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Genetic Etiology of Early-Onset Alzheimer's Disease in a Diverse Global Cohort

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Background

- EOAD = ~5% of AD cases; aggressive clinical course
- Only **5–10%** attributable to APP/PSEN1/PSEN2
- **Heritability >90%**, but genetic drivers remain largely unknown
- Lack of **ancestrally diverse** EOAD cohorts limits discovery

Objective

- Build a **global, diverse EOAD cohort**
- Identify **known pathogenic variants**
- Enable **genome-wide discovery** of novel EOAD risk factors

Cohort & Methods

~1,800 early-onset dementia cases assembled via **LEADS + 20+ global sites**
Whole-genome sequencing using GATK best practices

Analyses:

- Screening for known EOAD/FTD pathogenic variants
- Genome-wide variant discovery
- Phenotype summary (age at onset, sex, race/ethnicity)

Results

Table 1: Cohort Characteristics

N	1201
Mean age of onset (SD)	57.1 (5.2)
Sex (% female)	57.80%
Known pathogenic variant carriers (%)	1.44%
EOAD carriers (%)	88.24%
FTD carriers (%)	11.76%
Race/Ethnicity (%)	White(37.22%), Asian(24.98%), Black(0.33%), Other (37.47%)

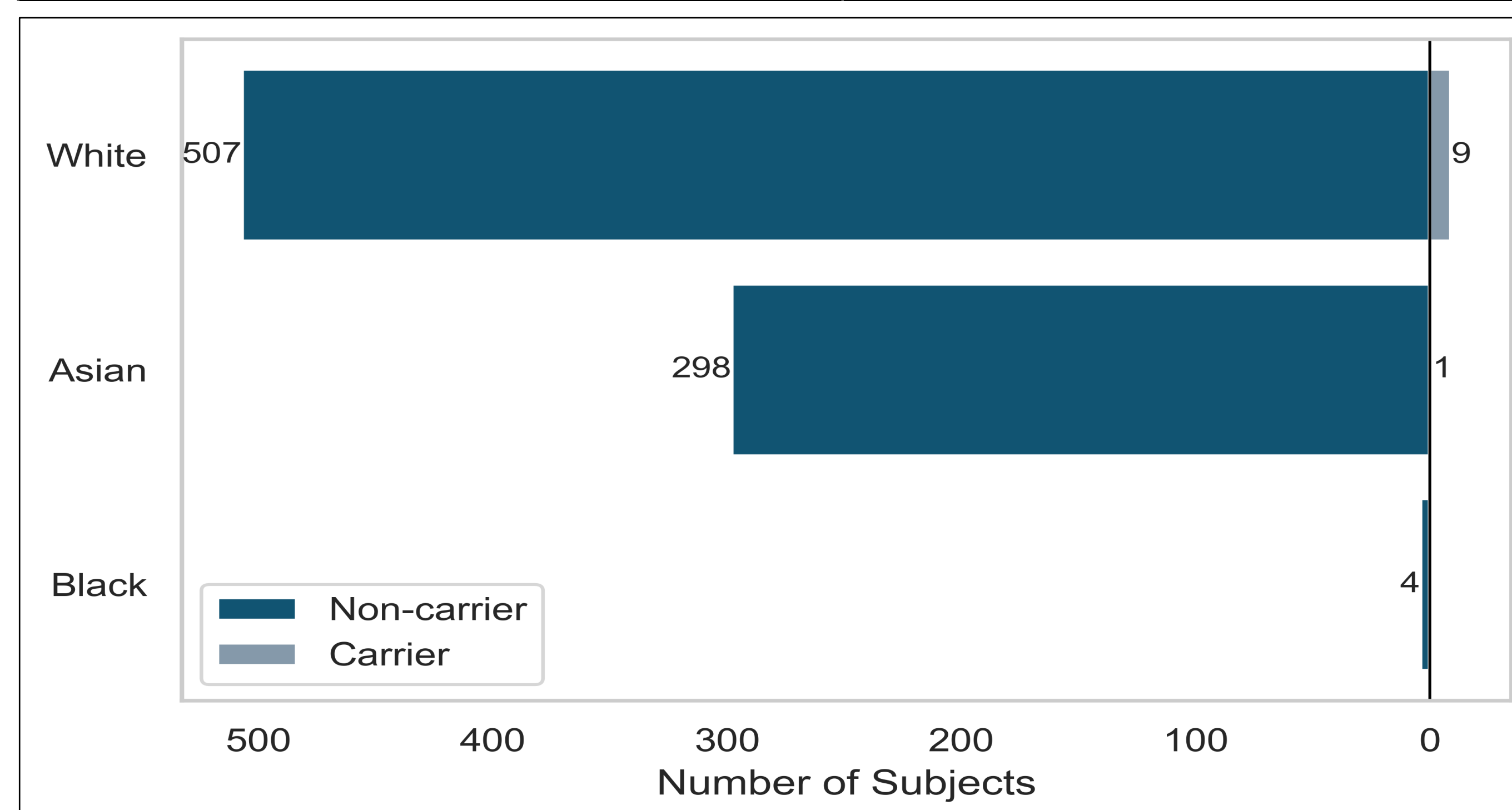


Figure 1. Carrier Status by Race: Distribution of known pathogenic variant carriers and non-carriers across self-reported racial groups in the EOAD cohort, demonstrating ancestral diversity and low carrier frequency across populations.

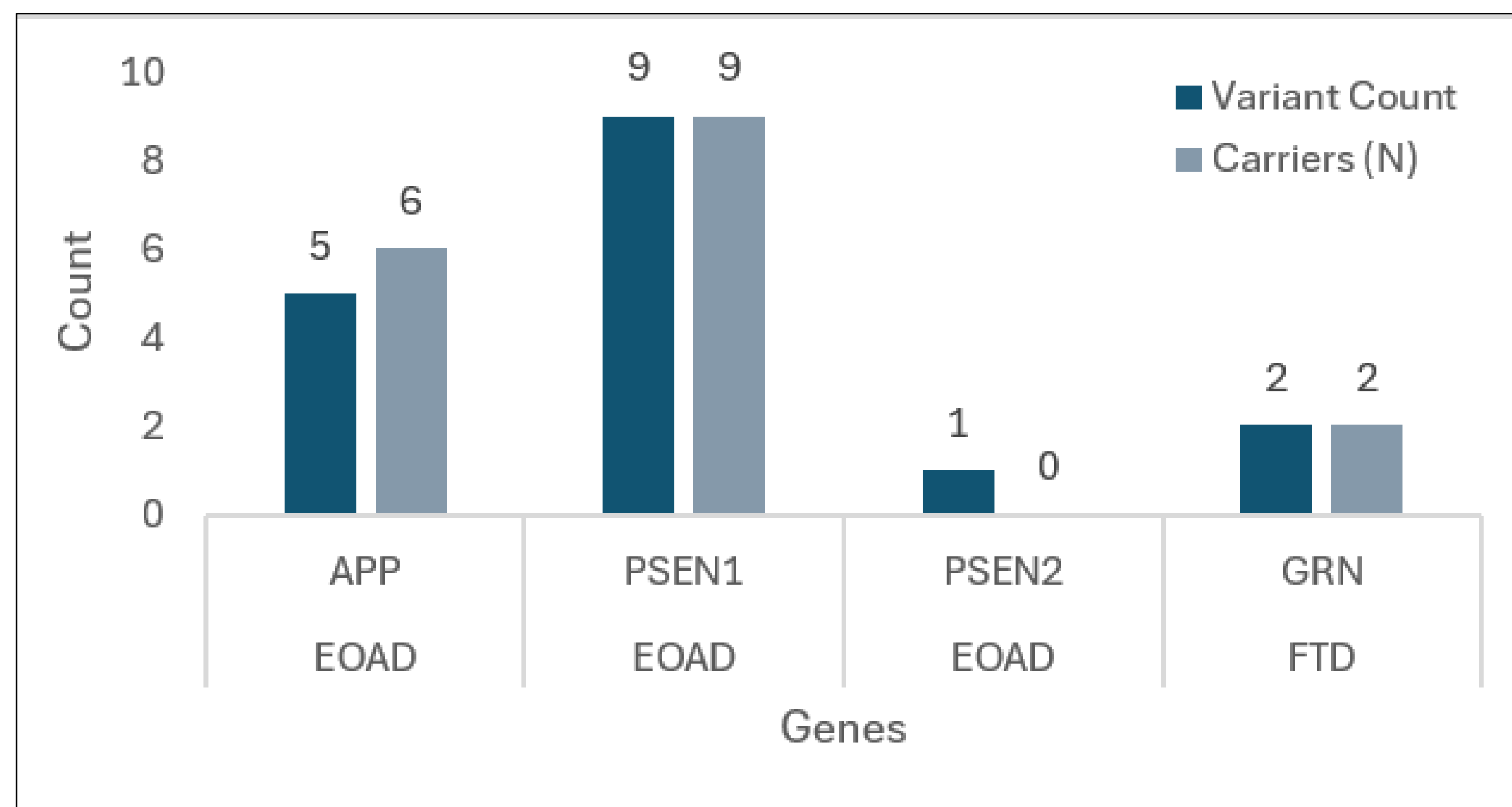


Figure 2. Distribution of pathogenic variant carriers and unique variants by gene.

Interpretation

- Low prevalence of known familial variants → majority idiopathic
- EOADCarrier frequency low across all ancestral groups
- Pathogenic burden concentrated in APP/PSEN1, consistent with prior LEADS findings

Future Work

- Genome-wide rare variant burden testing
- Structural variant discovery
- Functional annotation + gene prioritization
- Ancestry-stratified analyses

References

- Goldman JS et al. Genetics of Alzheimer's disease: update and future directions. *Alzheimers Dement.*
- Liana G. Apostolova et al. *LEADS: Longitudinal Early-Onset Alzheimer's Disease Study.* *Alzheimers Dement.*

