Burden of genetic polymorphisms in the mTOR regulated pathways predict Alzheimer's disease risk

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1. Background

- Effective prevention and early intervention in Alzheimer's disease (AD) requires reliable prediction of AD risk. Previous predictive models have been based on age, gender, education, ApoE genotype and GWAS-detected genetic variants (Chouraki et al., 2016; Wray et al., 2007).
- Our earlier work suggests that dysregulation of the mTOR pathway is associated with increased risk of Alzheimer's disease (Yates et al., 2013).
- The aim of this study was to examine whether the genetic variations associated with mTOR dysfunction are able to discriminate between Alzheimer patients and healthy controls.

2. Methods

- DNA samples and demographic data from 155 AD patients, 111 mild cognitive impairment (MCI) subjects and 408 healthy volunteers were provided by the Australian Imaging, Biomarkers and Lifestyle (AIBL) Study (https://aibl.csiro.au/about/).
- Inclusion criteria:
  - ✓ Age ≥65 when last seen (healthy controls) or at the age of onset (AD patients)
  - ✓ Known ApoE genotype
  - ✓ Probable AD subjects, diagnosed according to the NIA-AA or the NINCDS-ADRDA criteria; or
  - ✓ Cognitively normal controls demonstrating absence of a cognitive complaint with a MMSE score of at least 28.
  - ✓ European descent
- Exclusion criteria:
  - ✓ Evidence of familial Early Onset AD
  - ✓ Clinically diagnosed major depression
- Array analysis using the VariaTect Array (Affymetrix) was performed by the Ramaciotti Centre for Genomics.
- Data analysis was performed using the Ingenuity Variant Analysis (IVA) and Metaboanalyst software to determine the relationship between variation burden on mTOR regulated pathways and disease state.
- Regression analysis was performed to discover whether there is a relationship between last MMSE scores and SNP load on mTOR-regulated genes in 111 MCI subjects.
- ROC curves were used in order to evaluate the accuracy of our system in identifying AD and healthy control subjects.

3. Results

- Initial analysis of the demographic data indicated that the effect of the APOE4 genotype on AD risk was significantly higher than expected. To eliminate the bias from our analyses we have analysed the ApoE4 carriers and non-carriers separately.
- ROC curve analysis indicates that the genetic variation burden on the mTOR-regulated genes is associated with a significant risk of AD (Figure 1).
- Regression analysis in MCI subjects (n=111) revealed a statistically significant relationship between MMSE scores and the SNP load on mTOR-regulated genes (Figure 2).
- Comparison ROC analysis also indicates that our genetic risk score is independent of ApoE and contributes significantly to AD-risk identification (Figures 3A and 3B).

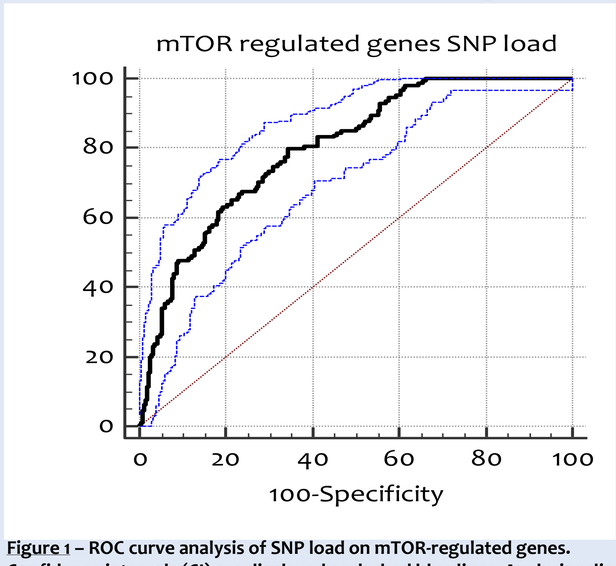

Figure 1 – ROC curve analysis of SNP load on mTOR-regulated genes. Confidence intervals (CI) are displayed as dashed blue lines. Analysis relies on 155 AD patients and 408 healthy volunteers.

Area under the ROC curve (AUC)	0.800
Standard Error [a]	0.0195
95% Confidence interval [b]	0.765 to 0.832
z statistic	15.390
Significance level P (Area=0.5)	<0.0001

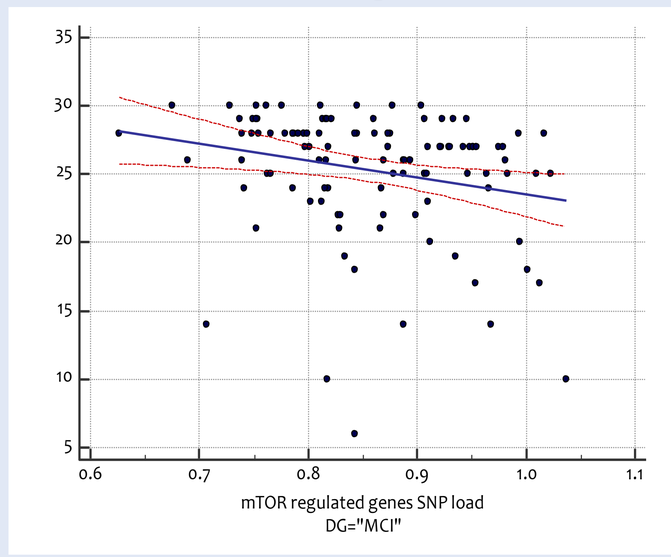

Figure 2 - Regression analysis of last MMSE scores and SNP load on mTOR-regulated genes in 111 MCI patients. Confidence intervals (CI) are displayed as dashed red lines (95% CI= -22.2896 to -2.7177; p=0.0128).

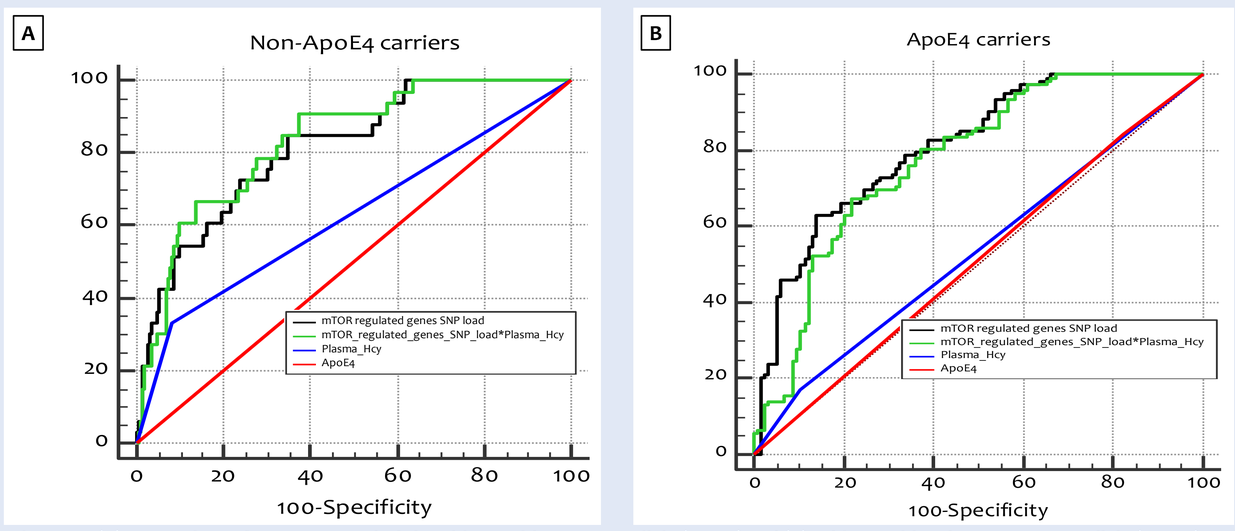

Figure 3 – (A) Comparison of ROC curve analysis in subjects with no ApoE4 allele (n=328) and (B) subjects with at least one ApoE4 allele (n= 235).

Variable	AUC	SE [a]	95% CI [b]
mTOR regulated genes SNP load	0.813	0.0371	0.767 to 0.854
mTOR regulated genes SNP load & Plasma Hcy	0.832	0.0339	0.787 to 0.871
Plasma Hcy	0.626	0.0424	0.571 to 0.679
ApoE4	0.500	0.000	0.445 to 0.555

Variable	AUC	SE [a]	95% CI [b]
mTOR regulated genes SNP load	0.810	0.0278	0.754 to 0.858
mTOR regulated genes SNP load & Plasma Hcy	0.775	0.0307	0.716 to 0.827
Plasma Hcy	0.533	0.0225	0.467 to 0.598
ApoE4	0.511	0.0244	0.445 to 0.576

4. Conclusions & Future Work

- In this study, we produced a predictive model of AD risk based on genetic variants associated with mTOR-regulated pathways in combination with age and plasma homocysteine (Hcy) levels.
- Our model provides an accurate prediction of Alzheimer's disease risk in populations of European descent.
- These findings support previous research linking dysfunction of the mTOR regulated pathways to AD susceptibility.
- The risk prediction based on our model is independent of the ApoE genotype and risk prediction is more accurate.
- The negative relationship between MMSE scores and SNP load on mTOR-regulated genes in MCI patients further supports the hypothesis that the dysfunction of mTOR- regulated pathways is related to cognitive deficit.
- The results support the possibility of providing an individual "patient-level" predictive test for AD risk in elderly subjects.

5. References

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3. Wray, N. R. et al. (2007). Prediction of individual genetic risk to disease from genome-wide association studies. *Genome Res.* 17, 1520–1528.
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6. Acknowledgements

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