Do Alzheimer's Risk Genes also Predict Cognitive Decline?

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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 now implicated >40 genes that appear to be associated with elevated disease risk[1-3]. 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 $\left(\frac{2}{3}\right)$ or validation $\left(\frac{1}{3}\right)$ data set
- Cognition was measured using a Pre-Alzheimer's Cognitive Composite (PACC)
  - Devised to detect early cognitive decline due to AD pathology[4]
  - Informed by the Mini Mental State Exam, Rey Auditory Verbal Learning, and the Weschler Logical Memory and Digit Symbol Coding subtests

Table 1. *Sample Sizes for Discovery GWAS and Validation (brackets) Datasets by Outcome and Cohort*

	Outcome		
Sample	***AD Risk***	***Baseline Cognition***	***Longitudinal Cognition***
Whole Cohort (WC)	2, 095 (1,038)	2,804 (1,322)	1,851 (898)
Cognitively Unimpaired (CU)	-	1,488 (759)	1,077 (525)
Mildly Cognitively Impaired (MCI)	-	761 (416)	539 (280)
Alzheimer's Disease (AD)	-	452 (260)	202 (128)

Genome Wide Association Studies (GWAS)
Search across the genome for associations between variant(s) and three outcomes

1. Alzheimer's Risk
- Binary Case vs Control status
- Additionally computed a reference PRS based on a large scale GWAS of AD risk by Kunkle et al. (2019)[1]

2. Baseline Cognition
- Cross-sectional PACC performance
- Linear regression

3. Longitudinal Cognition
- PACC scores over ≥ 3 observations
- Linear mixed effects model with random slope and intercept

Cognition GWASs were run in the whole cohort (WC) and repeated across disease stage substrata.
All models covaried for age, sex, education, top genetic principal component, and disease classification (WC only)*

Polygenic Risk Scores (PRS)
GWAS results were used to generate a score which optimally combined variant data to predict GWAS outcome in validation data set

Compare performance
PRSs were trained to predict AD risk (both from original and reference GWASs) evaluated against cognitive outcomes. Their performance was then compared against the cognition phenotype-specific PRSs

Figure 1. *Study Workflow*

aibl The Australian Imaging Biomarkers & Lifestyle Flagship Study of Ageing
ADNI Alzheimer's Disease Neuroimaging Initiative
OASIS Open Access Series of Imaging Studies

Results

Greater variability in cross-sectional and longitudinal PACC scores observed in MCI and AD

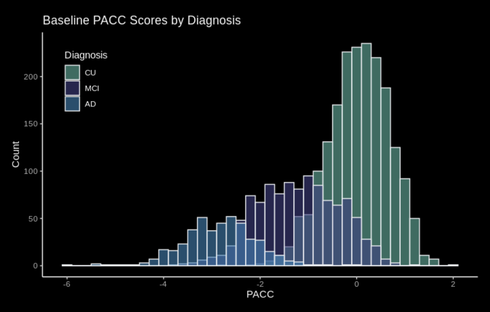


Figure 2. *Distribution of Baseline Cognitive Performance by clinical classification*

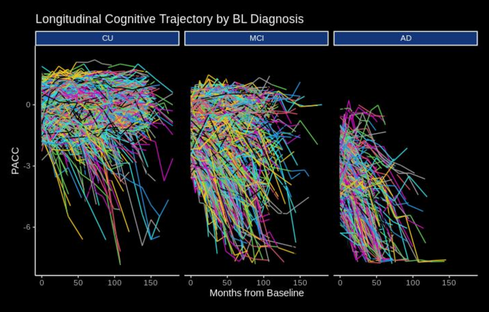


Figure 3. *Longitudinal Cognitive Performance by clinical classification*

GWAS hits varied by phenotype

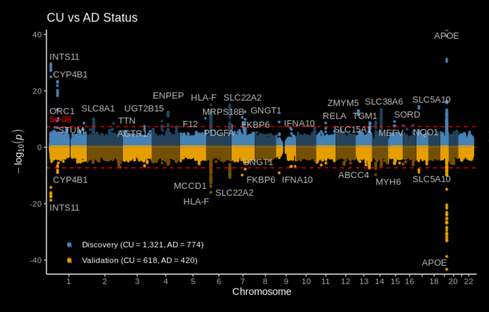


Figure 4. *Manhattan Plot of Case/Control GWAS*

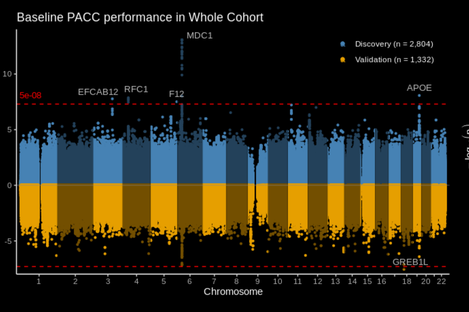


Figure 5. *Manhattan Plot of Baseline PACC GWAS (Whole Cohort)*

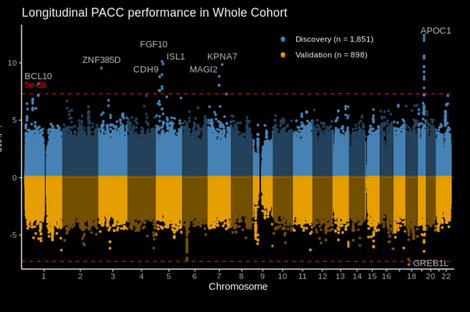


Figure 6. *Manhattan Plot of Longitudinal PACC GWAS (Whole Cohort)*

A novel association was identified between the Mediator of DNA Damage Checkpoint 1 *(MDC1)* gene and both baseline PACC and longitudinal PACC (validation set only). These effects were only observed in MCI.

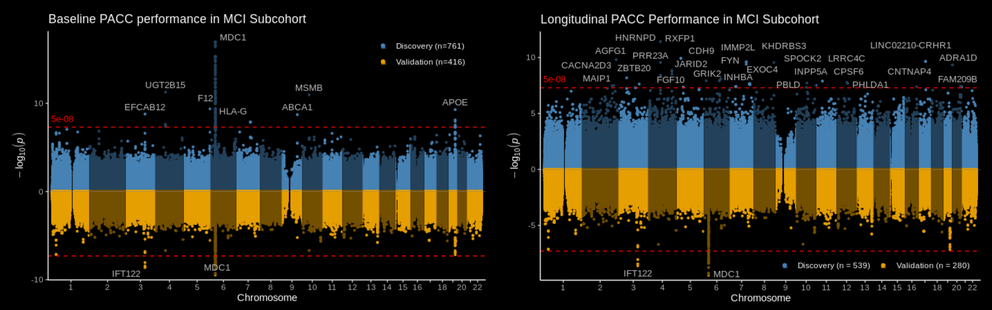
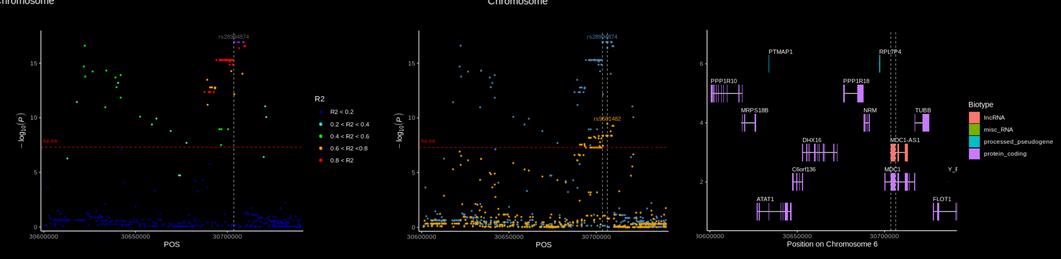


Figure 7. *Manhattan plot of GWAS results of cross-sectional (left) and longitudinal (right) PACC performance in MCI participants*

Figure 8. *Locus zoom plot showing the correlation structure of the lead variant in the discovery GWAS of baseline MCI PACC performance (left), a region plot showing the strength of association in the discovery and validation sets (middle), and a gene map of this region (right)*



While PRSs generally had low predictive utility, meaningful effect sizes were seen for cognition in MCI. For cross-sectional performance in MCI, the phenotype-specific PRS outperformed the AD risk PRS. Interestingly, of the 137 variants in the PRS, 35 were directly mapped to *MDC1* and a further 82 were mapped to nearby regions.

Table 2. *Performance of Polygenic Risk Scores by Derivations and Outcome*

Phenotype		Polygenic Risk Score Derivation					
		Kunkle[1] GWAS Summary Statistics		*AD Risk GWAS*		*Phenotype-Specific GWAS*	
		R^2	*P*	R^2	*P*	R^2	*P*
Case-control		15.6 %	2×10^{-24}	20.1%	6×10^{-28}	-	-
Baseline Cognition	(WC)	1.5 %	8×10^{-6}	< 1 %	4×10^{-3}	< 1 %	2×10^{-8}
	(CU)	< 1 %	0.09	< 1 %	0.26	< 1 %	2×10^{-8}
	(MCI)	**2.5 %**	$\mathbf{1 \times 10^{-3}}$	**8.2 %**	$\mathbf{3 \times 10^{-9}}$	**12.5%**	$\mathbf{1 \times 10^{-13}}$
	(AD)	< 1 %	0.66	< 1 %	0.33	< 1 %	0.27
Longitudinal Cognition	(WC)	< 1 %	0.01	1.5 %	2×10^{-4}	< 1 %	0.23
	(CU)	1.2 %	0.01	< 1 %	0.20	< 1 %	0.24
	(MCI)	**1.8 %**	**0.02**	**4.5 %**	$\mathbf{3 \times 10^{-4}}$	**1.0 %**	**0.09**
	(AD)	1.1 %	0.24	< 1 %	0.89	2.2 %	0.10

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[5] and has a primary role in DNA repair which has in turn been linked with AD[6]. 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 subcohort. For this group, cross-sectional performance was best predicted by the phenotype specific PRS (R^2 = 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 (R^2 = 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

[1] 10.1038/s41588-019-0358-2
[2] 10.1038/s41588-018-0311-9
[3] 10.1038/s41588-022-01126-8
[4] 10.1001/jamaneurol.2014.803
[5] 10.3233/JAD-140606
[6] 10.3390/ijms21051666

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Improving patient outcomes through the ethical application of Biological data to inform and enhance personalized healthcare