

Genetic polymorphism in *BIN1* rather than *APOE* is associated with poor recognition memory among men without dementia

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Abstract

Although several genetic polymorphisms have been linked with the risk of Alzheimer's disease, less is known about their impact on cognitive performance among cognitively healthy individuals. Our aim was to investigate the association of the genetic variant, rs744373 in the bridging integrator-1 gene (*BIN1*), the strongest genetic risk factor for Alzheimer's disease after the *APOE* ϵ 4 allele, with different cognitive domains among non-demented older men. Cognitive function was measured using the CogState Brief Battery (CBB), which assessed cognitive performance across four domains: psychomotor function, visual attention, recognition memory/learning and working memory. Linear regression analysis revealed that individuals with the *BIN1* risk allele performed poorly on the recognition memory task as compared to those without the risk allele. However, this was in contrast with the individuals who harboured the *APOE* ϵ 4 risk allele as they displayed better performance on the recognition task in comparison to those without the ϵ 4 risk allele. To the best of our knowledge, this is the first study that demonstrates genetic variation in *BIN1* to be a better predictor of recognition memory than *APOE*, which remains the biggest genetic risk factor for Alzheimer's disease.

Introduction

Late-onset Alzheimer's disease (LOAD) is a multifactorial disease that involves an interplay between several genetic and environmental factors. Despite this, research is mainly focused on the role of the *APOE* ϵ 4 allele towards the presentation of LOAD, as this remains the most studied genetic risk factor to date. Interestingly, LOAD can also develop among individuals without the *APOE* risk allele, highlighting the need to investigate other risk-conferring genetic polymorphisms. Large genome-wide association studies (GWAS) have identified several susceptibility genes/loci linked to high risk of LOAD. Among them, the single-nucleotide polymorphism (SNP) rs744373 in the bridging integrator 1 (*BIN1*) gene has displayed the highest effect size for LOAD, second only to the *APOE* ϵ 4 allele^{1,2}. The global frequency of the G allele (risk allele) is 37% and individuals harbouring the risk allele have at least 1.17 higher odds of developing LOAD according to several reports, including meta-analyses³⁻⁷. The locus rs744373 is located within 30 kb upstream of the coding region, which encodes for the protein Amphiphysin 2^{1,8}. It belongs to a family of BIN1/Amphiphysin/RVS167 (BAR) adaptor proteins that are involved in the regulation of lipid membrane dynamics⁹.

The association of *BIN1* rs744373 with LOAD has been replicated across different ethnic populations^{6,10}; however, its role in mediating LOAD risk remains uncertain. As Alzheimer's disease (AD) is believed to be preceded by a long preclinical phase, it is important to unravel the association of *BIN1* with cognitive function among non-demented individuals as this may provide evidence of the role *BIN1* has in the development of AD. A previous study conducted on a young Chinese population has revealed that cognitively normal individuals who were homozygous for the rs744373 allele had worse working memory performance and lower functional connectivity in comparison to their non-carrier counterparts, highlighting *BIN1*'s role in early cognitive changes¹¹. However, the impact of *BIN1* on multiple cognitive

domains has not been explored in large population-based cohorts, highlighting a gap in our understanding of its risk profile. Hence, the current study investigates the association between *BIN1* rs744373 SNP and cognitive performance across different domains and compares these findings with *APOE*, the most established risk factor for AD, among healthy ageing men free of severe cognitive impairment or dementia.

Material And Methods

Study cohort

The present study analysed data and blood samples collected from men recruited as a part of the Geelong Osteoporosis Study (GOS), an ongoing prospective population-based study. In brief, age-stratified samples of men and women were selected at random from electoral rolls for the Barwon Statistical Division, in south-eastern Australia¹². A total of 1,540 men were recruited at the baseline from 2001 to 2006 (67% participation), followed by 5-, 6- and 15-year re-assessment phases. This study includes a cross-sectional analysis of data and blood samples collected from 474 men during the 15-year follow-up phase (2016–2019). Participants were mostly Caucasian (~ 98%). They provided information on their lifestyle and demographic characteristics in addition to undergoing mental and physical health assessments. Inclusion criteria were a listing on the electoral rolls for the Barwon Statistical Division and residence in the area for a minimum of 6 months. All participants provided written informed consent to participate in the study, which was approved by the Human Research Ethics Committee at Barwon Health. All procedures performed were in accordance with the ethical standards of the institutional and national research committees and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Assessment procedures and sample collection

Cognitive function was evaluated using a computer-based neuropsychology battery, the CogState Brief Battery (CBB), which has been described previously^{13–15}. The CBB requires participants to respond to stimuli cards as a part of a detection task (DET), identification task (IDN), one-card learning task (OCL) and one-back task (OBK), that assess cognitive performance across four domains, namely psychomotor function, visual identification/attention, recognition memory/learning and working memory, respectively. Both a practice trial and a real test were included for each task. The tasks were completed by participants in a quiet room accompanied by a researcher. For the tasks DET, IDN and OBK, scores were calculated by measuring the time (milliseconds) taken to answer correctly, which was then normalised using a \log_{10} transformation. For the OCL task, scores were calculated based on the accuracy of participant response and normalised using an arcsine square-root transformation. Further, scores for overall cognitive function (OCF) were determined by combining the primary measures in the four domains. Thus, for the tasks DET, IDN and OBK, lower scores suggested better cognitive performance and for OCL and OCF, higher scores indicated better performance. The individual scores for the four tasks and composite scores were utilised

in the present analysis. In addition, participants underwent the Mini-Mental State Examination (MMSE) which assessed their overall cognitive function¹⁶.

Other measures

Details on sociodemographic variables such as education, smoking and marital status were acquired from self-reports. Education was defined as a nominal factor based on secondary education completion. Similarly, marital status (living with a partner) was defined as living with a partner (coded “1”) or not (coded “0”). Participants who reported smoking at least one cigarette per day were defined as current smokers. The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Non-patient edition (SCID-I/NP) was used to determine a lifetime history of mood disorders, as described previously¹⁷.

DNA extraction and genotyping

Blood collected from participants after overnight fasting was separated into different aliquots of serum, plasma and buffy coats, and stored at -80°C until use. Total genomic DNA was isolated from buffy coats using QIAamp® DNA Mini Kit (Qiagen, Hilden, Germany) as per the manufacturer’s instructions. The DNA samples were genotyped for the SNPs rs429358 (*APOE* ε4), rs7412 (*APOE* ε2) and rs744373 (*BIN1*) at the Australian Genome Research Facility, Brisbane using the Agena Bioscience MassARRAY® platform. The carrier status was defined by the presence of at least one copy of the risk allele. Hence, in the present study GG/GA and AA genotypes were referred as *BIN1* G+ and *BIN1* G-, respectively. Similarly, *APOE* ε4+ referred to the presence of at least one ε4 allele. The allelic distribution for both *BIN1* and *APOE* did not depart from the Hardy-Weinberg equilibrium.

Statistical analyses

Characteristics were compared across *BIN1* G+ and *BIN1* G- participants using Mann–Whitney U tests for continuous variables and chi-squared tests for categorical variables. Simple linear regression analyses were conducted to investigate the association between *BIN1* carrier status and cognitive function. The outcome, cognitive function included scores on each of the four tasks and OCF. Further, multivariable linear regression models adjusted for age and *APOE* were developed for each outcome. Similarly, unadjusted and age-adjusted linear regression analyses were conducted with *APOE* status as the exposure variable and cognitive function as the outcome. Finally, the association between *BIN1* carrier status and cognitive function was compared among *APOE* ε4 carriers and non-carriers to investigate whether the effect of *BIN1* differs between the two groups. Benjamini-Hochberg correction was applied to adjust for false discovery rate due to multiple testing¹⁸. All statistical analyses were performed using Stata/SE 17.0 and Python 3.8.5.

Results

Participant characteristics and intergroup differences

Participant characteristics are presented in Table 1. The study participants had a median age of 65.4 years (IQR 55-74.5) and roughly three quarters had completed secondary education (74.8%). No significant differences were observed between groups stratified by *BIN1* status.

Table 1

Demographic characteristics of the study participants. Data are presented as n (%) or median (IQR).

		Overall n = 474	<i>BIN1</i> G+ n = 240	<i>BIN1</i> G- n = 234	<i>p</i> - value
Age [years], median (IQR)		65.4 (55- 74.5)	66.8 (54- 76.1)	64.4 (55.8- 73.1)	0.297
Education, n (%)	Secondary education completed	354 (74.8)	171 (71.5)	183 (78.2)	0.095
	Secondary education not completed	119 (25.2)	68 (28.5)	51 (21.8)	
Marital status (living with a partner), n (%)	Living with a partner	383 (80.8)	192 (80)	191 (81.6)	0.654
	Not living with a partner	91 (19.2)	48 (20)	43 (18.4)	
Current smoker, n (%)	Yes	33 (7)	20 (8.3)	13 (5.6)	0.235
	No	441 (93)	220 (91.7)	221 (94.4)	
<i>APOE</i> ε4 carriage, n (%)	Yes	122 (26)	64 (27)	58 (24.9)	0.602
	No	348 (74)	173 (73)	175 (75.1)	
Lifetime history of mood disorder, n (%)	Yes	109 (23)	57 (23.8)	52 (22.2)	0.693
	No	365 (77)	183 (76.2)	182 (77.8)	
MMSE, median (IQR)		29 (28- 30)	29 (28- 30)	29 (28- 30)	0.052

Association of *BIN1* and *APOE* with the cognitive function

Table 2 shows results from the linear regression analyses for the association between *BIN1* carrier status and cognitive function. *BIN1* carrier status was associated with OCL ($\beta_{\text{coeff}} -0.03$ 95% CI [-0.05, -0.01], $p < 0.01$), suggesting that individuals with the risk allele had lower scores for OCL and displayed poorer performances in the learning task. Age and *APOE* status had no effect on the association between *BIN1* and OCL. Thus, the average OCL scores were 0.03 units lower for individuals with the *BIN1* risk allele, independent of age and *APOE* status. The association remained significant after the Benjamini-Hochberg

correction. *BIN1* also showed a trend for inverse association with the overall cognitive function that was approaching statistical significance ($\beta_{\text{coeff}} -0.11$ 95% CI [-0.23, 0.01], p 0.076).

Table 2. Linear regression analysis for predicting cognitive function using *BIN1* carrier status. IDN (identification task) measures visual identification/attention, DET (detection task) measures psychomotor function, OCL (one-card learning task) measures recognition memory/learning and OBK (one-back task) measures working memory. OCF refers to the overall cognitive function.

*Significant after false discovery rate (Benjamini–Hochberg) correction.

Outcome	Unadjusted model			Age and <i>APOE</i> adjusted model		
	β_{coeff} (95% CI)	p -value	Partial Eta-squared	β_{coeff} (95% CI)	p -value	Partial Eta-squared
IDN	0.002 (-0.012, 0.016)	0.808	< 0.01	-0.0004 (-0.01, 0.01)	0.95	0.19
DET	0.01 (-0.01, 0.03)	0.276	< 0.01	0.01 (-0.01, 0.03)	0.428	0.13
OCL	-0.03 (-0.05, -0.01)	< 0.01	0.03	-0.03 (-0.05, -0.01)	< 0.01*	0.13
OBK	0.01 (-0.01, 0.03)	0.21	< 0.01	0.01 (-0.01, 0.03)	0.31	0.23
OCF	-0.136 (-0.276, 0.002)	0.054	0.01	-0.11 (-0.23, 0.01)	0.076	0.28

When different cognitive function outcomes were regressed over *APOE* status in the unadjusted model, a significant association was observed for the outcome OCL ($\beta_{\text{coeff}} 0.03$ 95% CI [0.01, 0.05], $p < 0.01$) as shown in Table 3. However, this positive association indicated that individuals with the *APOE* $\epsilon 4$ allele performed better in the learning task and their average scores were 0.03 units higher. Similar results were obtained following adjustment for age. This contrasted with the results obtained for *BIN1*, which displayed a negative association with cognitive performance on the learning task.

Table 3. Linear regression analysis for predicting cognitive function using *APOE* carrier status. IDN (identification task) measures visual identification/attention, DET (detection task) measures psychomotor function, OCL (one-card learning task) measures recognition memory/learning and OBK (one-back task) measures working memory. OCF refers to the overall cognitive function.

*Significant after false discovery rate (Benjamini–Hochberg) correction.

Outcome	Unadjusted model			Age-adjusted model		
	β_{coeff} (95% CI)	<i>p</i> -value	Partial Eta-squared	β_{coeff} (95% CI)	<i>p</i> -value	Partial Eta-squared
IDN	0.01 (-0.01, 0.02)	0.306	< 0.01	0.019 (0.004, 0.034)	0.011*	0.19
DET	-0.01 (-0.03, 0.02)	0.601	< 0.01	0.01 (-0.02, 0.03)	0.56	0.13
OCL	0.03 (0.01, 0.05)	< 0.01	0.02	0.023 (0.003, 0.043)	0.023*	0.11
OBK	0.01 (-0.02, 0.03)	0.51	< 0.01	0.025 (0.003, 0.046)	0.02*	0.23
OCF	0.05 (-0.11, 0.21)	0.544	< 0.01	-0.08 (-0.21, 0.06)	0.277	0.28

Figure 1 outlines the comparison of cognitive scores on the OCL task (A) among *BIN1* carriers and non-carriers, and (B) among *APOE* carriers and non-carriers. In the age-adjusted model for *APOE*, significant positive associations were also observed for the outcomes IDN (β_{coeff} 0.019 95% CI [0.004, 0.034], *p* 0.011) and OBK (β_{coeff} 0.025 95% CI [0.003, 0.046], *p* 0.02), suggesting that the *APOE* ϵ 4 allele is associated with poorer performance on the visual attention and working memory tasks, respectively. These results survived the Benjamini-Hochberg correction.

Association of *BIN1* with cognitive function among *APOE* ϵ 4 carriers and non-carriers

When study participants were stratified according to *APOE* status, *BIN1* showed significant negative associations with the OCL domain among both ϵ 4 carriers (β_{coeff} -0.05 95% CI [-0.09, -0.01], *p* < 0.01) and non-carriers (β_{coeff} -0.023 95% CI [-0.043, -0.003], *p* 0.019), although a higher effect size was observed for the former, which also survived the Benjamini-Hochberg correction (Table 4). In addition, *BIN1* was also significantly associated with overall cognitive function among *APOE* ϵ 4 carriers (β_{coeff} -0.27 95% CI [-0.5, -0.03], *p* 0.027); however, no significant association was detected among non-carriers.

Table 4. Association of *BIN1* with cognitive function among *APOE* carriers and non-carriers. IDN (identification task) measures visual identification/attention, DET (detection task) measures psychomotor function, OCL (one-card learning task) measures recognition memory/learning and OBK (one-back task) measures working memory. OCF refers to the overall cognitive function.

*Significant after false discovery rate (Benjamini–Hochberg) correction.

	<i>APOE</i> ε4 non-carriers			<i>APOE</i> ε4 carriers		
Outcome	β_{coeff} (95%CI)	<i>p</i> -value	Partial Eta-squared	β_{coeff} (95%CI)	<i>p</i> -value	Partial Eta-squared
IDN	-0.01 (-0.02, 0.01)	0.42	0.19	0.02 (-0.01, 0.04)	0.261	0.2
DET	0.001 (-0.022, 0.024)	0.948	0.12	0.026 (-0.003, 0.056)	0.081	0.18
OCL	-0.023 (-0.043, -0.003)	0.019	0.09	-0.05 (-0.09, -0.01)	< 0.01*	0.18
OBK	0.01 (-0.01, 0.03)	0.431	0.2	0.01 (-0.02, 0.05)	0.48	0.31
OCF	-0.05 (-0.19, 0.09)	0.456	0.26	-0.27 (-0.5, -0.03)	0.027	0.36

Interaction between *BIN1* and *APOE* was also explored; however, it was not found to be statistically significant (results not shown).

Discussion

In this study, we examined cross-sectional associations between *BIN1/APOE* and cognitive function in non-demented men. In both the unadjusted and adjusted models, *BIN1* was inversely associated with cognitive performance on the OCL task that involved recognition memory. This resonates with a previous study where healthy individuals, homozygous for the rs744373 allele, displayed worse working memory performance, larger hippocampal volume and lower functional connectivity¹¹. In another study comprising healthy controls and participants with mild cognitive impairment (MCI), the risk allele was associated with worse memory performance, which was also mediated via elevated global tau levels³. Although the rs744373 allele has been identified as the second strongest genetic risk factor for LOAD only next to *APOE*, its mechanistic link with AD remains uncertain. A faster tau accumulation has been previously observed among *BIN1* G + participants and hence its role in modulating tau pathology has been ascribed as the biggest contribution to AD^{19,20}. Further, knockout mice models of *BIN1* have revealed that the loss of *Bin1* neuronal expression results in the impairment of spatial learning and memory, highlighting its role in memory function⁸.

Our findings also revealed the *APOE* ε4 allele to be associated with lower scores on the IDN and OBK tasks but higher scores on the OCL task. Having been identified as the strongest genetic risk factor for LOAD, *APOE* has been linked to poor cognitive function on numerous occasions and thus its association with better recognition memory appeared counterintuitive. However, a recent study comprising 398 cognitively normal individuals aged ~ 70 years revealed that carriers of the ε4 risk allele performed better on the visual working memory task as compared to the non-carriers²¹. The authors argued that the *APOE*

gene might be an example of antagonistic pleiotropy, conferring both beneficial and deleterious effects; therefore, contributing to the survival of this gene²¹. In another study, an age-based differential impact of *APOE* was observed on verbal memory performance, supporting the hypothesis of antagonistic pleiotropy²². Among individuals less than 57 years, the *APOE* ϵ 4 allele was associated with verbal memory improvement, whereas ϵ 4 carriers above 57 years displayed a decline in verbal memory²². This adds to the growing body of evidence that suggests *APOE* exerts a protective effect at a younger age. In addition to age, sex may also influence *APOE*'s relationship with cognitive performance as suggested by Zokaei and co-workers who found middle-aged males with the *APOE* ϵ 4 allele to have a cognitive advantage on the memory task²³. This beneficial effect of the *APOE* ϵ 4 allele was not observed among women²³ who historically have been at a higher risk of developing AD²⁴.

We also found *BIN1* to be negatively associated with recognition memory, regardless of *APOE* status, although a greater effect size was observed for the *APOE* ϵ 4 carriers. In addition, *BIN1* was also found to be significantly associated with overall cognitive function only among the ϵ 4 carriers. We suspect that the risk alleles may have additive effects; however, no interaction was detected between the two risk alleles. It is interesting to note that in our study *BIN1* showed associations primarily with recognition memory and not with other cognitive domains. However, this was an exploratory study that needs to be replicated across larger cohorts with a longitudinal study design. It would be worthwhile to investigate whether any differences exist between *APOE* and *BIN1* in predicting long-term change for different cognitive domains. Therefore, a major limitation of our study was the use of cross-sectional data only for men. In addition, the population was mostly Caucasian and hence the findings may not be generalisable to other populations. Some of the strengths of our study include a population-based cohort as participants were drawn at random from the general population and were not selected on the basis of disease. Also, individuals with severe cognitive impairment or dementia were excluded from the study.

Overall, our study suggests that *BIN1* may be a better indicator of poor recognition memory than *APOE* in non-demented older men. In light of the above evidence, it is important to investigate the effect of genetic risk factors other than *APOE* on different cognitive domains and their biological function in the brain as this may improve our understanding of the pathophysiology of AD and provide novel therapeutic targets. The underlying role of these genes in AD pathogenesis may be different, and as a result, their impact on different cognitive domains among non-demented individuals may vary. Furthermore, the interaction between genetic risk factors and sex in modulating cognitive performances remains an area worth investigating. It would be interesting to see whether sex modifies *BIN1*'s association with memory function. Therefore, future prospective studies are required to further evaluate these findings along with brain imaging information in order to correlate them with the A β and tau pathology.

Data availability

The genetic data analysed in this study are provided in the supplementary material.

Declarations

Acknowledgements

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Author contributions

K.M. and V.B.G. conceived the study. K.M. was responsible for the experiments and conducted the statistical analyses in consultation with M.M. The funding was acquired by J.A.P., L.J.W. and V.B.G. The original draft was written by K.M., and M.M., J.A.P., L.J.W., K.W. and B.L.N. critically revised the manuscript. All authors agree to be accountable for the work and to ensure that any questions relating to the accuracy and integrity of the paper are investigated and properly resolved.

Competing interests

The authors declare no competing interests.

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Figures

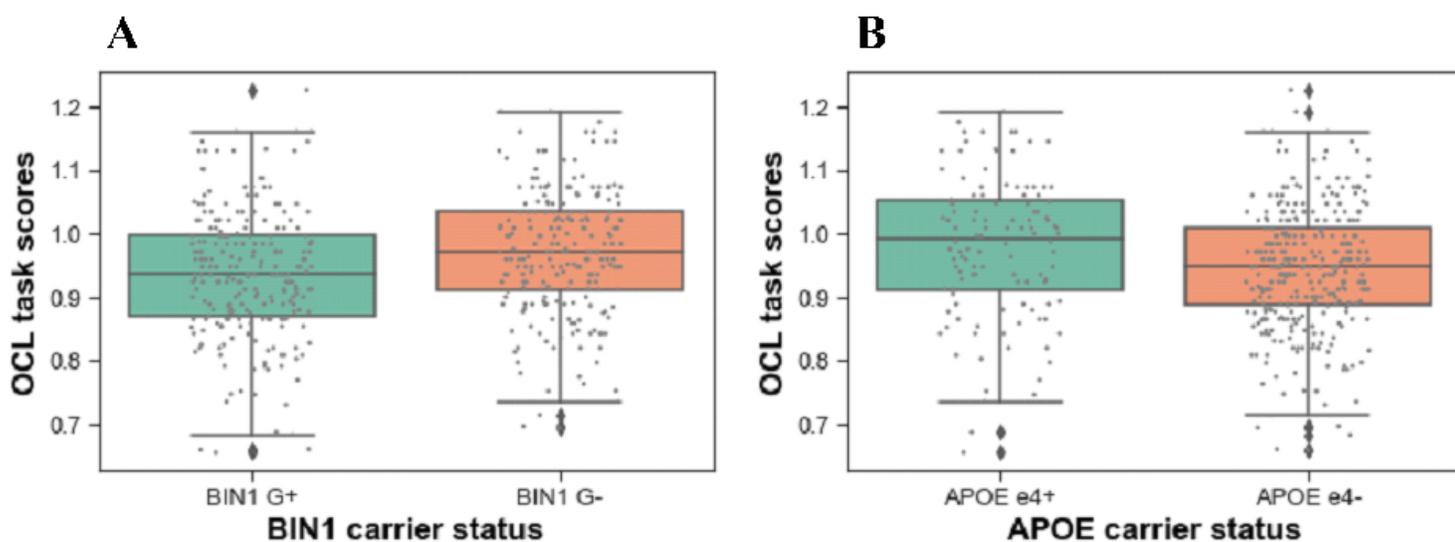


Figure 1

Boxplot depicting a comparison of the OCL task scores. (A) Among *BIN1* risk allele carriers and non-carriers. (B) Among *APOE* risk allele carriers and non-carriers.

Supplementary Files

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- [SupplementaryBIN1sassociationwithcognitivefunction.xlsx](#)