Do Alzheimer’s Risk Genes also Predict Cognitive Decline?

Introduction

- It is the priority of candidate Alzheimer’s disease (AD) therapeutics to slow progression and preserve quality of life for those on the disease trajectory.
- To effectively demonstrate and measure this, randomised controlled trials would ideally control for factors that alter rates of cognitive decline independent of the intervention under study.
- Genome-wide association studies (GWAS) have implicate ~40 genes that appear to be associated with elevated disease risk. The pathways involved have shed light on possible underlying disease mechanisms.
- Could these (or other) genes help to predict rates of cognitive decline?

Methods

- Samples came from three well-characterised longitudinal cohort studies of ageing: the Australian Imaging Biomarkers and Lifestyle study, the Alzheimer's Disease Neuroimaging Initiative, and the Open Access Series of Imaging Studies.
- Participants were randomly allocated to either a discovery or validation data set.
- Cognition was measured using a Pre-Alzheimer’s Cognitive Composite (PACC)
  - Devised to detect early cognitive decline due to AD pathology.
  - Informed by the Mini Mental State Exam, Rey Auditory Verbal Learning, and the Wechsler Logical Memory and Digit Symbol Coding subtests.

Results

- Greater variability in cross-sectional and longitudinal PACC scores observed in MCI and AD.
- GWAS hits varied by phenotype.
- Greater PACC performance in MCI, while PRSs generally had low predictive utility, meaningful effect sizes were seen for cognition in MCI.
- PRSs were trained to predict AD risk (both from original and reference GWASs) evaluated against cognitive performance in MCI. For cross-sectional performance in MCI, the phenotype-specific PRS outperformed the AD risk PRS. Interestingly, of the 157 variants in the PRS, 35 were directly mapped to MDC1 and further 82 were mapped to nearby regions.

Conclusions and Future Directions

- We noted a strong effect for MDC1 for cross-sectional PACC performance in MCI only. The gene was also genome-wide significant in the validation longitudinal models in MCI. The lack of effect in the discovery longitudinal model may be due to the small sample size for that phenotype.
- MDC1 has been observed to be upregulated in AD and has a primary role in DNA repair which has in turn been linked with AD. Given this and our findings, MDC1 may be a genetic variant of interest.
- The utility for PRSs in predicting cognition was restricted to the MCI subgroup. For this group, cross-sectional performance was best predicted by the phenotype-specific PRS (R² = 12.5% vs 8.2% for the AD Risk PRS).
- Conversely, for the longitudinal phenotype in MCI, the AD Risk PRS explained 4.5% of the variance in rates of change, while no effect was seen for the phenotype-specific PRS (R² = 1%, p = 0.09).
- A larger sample has been acquired for future analyses. This will allow us to better model cognitive change by stratifying by APOE, controlling for amyloid pathology, and extracting individuals who convert between clinical classifications and aligning their starting points as their point of conversion.

References

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