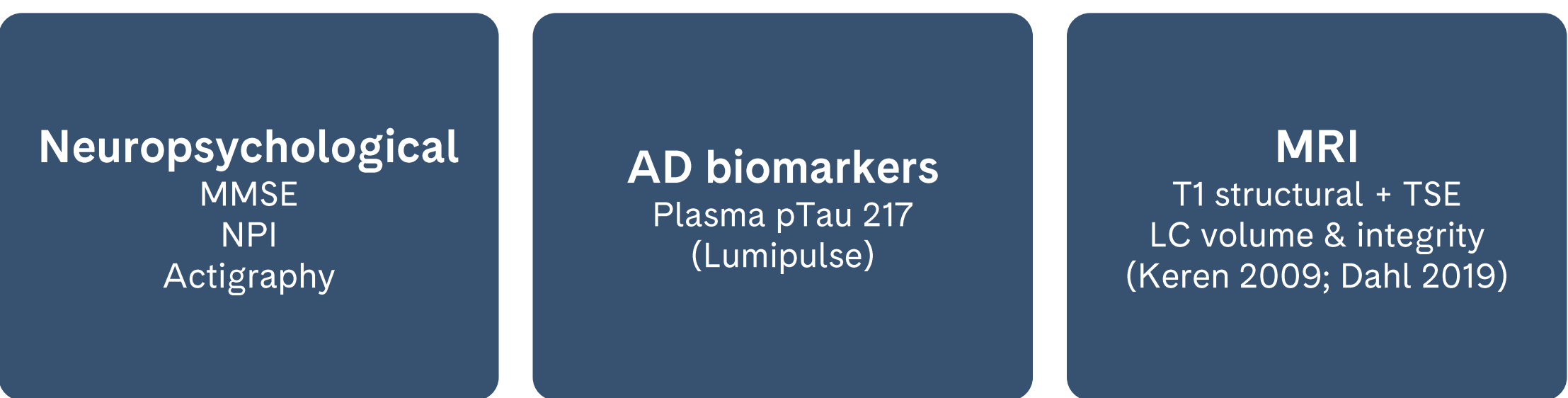
## METHODS

Recruitment from the ADAD cohort from the Genetic Counseling and Information Program for familial dementias (PICOGEN) at Hospital Clínic de Barcelona began in September 2024 and is ongoing

### 1. Participants (3 groups)



### 2. Comprehensive assessment



### 3. Statistical analysis

Group differences + correlations with age, EYO, MMSE, CDR and NPI scores

## RESULTS

Thus far, 22 participants have been recruited (7 AMC, 7 SMC, 8 healthy controls). All participants completed NPI and 15 completed the MRI protocol (6 AMC, 4 SMC, 4 HC). HC were younger compared to the other groups (**Table 1**).

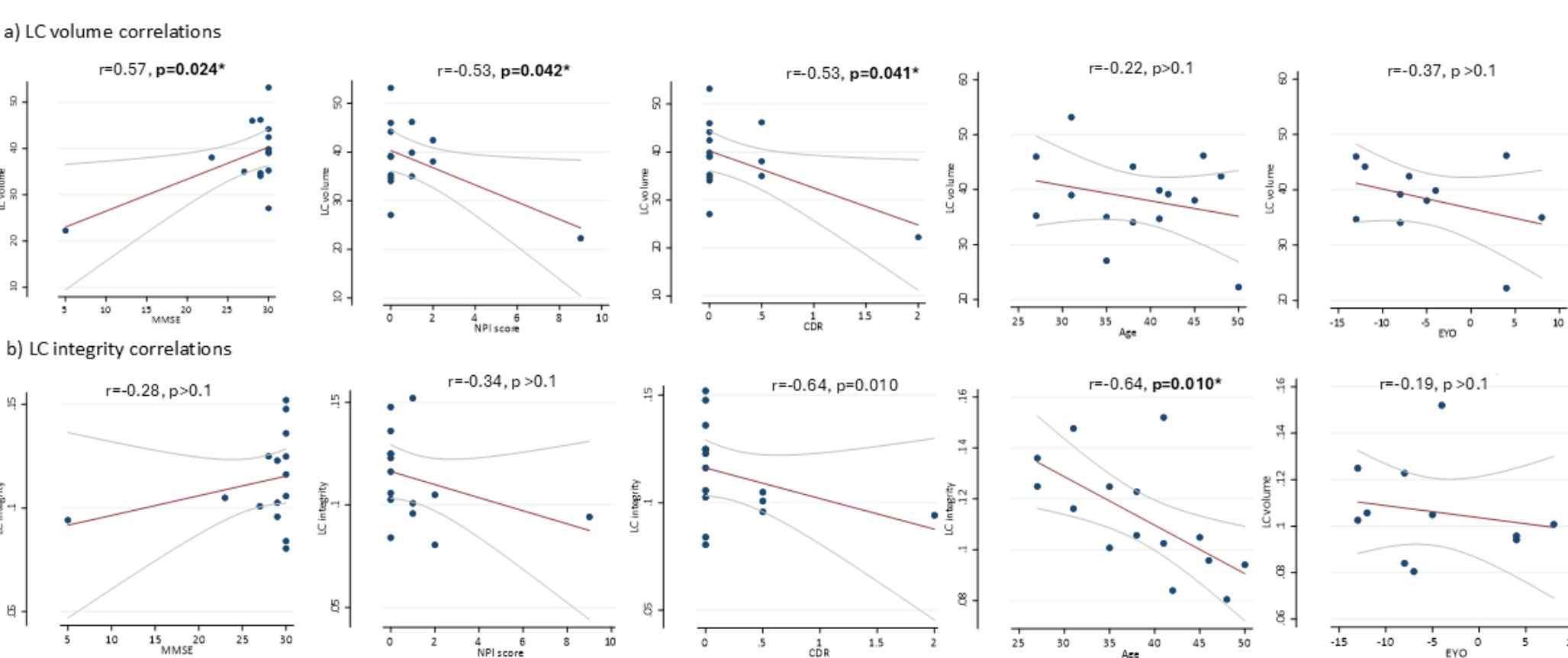
As expected, SMC exhibited lower EYO, MMSE, and CDR scores and higher NPI than AMC and HC. SMC had lower LC integrity compared to HC (**Table 1**).

Correlation analyses showed a significant negative association between LC volumes and NPI scores ( $r=-0.53$ ,  $p=0.04$ ) and CDR scores ( $r=-0.53$ ,  $p=0.04$ ), and a positive association with MMSE ( $r=0.57$ ,  $p=0.02$ ). LC integrity was negatively associated with age ( $r=-0.64$ ,  $p<0.01$ ) (see **Figure 1**).

**Table 1.** Demographic and clinical data.

|                  | SMC (n=7)  | AMC (n=7)  | HC (n=8)   | Significance |           |            |
|------------------|------------|------------|------------|--------------|-----------|------------|
|                  |            |            |            | HC vs SMC    | HC vs AMC | AMC vs SMC |
| Age              | 41±6       | 39.3±6     | 32.4±6     | $p=0.02$     | $p<0.01$  | ns         |
| Sex (women)      | 100%       | 57%        | 50%        | $p=0.02$     | ns        | $p=0.04$   |
| EYO              | 1±6.1      | -9.3±4     | N/A        | N/A          | N/A       | $p<0.01$   |
| MMSE             | 18.1±9     | 29.4±0.7   | 30±0       | $p=0.03$     | ns        | $p<0.01$   |
| CDR              |            |            |            | $p<0.01$     | ns        | $p<0.01$   |
| 0                | 0%         | 100%       | 100%       |              |           |            |
| 0.5              | 43%        | 0%         | 0%         |              |           |            |
| 1                | 29%        | 0%         | 0%         |              |           |            |
| 2                | 28%        | 0%         | 0%         |              |           |            |
| NPI              | 4.1±3.5    | 0.4±0.8    | 0.13±0.4   | $p<0.01$     | ns        | $p<0.01$   |
| pTau 217 (pg/mL) | 1.56±0.6   | 0.59±0.6   | N/A        | N/A          | N/A       | $p=0.03$   |
| LC integrity     | 0.098±0.01 | 0.110±0.02 | 0.131±0.01 | $p=0.01$     | $p=0.07$  | ns         |
| LC volume        | 35.3±9.9   | 39.7±4.8   | 38.6±11    | ns           | ns        | ns         |

**Figure 1.** Correlation analyses



## CONCLUSIONS

- **LC integrity and volume are associated with cognitive and neuropsychiatric outcomes in ADAD individuals**, mirroring findings in sporadic AD.
- Ongoing recruitment will increase sample size, and actigraphy-based sleep studies will help clarify the role of LC degeneration in sleep disturbances.
- The **PICOGEN Clínic Barcelona Cohort** offers a **unique opportunity** to elucidate LC's role in the physiopathology of ADAD.

## CONTACT

Neus Falgàs  
nfallgas@clinic.cat

Raquel Sánchez-Valle  
rsanchez@clinic.cat

