

Linking Genetic Susceptibility to Alzheimer’s progression

Michael Vacher^{1,2}, Timothy Cox¹, Tenielle Porter^{2,3,4}, Eleanor O’Brien^{2,3}, Simon M. Laws^{2,3,4}, James D. Doecke^{2,5}, AIBL Research Group

¹ The Australian eHealth Research Centre, CSIRO Health and Biosecurity, Kensington 6151, Australia.

² Centre for Precision Health, School of Medical and Health Sciences, Edith Cowan University, Joondalup, 6027, Western Australia, Australia.

³ Collaborative Genomics and Translation Group, School of Medical and Health Sciences, Edith Cowan University, 270 Joondalup Drive, Joondalup Western Australia 6027, Australia.

⁴ Curtin Medical School, Curtin University, Kent Street, Bentley Western Australia 6102, Australia.

⁵ The Australian eHealth Research Centre, CSIRO Health and Biosecurity, Herston 4029, Queensland, Australia.

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Polygenic risk score (PRS) is strongly associated with earlier Alzheimer’s disease onset along the biological trajectory, independent of APOE ε4. However, marked discordance between genetic risk and disease age identifies individuals with potential resilience or additional non-genetic drivers of disease progression.

Introduction

Polygenic risk scores (PRS) are widely used to estimate genetic susceptibility to Alzheimer’s disease (AD), but their relationship with disease progression remains unclear. Natural history modelling enables estimation of disease age (DA), providing a biologically grounded measure of an individual’s position along the AD trajectory. This study investigates whether genetic risk, quantified by PRS excluding chromosome 19 (APOE), is associated with disease timing, and whether deviations from this relationship reveal biologically informative subgroups.

Methods

Genotype data from 1,759 participants in the Australian Imaging, Biomarkers and Lifestyle (AIBL) study were used to compute a PRS predicting amyloid positivity (Centiloid >20), excluding chromosome 19. Analyses were restricted to 719 individuals classified as amyloid accumulators based on longitudinal amyloid-PET (≥3 scans).

Disease age (DA) was estimated using natural history modelling. Age offset (DA – chronological age) was used as a measure of disease timing, with higher values indicating earlier onset.

Standardised PRS and age offset were dichotomised using a ±0.5 SD threshold. Associations were assessed using correlation analysis. To evaluate independence from covariates, both variables were adjusted for age, sex, and APOE ε4 carriage using linear regression, and correlations were calculated on model residuals.

Results

Higher PRS was associated with earlier disease timing, with individuals showing higher age offset having significantly elevated PRS ($p < 2.2 \times 10^{-16}$). The PRS–age offset correlation was moderate unadjusted ($r = 0.54$) and strengthened after adjustment for age, sex, and APOE ε4 ($r = 0.69$, $p = 5.76 \times 10^{-105}$), indicating a strong independent association. Non-APOE genetic effects were evident, with some non-carriers exhibiting higher PRS than ε4 carriers (Figure 1). Residual variability suggests additional factors influence disease timing.

Conclusion

Polygenic risk is strongly associated with Alzheimer’s disease timing, independent of APOE ε4, supporting a key role for non-APOE genetic architecture in accelerating disease progression. Residual variability around this relationship suggests additional biological and environmental modifiers of disease onset. These findings support the integration of PRS into disease modelling and highlight its potential utility for risk stratification and clinical trial enrichment.



Figure 1: Higher polygenic risk is associated with earlier Alzheimer’s disease timing. PRS shows a strong, independent relationship with age offset after adjustment for age, sex, and APOE ε4, while residual variability suggests additional modifiers of disease progression.