Genome-Wide Association Study of Quantitative Biomarkers Identifies a Novel Locus for Alzheimer's Disease at 12p12.1

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1. Introduction

Identifying genetic basis of quantitative biomarkers in Alzheimer's disease (AD) is a promising method to help deconvolute mechanistic complexity of AD and may lead to a better understanding of disease subtypes. Quantitative Templates for the Progression of Alzheimer's disease (QT-PAD, see [1]) provides a single, common and shared data freeze from Alzheimer's Disease Neuroimaging Initiative (ADNI), including 16 imaging, cognitive and fluid AD biomarkers. To reveal novel AD genetic factors, we perform a genome-wide association study (GWAS) of QT-PAD biomarkers.

2. Materials And Methods

Participants included 1,576 subjects from the ADNI QT-PAD cohort with both biomarker concentration and genotyping data available. GWAS was performed to examine genetic associations between 565,373 SNPs (after going through a standard QC procedure) and concentrations of 16 key QT-PAD biomarkers (see Figure 1, right), with age, gender, and education as covariates. GWAS was performed for the baseline, m06, m12, and m24 QT-PAD data.

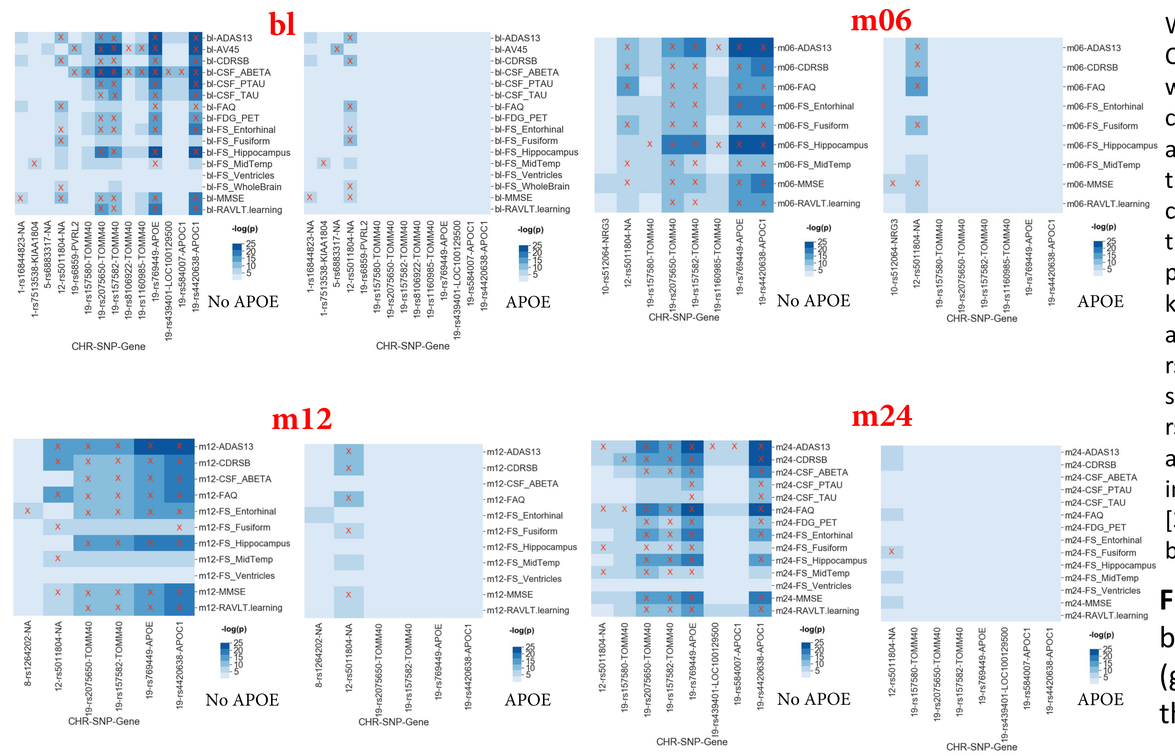
References

[1] Portland Institute for Computational Science, Alzheimer's Disease Modelling Challenge.
URL http://www.pi4cs.org/qt-pad-challenge

[2] J. M. Vonk, S. Scholtens, et al. Adult onset asthma and interaction between genes and active tobacco smoking: The GABRIEL consortium. PLoS ONE, 12 (3) (Mar 2017). doi:10.1371/journal.pone.0172716.

[3] D. P. Hibar, J. L. Stein, et al. Common genetic variants influence human subcortical brain structures. Nature 520 (7546) (2015) 224–229. doi:10.1038/nature14101.

3. Results



We identified a novel locus rs5011804 on Chr 12 ($p < 5E\text{-}8$) significantly associated with several biomarkers at several visit codes, suggesting the variation (minor allele C) plays a role in affecting these three AD biomarkers. Figure 1 shows the complete GWAS findings at baseline using the genome-wide significance threshold of $p < 5 \cdot 10^{-8}$. This result not only affirms the key AD genes (APOE, TOMM40, PVRL2) but also suggests the promising role of rs5011804 due to its associations with seven QT-PAD biomarkers. The SNP rs5011804 has a reported association with adult asthma [2] and slightly affects intracranial volume (corrected p = 0.05934) [3] but has not been associated with AD before.

Figure 1. GWAS results on QT-PAD biomarkers. Entries with p<5e-8 (genome-wide significance threshold) are marked with **X**.

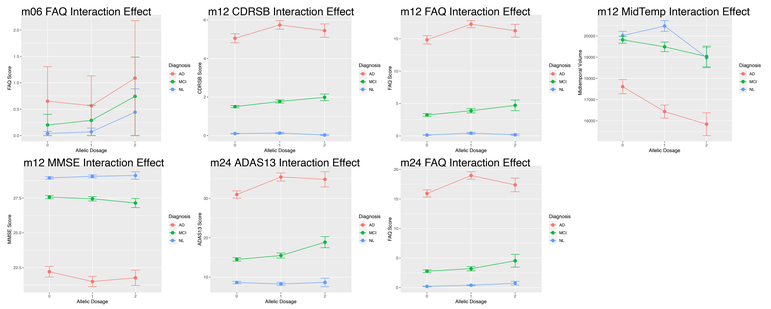


Figure 2. SNP-by-diagnosis interaction analysis results on QT-PAD biomarkers emphasize the association between the SNP rs5011804 and AD diagnosis.

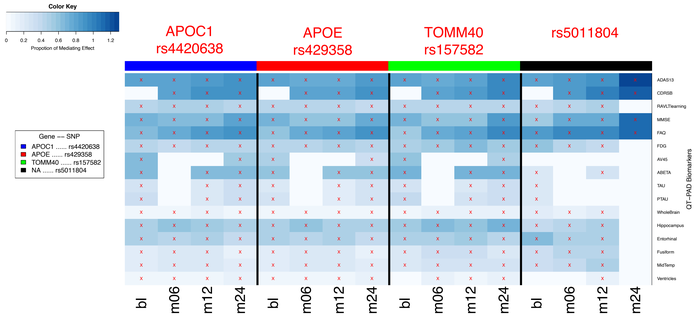


Figure 3. Mediation analysis results on QT-PAD biomarkers show how the effect of the SNP rs5011804 on AD diagnosis is 'through' cognitive and imaging biomarkers (significant mediating relationships represented with **X**.

4. Conclusions

QT-PAD provides a standardized method for measuring the AD progression and allows for new quantitative genetics research. Genetic analysis of QT-PAD biomarkers identified a novel locus in Chr12 (rs5011804) associated with multiple QT-PAD biomarkers. The identified locus warrants further investigation in independent cohorts as a potential AD risk factor.

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