Effects of Cognitive- and Sleep- Related Single Nucleotide Polymorphisms on Cognitive Functions in the Han Chinese Community-dwelling Elderly

Jing Li

Institute of Psychology Chinese Academy of Sciences <https://orcid.org/0000-0003-4436-2276>

Jiangning Fu

Institute of Psychology Chinese Academy of Sciences

Zhiwei Zheng

Institute of Psychology Chinese Academy of Sciences

Xinyi Zhu

Institute of Psychology Chinese Academy of Sciences

Xiaoyan Han

Chaoyang District Center for Diseases Prevention and Control of Beijing

Juan Li (✉ lijuan@psych.ac.cn)

Research article

Keywords: cognitive impairment, single-nucleotide polymorphism, ABCC9, gene-gene interaction

Posted Date: May 26th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-25884/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Objective: The genetic biomarkers on Alzheimer's disease (AD) have been widely studied in different groups. Since the lack of efficacy therapeutic methods for AD, early recognition in preclinical stage becomes increasingly important. Evidence of AD and cognitive-related single nucleotide polymorphisms (SNPs) in high risk population is insufficiency. Our aim was to assess whether these SNPs within cognitive- and sleep-associated genes are correlated with cognitive impairment independently or through gene-gene interactions in community-dwelling elderly in Beijing.

Methods: Eight single-nucleotide polymorphisms (SNPs) were genotyped in 2133 Northern Han Chinese elderly from ten communities in Chaoyang District, Beijing. The short version of the Montreal Cognitive Assessment-Beijing (MoCA-s), Ascertain Dementia 8 (AD8), Digit Span Backwards (DSB), Digital Symbol Substitution Test (DSST), and Paired Associative Learning Test (PALT) were used to detect different cognitive domains.

Results: Logistic regression analyses showed a significant correlation between APOE (rs429358), ABCC9 (rs11046205) and cognitive impairment, and an interaction between ABCC9 (rs11046205)/APOE promoter (rs405509) and APOE ϵ 4 status. Additionally, we found a significant negative association between the additive model of APOE (rs429358) and MMSE score. Moreover, our analysis revealed that the gene-gene interaction between ABCC9 (rs11046205) and APOE (429358) may contribute to the etiology of cognitive impairment.

Conclusions: This study confirmed the independent contribution of AD, memory and sleep-related genes in the cognitive impairment of the community-dwelling elderly in China, as well as through gene-gene interactions.

Background

The aging population is increasing in China with a dramatic rise in the number of cognitive impairments, ranging from 7.7–22.2% [1–3]. Cognitive impairment is the stage between normal aging and dementia, with the typical characteristic of memory deficit. The high incidence and huge financial burden warrants paying more attention to prevention and early recognition, especially for Alzheimer's disease (AD), a severe cognitive impairment [4, 5], since there lacks safe and effective therapeutic drugs [6]. It is well-known that except for environment and lifestyle, genes are another main risk factor in cognitive impairment and AD. Nearly 60% of the cognitive phenotypic variance in adulthood and old age comes from heritable factors [7]. But the evidence of genetic biomarker in the preclinical population of AD is insufficiency.

One of the most well-established risk genes is apolipoprotein E (APOE) ϵ 4, which could significantly increase the incidence of AD and the speed of cognitive decline in preclinical population [8, 9]. This situation is similar with several other AD-related genes [10]. For prevention, we should not only focus on the genes which have been proven to be associated with AD, but also the ones related to general cognitive functions and simultaneous phenomena, which were not fully explored in the previous researches.

Here we chose some candidate risk SNPs of AD including APOE (genotypes with 2 SNPs: rs429358 and rs7412), TOMM40 (rs2075650), SORL1 (rs2070045) and APOE promoter polymorphisms – 219 (rs405509), with the evidence to be associated with increased risk of dementia and cognitive impairment in Chinese

elderly [11, 12]. For aspects of cognitive function, the deficit of memory is a typical characteristic of people with cognitive impairment, in the transitional stage between normal aging and dementia, especially episodic memory [13, 14]. Two related genes, DTNBP1 (rs1047631) and CLSTN2 (rs6439886), have been found to be involved in memory phenotype. The DTNBP1 variation, which could influence glutamate signaling and used to be associated with schizophrenia, has been proven to be associated with general cognitive ability (especially working memory) and cognitive impairment [15, 16]. As the most typical factor in cognitive impairment, episodic memory has been paid more attention in the research of the preclinical stage of dementia. As one of the well-known genes associated with episodic memory, CLSTN2 (rs6439886) was also included in our research [17, 18].

Numerous cross-section and cohort studies have confirmed the relationship between sleep problem and the risk of developing cognitive impairment [19, 20]. About 60% of people with cognitive impairment have trouble sleeping [21]. Due to the high incidence of sleep disorder in this population, we selected the ABCC9 (rs11046205) gene in our research, a SNP which has been proved to be associated with sleep duration [22].

In this study, we intended to verify the correlation between AD-related risk SNPs and cognitive impairment susceptibility in the community-dwelling elderly in Beijing, and attempted to discover potential pathways the cognitive- and sleep- related SNPs may serve in the early recognition.

Methods

Study population

We recruited 2084 participants (and excluded three participants who didn't finish the MMSE) consecutively from ten communities in Chaoyang District, Beijing, China, between November 2018 and May 2019. The inclusion criteria were: 1) have permanent-resident status in Beijing; 2) community residence; 3) age 50–85; 4) no history of severe brain injury; 5) normal daily living ability; 6) ethnic Han; 7) and no neuropsychiatric diseases (such as Alzheimer's disease, depression, Parkinson's disease, etc.). We excluded those participants who could not guarantee the entire study would be completed and each signed the approved informed consent form. The trial protocol was approved by the research ethics committees of the Institute of Psychology, Chinese Academy of Science (H11036) (ChiCTR1900025487).

General Information Collection

Trained personnel visited all the participants at the local hospital for data collection, including socio-demographic characteristics, lifestyle habits and patient history by using a designed questionnaire. Smoking status was divided into current smoking and non-smoking (including never smoking and smoking cessation); alcohol drinking frequency was divided into high and low frequency – depending on whether 3 or more times per week. Physical activity was divided into active and inactive groups depending on the amount of time people spent and defined as: 0 = no activity, 1 = less than 1 day per month, 2 = 1–3 days per month, 3 = 1–2 days per week, 4 = 3–4 days per week, 5 = 5–6 days per week and 6 = every day, and we combined the 0–2 as 0, 3–6 as 1. Past medical history including hypertension, diabetes, heart disease and cerebral infarction were

all collected and defined as: 0 = none and unknown, 1 = did have. The missing values of medical history were all coded as 0, which accounts for 11.4% for the total.

Cognitive Assessment

The global cognitive assessment was measured by the Mini-Mental State Examination (MMSE), which includes orientation, registration, attention and calculation, recall and language domains. Since the education year of the participants in the study varied, we divided the participants by using both education year and MMSE scores. Based on a previous study of a Chinese residential population aged 55 years and over in the urban and rural areas of Beijing [23], the cutoff for determining the presence of cognitive impairment is 19 for illiterate, 22 for elementary and 26 for more than high school. The short version of the Montreal Cognitive Assessment-Beijing (MoCA-s) was used to assess the cognitive status of the participants. The MoCA-s was revised by our research group, which contains 15 items. The total score is 17, higher scores indicate better cognitive status. The discrimination of MoCA-s was confirmed equal to the full version. The Ascertain Dementia 8 (AD8) questionnaire with 8 questions was developed by Washington University. It is a screening tool for differentiating non-demented from demented individuals (even at the very early stage) and used in our project as a self-rated test. The higher score of AD8 indicate higher risk of dementia. A series of tests were used to detect different cognitive domains, including (1) working memory (Digit Span Backwards, DSB) [24]; (2) attention (Digital Symbol Substitution Test, DSST) [25]; (3) episodic memory (Paired Associative Learning Test, PALT) [26].

We used the Center for Epidemiological Studies-Depression (CESD) scale [27] to assess the emotional state of the elderly. Higher scores indicate higher depression level.

Genotyping

Genomic DNA was isolated from 5 mL wholeblood samples for all participant. The $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$ alleles of APOE were determined by 2 SNPs (rs429358 and rs7412) together[28]. The APOE status was divided into $\epsilon 4$ carriers, including $\epsilon 2/\epsilon 4$, $\epsilon 3/\epsilon 4$ and $\epsilon 4/\epsilon 4$, and $\epsilon 4$ noncarriers, including $\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$ and $\epsilon 3/\epsilon 3$. Genotyping of single nucleotide polymorphism (SNP) was performed using the Sequenom iPLEX gold assay and the MassARRAY MALDI-TOF mass spectrometry platform (San Diego, CA, USA). The polymerase chain reactions were designed by Assay Designer 3.1. After genotyping, the effective sample is 1924 with 1513 in the normal group and 411 in the cognitive impairment group.

Statistical Analysis

Differences in the demographic characteristics and cognitive tests of each group were evaluated by the t or X^2 test. The Fisher's exact test was also used to assess whether the genotypic frequencies conformed to Hardy-Weinberg equilibrium (HWE). And the Pearson's Chi-square test was used to compare the genotypic and allelic frequencies between the cognitive impairment and control group. Differences in groups and cognitive function between the participants carrying the different genotypes were calculated by the Mann-Whitney U test. Logistic regression analyses, adjusting for gender, age, education year, smoking status, alcohol drinking

frequency, physical activity, hypertension, diabetes, heart disease, cerebral infarction, CESD and APOE status (except for rs429358 and rs7412), were used to estimate 95% confidence interval (CI) and ORs under additive genetic models which was defined as 0 (AA) vs 1 (Aa) vs 2 (aa). The significance of SNP and APOE interaction was also tested for each additive model of the SNP by logistic regression. Multiple linear regression analyses, adjusting for gender, age, education year, smoking status, alcohol drinking frequency, physical activity, hypertension, diabetes, heart disease, cerebral infarction, CESD and APOE status (except for rs429358), were used to estimate the association between additive model and different cognitive domains. All the analyses were conducted by using SPSS 22.0 software, and two-tailed $p < 0.05$ was considered statistically significant.

To further investigate the interactions between gene-gene and gene-lifestyle, we employed the generalized multifactor dimensionality reduction (GMDR) method [29], which permits adjustment for covariates and provides a unified framework for coherently handling both dichotomous and quantitative phenotypes. We used 10-fold cross-validation to test two to four-way interactions. Here are some output parameters from GMDR, such as testing accuracy, sign test and cross-validation consistency. The age, gender, and education year were used as covariates for gene-gene and gene-lifestyle interaction analyses (including smoking status, alcohol drinking frequency and physical activity), and we also used both logistic and linear regression models (using MMSE as the dependent variable) in the interaction analyses. Statistical significance was set at two-tailed $p < 0.05$.

Results

Characteristics of the study group

The baseline characteristics of all participants in the study are summarized in Table 1. We studied 1924 ethnic Han community-dwelling elderly including a total of 411 cognitively impaired participants (21.4%). There were significant differences between groups in terms of age ($p < 0.001$), gender ($p = 0.002$), education year ($p = 0.001$), and all the cognitive tests ($p < 0.001$) and CESD score ($p = 0.003$). The frequency of the APOE $\epsilon 4$ allele was higher in the cognitive impairment group than in the normal group ($\chi^2 = 12.76$, $p < 0.001$), which indicates that APOE $\epsilon 4$ increases the risk of cognitive impairment in the Han community-dwelling elderly.

Allele And Genotype Distribution Of The Snps

All these SNPs were consistent with the Hardy-Weinberg equilibrium in both normal and cognitive impairment groups ($p > 0.05$) (see supplementary material Table S1). Here we observed significant differences in the minor allele frequency of rs2075650 ($p = 0.047$), rs429358 ($p = 0.002$) and rs6439886 ($p = 0.040$) between normal and cognitive impairment groups. We detected the ORs of 1.309, 1.557 and 0.717 for rs2075650, rs429358 and rs6439886, respectively.

According to APOE $\epsilon 4$ status, we stratified the participants into APOE $\epsilon 4$ allele carrier and non-carrier subgroups (see supplementary material Table S2). The allele frequency and genotype distribution of SNPs in each subgroup are supplied. For rs1047631, the distribution of genotype showed significantly difference between normal and cognitive impairment groups in APOE $\epsilon 4$ carriers ($p = 0.020$). For rs11046205, the

frequency of genotype and allele showed significant difference between normal and cognitive impairment groups in APOE ϵ 4 carriers, with the minor allele (A allele) significantly decreasing the cognitive impairment risk (genotype: $p = 0.003$, allele: OR = 0.387, 95%CI = 0.191–0.784, $p = 0.008$). For rs2070045, the genotype distribution showed a significant difference between normal and cognitive impairment groups in both the whole group ($p = 0.010$) and the APOE ϵ 4 non-carriers group ($p = 0.018$). For rs2075650, the genotype distribution differed significantly between normal and cognitive impairment groups ($p = 0.034$). For rs405509, allele frequency and genotype distribution showed significant difference between normal and cognitive impairment groups in APOE ϵ 4 carriers, with the minor allele (G allele) significantly increasing the cognitive impairment risk (genotype: $p = 0.001$, allele: OR = 2.242, 95%CI = 1.397–3.600, $p = 0.001$). For rs429358 (one of the APOE SNPs), the allele frequency and genotype distribution showed significant difference between normal and cognitive impairment groups, with the minor allele (C allele) significantly increasing the cognitive impairment risk (genotype: $p = 0.001$, allele: OR = 1.611, 95%CI = 1.217–2.132, $p = 0.001$). For rs6439886 and rs7412, both the genotype distribution and minor allele frequency showed significant differences between the two groups even after stratified by APOE ϵ 4 status ($p > 0.05$).

The Association Between Snps And Cognitive Impairment

Furthermore, a logistic regression analysis was performed to assess the effect of each SNP additive model and SNP $\times$ APOE interaction on cognitive impairment risk [adjusting for gender, age, education year, APOE status (except for rs429358 and rs7412), smoking status, alcohol drinking frequency, physical activity, hypertension, diabetes, heart disease, cerebral infarction and CESD], listed in table 2. For rs11046205, the additive model showed a protective role in cognitive impairment development (OR = 0.775, 95%CI = 0.607–0.900, $P = 0.041$). For rs429358, the additive model showed positive association with cognitive impairment (OR = 1.639, 95%CI = 1.223–2.196, $P = 0.001$). Otherwise, there was significant interaction between rs11046205/rs405509 and APOE status.

We further analyzed the impact of rs11046205/rs405509 on the APOE ϵ 4 risk for cognitive impairment (table 3). After adjusting for rs11046205, the OR of APOE ϵ 4 decreased from 1.759 to 1.752 ($P < 0.001$). When adjusted for rs405509, the OR of APOE ϵ 4 increased from 1.759 to 1.816 ($P < 0.001$).

Effect Of Snp Genotype On Cognitive Test Scores

Selected by logistic regression, ABCC9 (rs11046205) and APOE (rs429358) were included in these analyses. Since there is only 1 participant that had the C/C genotype in rs429358, we regrouped the two SNPs into AA or a-carrier (A: major, a: minor), and compared the different cognitive scores in the two groups (see supplementary material Table S3). The scores of the MMSE, MoCA-s, AD8, DSB, DSST and PALT were stratified according to genotype. For rs429358, participants carrying the C allele had significantly higher AD8 score than non-carriers in the cognitive impairment group ($p = 0.002$, Fig. 1). There is no significant difference in cognitive scores between the genotypes of rs11046205.

Snp And Phenotype Association Analysis

The association analyses were performed using an additive model adjusted by age, gender, educational year, smoking status, alcohol drinking frequency, hypertension, diabetes, heart disease, cerebral infarction, physical status, CESD and APOE status (except for rs429358). For rs429358, there was a significant negative association between the additive model and MMSE score ($p = 0.003$). None of the other SNPs showed an association with cognitive scores ($p > 0.05$) (table 4).

Gene-gene And Gene-lifestyle Interaciton

Then, we selected two key SNPs into the subsequent analyses with evidence of cognitive impairment association, including ABCC9 rs11046205 ($p = 0.039$) and APOE rs429358 ($p < 0.001$). We used GMDR analysis to assess the gene-gene and gene-lifestyle interaction between the two SNPs and smoking, alcohol drinking frequency and physical activity - including gender, age and education year as covariates. Cognitive impairment and MMSE score were employed as outcome for both gene-gene and gene-lifestyle interaction analysis. Table 5 summarizes the results obtained from the GMDR analysis for gene-gene interaction models after adjusting covariates. In the logistic regression analyses, there were significant interaction models involving rs11046205 and rs429358 ($p = 0.0107$, CV = 10/10). This result indicate potential gene-gene interactions between ABCC9 and APOE on influencing cognitive impairment. In the linear regression analyses, there were significant interaction models involving rs429358 and physical activity ($p = 0.0107$, CV = 6/10), indicating potential gene-lifestyle interactions between APOE (rs429358) and lifestyles on influencing general cognitive function (MMSE). (Table 6)

Discussion

Due to the increased prevalence of AD in the elderly, relevant risk genes for AD are widely utilized in cognitive aging research, such as BDNF, TOMM40, COMT, DTNBP1 and SORL1 [6, 30]. These related risk genes have been identified by genomewide association studies (GWASs) in many populations[31]. Evidence confirms that the most well replicated gene is APOE, which accounts for 50% or less in the risk of developing AD [32]. These results remind us of the polygenic trait character of the disease and the importance of prevention - not only identification; we should not only focus on the genes directly associated with AD, but the ones related with general cognitive function and simultaneous phenomena. In this study, we verified the association between AD risk genes and cognitive impairment in our Han community-dwelling elderly. The allele or genotype frequency of APOE (rs429358), APOE promoter (rs405509), TOMM40 (rs2075650) and SORL1 (rs2070045) showed a significant difference between normal and cognitive impairment groups and APOE $\epsilon 4$ stratified subgroups. Logistic regression analyses showed a significant correlation between APOE (rs429358), ABCC9 (rs11046205) and cognitive impairment and an interaction between ABCC9 (rs11046205)/APOE promoter (rs405509) and APOE $\epsilon 4$ status. A conditional analysis test was used to find whether APOE $\epsilon 4$ has an association independent of the ABCC9 (rs11046205)/APOE promoter (rs405509) SNPs. After adjusting the covariates and ABCC9 (rs11046205)/APOE promoter (rs405509) SNPs, there is still significant risk for APOE $\epsilon 4$ in cognitive impairment. The ABCC9 (rs11046205) could reduce the risk of APOE $\epsilon 4$, and APOE promoter (rs405509) could increase the risk of APOE $\epsilon 4$ in cognitive impairment. We further substantiated the linkage between these risk genes and cognitive phenotypes. For the additive model of APOE (rs429358) showed a

significant negative association with MMSE scores. Additionally, our data revealed that gene-gene interaction between ABCC9 and APOE may contribute to the etiology of cognitive impairment.

As the 2 SNPs relevant to classifying the APOE genotype, the rs429358 (not rs7412) significantly increased the risk of cognitive impairment in the Han community-dwelling elderly in our data, with an OR of 1.639(1.223–2.196), and the interaction between the APOE ϵ 4 status and APOE promoter (rs405509) could increase the OR of APOE ϵ 4 from 1.759 to 1.816. TOMM40 (rs2075650) in our sample could also increase the risk of cognitive impairment with an OR of 1.309(1.007–1.702). The genes we conducted above were all in the APOE/TOMM40 region, which has recently been proven to be associated with cognitive aging [8, 33]. There is no clear boundary between cognitive aging and cognitive impairment, the genetic contribution to ‘normal’ and ‘pathological’ cognitive variation in old age overlaps [8]. Here we confirmed these results in cognitively impairment elderly in Han community-dwelling in Beijing.

The DTNBP1 (rs1047631) and CLSTN2 (rs6439886) were two genes which have been proven to be associated with general cognitive function (working memory and episodic memory) [34]. In our data, the genotype of rs1047631 and minor allele of rs6439886 polymorphisms showed protective effect in the development of cognitive impairment in the APOE ϵ 4 carrier and whole sample, respectively. Up to now, the evidence for DTNBP1 mainly focused on Schizophrenia [35, 36], which could influence the risk of the disease. However, recently the variation of DTNBP1 has also been linked with human cognitive functioning, although the evidence is inconsistent [37]. The association studies differed across study population (vary in sample size, ethnic composition, age and educational background), which could add complexity to the genotype-phenotype association, but were generally observed for memory traits in the two older cohorts [38]. Our results are consistent with the situation above and another research in Japanese older adults [39]. The CLSTN2 (rs6439886) gene has confirmed the association with episodic memory by GWAS studies in young adults (age range: 18–48 years) [40]. The protective effect of CLSTN2 (rs6439886) on cognitive function has been proven in both young adults and the elderly, which was consistent with our results [41, 42].

We found the additive model of the ABCC9 (rs11046205) gene had a protective effect for the development of cognitive impairment (OR = 0.775, 95%CI = 0.607-0.900), and the interaction between ABCC9 and the APOE ϵ 4 status could reduce the OR of APOE ϵ 4 from 1.759 to 1.752. As an ATP-sensitive potassium channel, the ABCC9 gene has been proven to be related with sleep duration in samples from two large European consortiums (n = 4251 and n = 5949) [43, 44]. The minor allele (A-allele) distribution showed protective effect in the development of cognitive impairment in the APOE ϵ 4 carrier, which is the same genotype that has been previously associated with longer sleep duration [44]. The U-shape association between cognitive impairment and night sleep duration has been confirmed in a study of Northern Chinese elderly, which means the cognitive impairment was linked to getting either too little or too much sleep [19]. We cannot assess the sleep duration of the A-allele represented, but it should not exceed the normal time horizon since it showed a protective effect for people with depression, which is one of the risk factors for AD [22]. Given the high incidence of disturbed sleep in cognitive impairment (60% in dementia and MCI) [21], it is reasonably believe that the same SNP which increases sleep duration having a protective effect on cognitive impairment. To our knowledge, this is the first association of cognitive impairment-related traits with an ATP-sensitive potassium channel gene, which may suggest that this group of potassium channels serves as an additional pathway to affect the development of cognitive impairment.

In the GMDR analysis of gene-gene interactions, we found the interaction between ABCC9 (rs11046205) and APOE (rs429358) with cognitive impairment ($p < 0.05$). ABCC9 is a K(ATP) channel gene which affects sleep duration [44], and we have proven the protective effect of rs11046205 in cognitive impairment above. The interaction between APOE (rs429358) and ABCC9 (rs11046205) here further proofed the underlying effect of potassium channels in cognitive impairment. Here we also tracked down the interplay between MMSE scores (general cognitive function) and APOE (rs429358) with a kind of lifestyles, which is physical activity. The result were consistent with others' [45]. Evidence showed that APOE-lifestyle interaction could increase the risk of late-life cognitive decline by 11 times, in which sedentary lifestyles is included [46]. It was well known that the multifactorial characteristic of cognitive impairment including genetic, lifestyle and environmental factors [47] suggesting the essential role of lifestyle and gene-lifestyle interaction in the future studies.

Several limitations of this study should be acknowledged. First, we didn't make a distinction between MCI and cognitive impairment in our study participants. Second, we didn't examine the interaction between genetic variants and measurable physiology, such as blood lipids and glucose, which may add more information to the pathological character of cognitive impairment [48]. Further studies may add more physiological data into account to reveal potential interactions.

In conclusion, the current study support the association of APOE (rs429358), APOE promoter (rs405509) and SORL1 (rs2070045) polymorphisms with the risk of cognitive impairment in the Han community-dwelling elderly in Beijing. The interaction of the APOE promoter and APOE $\epsilon 4$ could increase the risk of APOE $\epsilon 4$, whereas the ABCC9 could decrease it. The gene-gene interaction analysis revealed that the effect of APOE (rs429358) and ABCC9 (rs11046205) in the development of cognitive impairment may through independent or complex gene-gene interactions. Future replication studies with measurable physiological data will likely to reveal more valuable information into the multiple complex pathogeneses of cognitive impairment.

Abbreviations

AD: Alzheimer's disease; MCI: mild cognitive impairment; SNP: single-nucleotide polymorphisms; MMSE: Mini-Mental State Examination; MoCA-s: the short version of the Montreal Cognitive Assessment-Beijing; AD8: Ascertain Dementia 8; DSB: Digit Span Backwards; DSST: Digital Symbol Substitution Test; PALT: Paired Associative Learning Test; APOE: apolipoprotein E; CESD: Center for Epidemiological Studies-Depression; HWE: Hardy-Weinberg equilibrium; GMDR: generalized multifactor dimensionality reduction; CI: confidence interval; OR: odds ratio; MAF: minor allele frequency; CV: cross-validation consistency; GWAS: genomewide association studies;

Declarations

Authors' contributions

LJ drafted the manuscript and did the genetic analysis. FJN collected the clinical data and revise the manuscript. ZZW and ZXY did the study supervision. HXY coordinated community work. LJ designed and supervised the study. All authors have read and approved the manuscript.

Acknowledgments

We are grateful to all the participants who agreed to participate in this study and the fully support by the staff of local hospital.

Funding

This study was supported by grants from the Beijing Municipal Science & Technology Commission (Z171100000117006). The funding supported the collection of the participants' data.

Availability of data and materials

The datasets used and analyzed in the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the research ethics committees of the Institute of Psychology, Chinese Academy of Science (H11036) (ChiCTR1900025487). All participants or, where appropriate, their nearest relatives provided written informed consent to participate.

Consent for publication

Not applicable.

Competing interests

The author declare that they have no conflict of interest.

References

1. Lu J, Li D, Li F, Zhou A, Wang F, Zuo X, et al. Montreal Cognitive Assessment in Detecting Cognitive Impairment in Chinese Elderly Individuals: A Population-Based Study. *Journal of Geriatric Psychiatry & Neurology*.24(4):184-90.
2. Li X, Ma C, Zhang J, Liang Y, Chen Y, Chen K, et al. Prevalence of and Potential Risk Factors for Mild Cognitive Impairment in Community-Dwelling Residents of Beijing. *Journal of the American Geriatrics Society*.61(12):2111-9.
3. Wu MS, Lan TH, Chen CM, Chiu HC, Lan TY. Socio-demographic and health-related factors associated with cognitive impairment in the elderly in Taiwan. *BMC public health*. 2011;11(1):22.
4. Wimo A, Jönsson L, Bond J, Prince M, Winblad B. The worldwide economic impact of dementia 2010. 2013;9(1):1-11.e3.
5. Pei JJ. Dementia studies in Chinese populations. 2014.
6. Eid A, Mhatre I, Richardson JR. Gene-environment interactions in Alzheimer's disease: A potential path to precision medicine. *Pharmacol Ther*. 2019;199:173-87.
7. Plomin R, Kosslyn SM. Genes, brain and cognition. *Nature Neuroscience*. 2002;4(12):1153-4.

8. Davies G, Armstrong N, Bis JC, Bressler J, Deary IJ. Genetic contributions to variation in general cognitive function: A meta-analysis of genome-wide association studies in the CHARGE consortium (N=53 949). *Molecular psychiatry*. 2015;20(2).
9. Small BJ, Rosnick CB, Fratiglioni L, Bäckman L. Apolipoprotein E and Cognitive Performance: A Meta-Analysis. *Psychology & Aging*. 19(4):592-600.
10. Bertram L, McQueen MB, Mullin K, Blacker D, Tanzi RE. Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. *Nat Genet*. 2007;39(1):17-23.
11. Xiao Q, Liu ZJ, Tao S, Sun YM, Wu Z-Y. Risk prediction for sporadic Alzheimer's disease using genetic risk score in the Han Chinese population. *Oncotarget*. 2015;6(35):36955-64.
12. Liang Y, Li H, Lv C, Shu N, Chen K, Li X, et al. Sex Moderates the Effects of the Sorl1 Gene rs2070045 Polymorphism on Cognitive Impairment and Disruption of the Cingulum Integrity in Healthy Elderly. *Neuropsychopharmacology*. 2015;40(6):1519-27.
13. Nordahl CW, Ranganath C, Yonelinas AP, DeCarli C, Reed BR, Jagust WJ. Different mechanisms of episodic memory failure in mild cognitive impairment. 43(11):1688-97.
14. Wang QS, Zhou J-N. Retrieval and encoding of episodic memory in normal aging and patients with mild cognitive impairment. *Brain Research*. 924(1):113-5.
15. Wolf C, Jackson MC, Kissling C, Thome J, Linden DEJ. Dysbindin-1 genotype effects on emotional working memory. 2011;16(2):145-55.
16. Karlsgodt KH, Bachman P, Winkler AM, Bearden CE, Glahn DC. Genetic influence on the working memory circuitry: Behavior, structure, function and extensions to illness. 225(2):0-622.
17. Papassotiropoulos A, Quervain DJ-Fd. Genetics of human episodic memory: dealing with complexity. 15(9):0-387.
18. Sabb FW, Burggren AC, Higier RG, Fox J, He J, Parker DS, et al. Challenges in phenotype definition in the whole-genome era: multivariate models of memory and intelligence. *Neuroscience*. 2009;164(1):88-107.
19. Song QF, Liu XX, Hu WN, Han XC, Zhou WH, Lu AD, et al. Night Sleep Duration and Risk of Cognitive Impairment in a Chinese Population: A Cross-sectional Study. *Biomed Environ Sci*. 2017;30(10):749-57.
20. Suh SW, Han JW, Lee JR, Byun S, Kwon SJ, Oh SH, et al. Sleep and cognitive decline: A prospective nondemented elderly cohort study. *Ann Neurol*. 2018;83(3):472-82.
21. Guarnieri B, Adorni F, Musicco M, Appollonio I, Bonanni E, Caffarra P, et al. Prevalence of sleep disturbances in mild cognitive impairment and dementing disorders: a multicenter Italian clinical cross-sectional study on 431 patients. *Dementia and geriatric cognitive disorders*. 2012;33(1):50-8.
22. Parsons MJ, Lester KJ, Barclay NL, Nolan PM, Gregory AM. Replication of Genome-Wide Association Studies (GWAS) loci for sleep in the British G1219 cohort. *American Journal of Medical Genetics Part B Neuropsychiatric Genetics*. 2013;162(5):431-8.
23. Zhang Z, Hong X, Li H, Zhao J, Huang J, Wei J, et al. The mini-mental state examination in the Chinese residents population aged 55 years and over in the urban and rural areas of Beijing. *Chinese Journal of Neurology*. 1999;32:149-53.
24. Wechsler D. WAIS-R manual: Wechsler adult intelligence scale-revised: Psychological Corporation; 1981.
25. Dumont R, Willis JO. Wechsler Adult Intelligence Scale—Third Edition: John Wiley & Sons, Inc.; 2008.

26. Xu S, Wu Z. The construction of 'The Clinical Memory Test'. *Acta Psychologica Sinica*. 1986;18(1):100-8.
27. Roberts RE, Vernon SW. The Center for Epidemiologic Studies Depression Scale: its use in a community sample. *The American journal of psychiatry*. 1983;140(1):41-6.
28. Chen C-S, Ouyang P, Yeh Y-C, Lai C-L, Liu C-K, Yen C-F, et al. Apolipoprotein E polymorphism and behavioral and psychological symptoms of dementia in patients with Alzheimer disease. *Alzheimer disease and associated disorders*. 2012;26(2):135-9.
29. Lou X-Y, Chen G-B, Yan L, Ma JZ, Zhu J, Elston RC, et al. A generalized combinatorial approach for detecting gene-by-gene and gene-by-environment interactions with application to nicotine dependence. *Am J Hum Genet*. 2007;80(6):1125-37.
30. Jack CR. A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers. *Neurology*. 2016;87(5):539-47.
31. Trampush JW, Yang MLZ, Yu J, Knowles E, Davies G, Liewald DC, et al. GWAS meta-analysis reveals novel loci and genetic correlates for general cognitive function: a report from the COGENT consortium. *Molecular psychiatry*. 2017;22(3):336-45.
32. Ashford JW, Mortimer JA. Non-familial Alzheimer's disease is mainly due to genetic factors. *Journal of Alzheimer's disease : JAD*. 2002;4(3):169-77.
33. Davies G, Harris SE, Reynolds CA, Payton A, Knight HM, Liewald DC, et al. A genome-wide association study implicates the APOE locus in nonpathological cognitive ageing. *Molecular psychiatry*. 2014;19(1):76-87.
34. Kremen WS, Panizzon MS, Franz CE, Spoon KM, Vuoksimaa E, Jacobson KC, et al. Genetic complexity of episodic memory: a twin approach to studies of aging. *Psychology and aging*. 2014;29(2):404-17.
35. Bray NJ, Preece A, Williams NM, Moskvina V, Buckland PR, Owen MJ, et al. Haplotypes at the dystrobrevin binding protein 1 (DTNBP1) gene locus mediate risk for schizophrenia through reduced DTNBP1 expression. *Human molecular genetics*. 2005;14(14):1947-54.
36. Mohamed ZI, Tee SF, Tang PY. Association of functional polymorphisms in 3'-untranslated regions of COMT, DISC1, and DTNBP1 with schizophrenia: a meta-analysis. *Psychiatric genetics*. 2018.
37. Zhang J-P, Burdick KE, Lencz T, Malhotra AK. Meta-analysis of genetic variation in DTNBP1 and general cognitive ability. *Biological psychiatry*. 2010;68(12):1126-33.
38. Luciano M, Miyajima F, Lind PA, Bates TC, Horan M, Harris SE, et al. Variation in the dysbindin gene and normal cognitive function in three independent population samples. 2009.
39. Hashimoto R, Noguchi H, Hori H, Ohi K, Yasuda Y, Takeda M, et al. Association between the dysbindin gene (DTNBP1) and cognitive functions in Japanese subjects. *Psychiatry and clinical neurosciences*. 2009;63(4):550-6.
40. Papassotiropoulos A, Stephan DA, Huentelman MJ, Hoerndli FJ, Craig DW, Pearson JV, et al. Common Kibra alleles are associated with human memory performance. *Science (New York, NY)*. 2006;314(5798):475-8.
41. Schneider A, Huentelman MJ, Kremerskothen J, Duning K, Spoelgen R, Nikolich K. KIBRA: A New Gateway to Learning and Memory? *Frontiers in aging neuroscience*. 2010;2:4-

42. Laukka EJ, Lövdén M, Herlitz A, Karlsson S, Bäckman L. Genetic Effects on Old-Age Cognitive Functioning: A Population-Based Study. *Psychology & Aging*. 2012;28(1).
43. Allebrandt KV, Teder-Laving M, Akyol M, Pichler I, Müller-Myhsok B, Pramstaller P, et al. CLOCK gene variants associate with sleep duration in two independent populations. *Biological psychiatry*. 2010;67(11):1040-7.
44. Allebrandt KV, Amin N, Muellermysok B, Esko T, Tederlaving M, Azevedo RVDM, et al. A K(ATP) channel gene effect on sleep duration. 2013;18(1):122.
45. Lin E, Tsai SJ, Kuo PH, Liu YL, Kao CF. Association and interaction effects of Alzheimer's disease-associated genes and lifestyle on cognitive aging in older adults in a Taiwanese population. *Oncotarget*. 2017;8(15):24077-87.
46. Wajman JR, Mansur LL, Yassuda MS. Lifestyle Patterns as a Modifiable Risk Factor for Late-life Cognitive Decline: A Narrative Review Regarding Dementia Prevention. *Current aging science*. 2018.
47. Konar A, Singh P, Thakur MK. Age-associated Cognitive Decline: Insights into Molecular Switches and Recovery Avenues. *Aging Dis*. 2016;7(2):121-9.
48. Raz N, Lustig C. Genetic variants and cognitive aging: destiny or a nudge? *Psychology and aging*. 2014;29(2):359-62.

Tables

Table 1
Demographic and clinical characteristics of the two groups:

	Whole group (n=1924)	Normal group (n=1513)	Cognitive Impairment group (n=411)	<i>t/</i> χ^2	<i>p</i>
Age					
Mean (SD)	69.29 (5.96)	68.98 (5.71)	70.44 (6.68)	-4.43	<0.001*
Range	50-85	50-84	54-85		
Gender (M/F)					
N (%)	634 (32.95)	472 (31.20)	162 (39.42)	9.88	0.002#
Education year					
Mean (SD)	10.09 (3.48)	10.23 (3.55)	9.55 (3.16)	3.514	0.001*
Range	0-22	0-22	0-18		
AD8					
Mean(SD)	1.83 (1.75)	1.74 (1.67)	2.16 (1.98)	-4.43	<0.001*
MMSE					
Mean (SD)	27.31 (2.70)	28.27 (1.60)	23.76 (2.95)	41.20	<0.001*
MoCA-s					
Mean(SD)	13.91 (2.82)	14.47 (2.47)	11.84 (3.10)	18.02	<0.001*
PALT					
Mean (SD)	7.30 (4.12)	7.89 (4.08)	5.14 (3.51)	12.46	<0.001*
DSB					
Mean(SD)	4.46 (1.47)	4.64 (1.45)	3.78 (1.36)	10.75	<0.001*
DSST					
Mean (SD)	29.53 (11.78)	31.05 (11.48)	23.96 (11.16)	11.34	<0.001*
CESD					
Mean (SD)	6.94 (8.35)	6.65 (8.07)	8.00 (9.24)	-2.93	0.003*
APOE ϵ4 carrier					
N	250(13.54) N=1847	175 (12.05) N=1452	75 (18.99) N=395	12.76	<0.001#

AD8, Ascertain Dementia 8; MMSE, Mini-Mental State Examination; MoCA-s, Montreal Cognitive Assessment

short edition; DSST, Digital Symbol Substitution Test; PALT, Paired Associative Learning Test; CESD, Center for Epidemiological Studies Depression Scale. * t test; # χ^2 test.

Table 2

Logistic regression analysis of SNPs additive model stratified by the APOE $\epsilon 4$ allele.

SNP		MAF		OR(95%CI)	P not adjusted APOE	P adjusted APOE	P for APOE interaction	OR(95%CI)
		Case	Control					
DTNBP1	Rs1047631	0.013	0.021	0.719(0.371-1.394)	0.328	0.292	0.999	-
ABCC9	Rs11046205	0.119	0.139	0.775(0.607-0.900)	0.041	0.046	0.007	0.365(0.175-0.759)
SORL1	Rs2070045	0.412	0.450	0.875(0.744-1.029)	0.106	0.114	0.331	0.821(0.551-1.222)
TOMM40	Rs2075650	0.101	0.079	1.308(0.985-1.737)	0.064	0.789	0.405	0.784(0.441-1.392)
APOE promoter	Rs405509	0.302	0.288	1.078(0.905-1.284)	0.399	0.173	<0.001	2.735(1.574-4.752)
APOE	Rs429358	0.097	0.065	1.639(1.223-2.196)	0.001	0.453	-	-
CLSTN2	Rs6439886	0.062	0.084	0.732(0.531-1.009)	0.057	0.056	0.227	0.620(0.285-1.347)
APOE	Rs7412	0.085	0.082	1.070(0.802-1.429)	0.645	0.505	0.397	1.438(0.620-3.334)

MAF, minor allele frequency.

Adjusted for age, gender, education year, APOE status (except for rs429358), smoking status, alcohol drinking frequency, physical activity, hypertension, diabetes, heart disease, cerebral infarction and CESD.

Table 3

The association between APOE $\epsilon 4$ and cognitive impairment.

Models	Total sample					
	P^a	OR(95%CI)	P^b	OR(95%CI)	P^c	OR(95%CI)
APOE $\epsilon 4$	<0.001	1.759(1.296-2.386)	<0.001	1.752(1.290-2.378)	<0.001	1.816(1.333-2.474)

^aAdjusted for age, gender, education year, smoking status, alcohol drinking frequency, physical activity, hypertension, diabetes, heart disease, cerebral infarction and CESD.

^bAdjusted for age, gender, education year, smoking status, alcohol drinking frequency, physical activity, hypertension, diabetes, heart disease, cerebral infarction, CESD and rs11046205 additive model.

^cAdjusted for age, gender, education year, smoking status, alcohol drinking frequency, physical activity, hypertension, diabetes, heart disease, cerebral infarction, CESD and rs405509 additive model.

Table 4

Multiple linear regressions of SNPs additive model and cognitive phenotype.

Gene	SNP	MMSE	
		$\beta \pm se$	P^{Model}
APOE	rs429358	-0.474 $\pm$ 0.159	0.003

Adjusted for age, gender, educational year, smoking status, alcohol drinking frequency, hypertension, diabetes, heart disease, cerebral infarction, physical status, CESD and APOE status (except for rs429358).

MMSE, Mini-Mental State Examination.

Table 5

Gene-gene interaction models identified by the GMDR method (logistic regression).

Interaction model	Testing accuracy (%)	<i>P</i> (CV)
Rs11046205, rs429358	54.04	0.0107(10/10)

Abbreviations: GMDR=general multifactor dimensionality reduction; CV=Cross-validation consistency. Adjusted for age, gender and education year.

Table 6

Gene-lifestyle interaction models with MMSE identified by the GMDR method (linear regression).

Interaction model	Testing accuracy (%)	<i>P</i> (CV)
Rs429358, physical	53.98	0.0107(6/10)

Abbreviations: GMDR=general multifactor dimensionality reduction; CV=Cross-validation consistency. Adjusted for age, gender and education year.

Figures

Figure 1

The difference in AD8 scores between rs429358 genotypes in the cognitive impairment group.