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Original Article

Association of *ABCA1* with Mild Cognitive Impairment

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SUMMARY

Background: Mild cognitive impairment (MCI), as a neurodegenerative disease characterized by a moderate decline in one or more cognitive functions with a preserved autonomy in daily life activities, is the early stage and a high-risk state of Alzheimer's disease (AD). The adenosine triphosphate-binding cassette transporter A1 (*ABCA1*) is a cell membrane transporter protein involved in cholesterol reverse transport, sterol metabolism, and high-density lipoprotein (HDL) metabolism. The aim of this study was to investigate the relationship between polymorphism of C/T (rs4149268) in *ABCA1* gene with MCI in a Chinese population.
Methods: This study involved 1,654 subjects, including 278 MCI patients and 1376 healthy subjects. Genotypes of 1,616 samples were measured using matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF-MS) technique.
Results: The analysis of rs4149268 polymorphism of *ABCA1* gene showed that there were significant differences between MCI and controls ($p < 0.05$). When adjusting for age, sex, marital status, education, non-alcoholic fatty liver disease (NAFLD), and alcohol drinking, results showed that rs4149268 polymorphism was significantly correlated with MCI in codominant, dominant, and log-additive models. Logistic regression analysis showed that rs4149268 T/T carriers were 1.761 times more susceptible than C/C carriers (95% confidence interval: 1.108–2.800).
Conclusions: Rs4149268 polymorphism of *ABCA1* gene was shown to be a genetic risk factor for MCI.

1. Introduction

Mild cognitive impairment (MCI) is an intermediate state between normal cognitive aging and dementia. The prevalence of MCI ranges from 10% to 20% in adults older than 65 years.[1] A recent study has demonstrated an overall MCI prevalence of 15.5% (15.2%–15.9%), representing 38.77 million (37.95–39.62) people in China, and the prevalence of MCI might substantially increase with an aging population.[2] Although studies have found that 20%–30% of people with MCI will return to normal cognition, there is a 5%–10% annual rate of progression to dementia in those with MCI, which is much higher than the 1%–2% annual incidence among the general population. Therefore, the researchers suggest that it might be possible to intervene in MCI to delay the development of dementia.

MCI is a complex disease caused by a combination of genetic and environmental factors. Currently, several genes have been related to MCI, including amyloid precursor protein (*APP*), apolipoprotein E gene (*APOE*), etc.[3] *APOE*, as a plasma protein, is mainly involved in cholesterol balance and lipid metabolism, and associated with tau deposition in the cerebrospinal fluid of patients with MCI, while *APOE* lipidosis is the result of co-regulation of the adenosine triphosphate-binding cassette transporter A1 (*ABCA1*) and adenosine triphosphate-binding cassette transporter G1 (*ABCG1*).[4]

ABCA1, a complete membrane protein for cholesterol transport that mainly mediates the transport of intracellular cholesterol, phospholipids, and other lipophile molecules on the cell membrane, which exports excess cholesterol through HDL pathways to reduce cholesterol accumulation in macrophages. Studies showed that sequence variants of *ABCA1* are closely associated with Alzheimer's disease (AD).[5] However, there are few studies on the association between *ABCA1* and MCI. Therefore, the objective of this study was to examine the relationship between eight polymorphisms of *ABCA1* gene and MCI.

2. Materials and methods

2.1. Subjects

Individuals in five communities, including three communities in Yinchuan and two communities in Wuzhong, who participated in the health examination for urban and rural residents' program during 2013–2016, were selected from Ningxia Hui Autonomous Region by convenience cluster sampling method. Inclusion criteria were (a) patients aged ≥ 55 years; (b) living in the community for at least six months; Exclusion criteria comprised (a) patients diagnosed with de-

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mentia or other diseases affecting cognitive function; (b) failure to complete the investigation because of impaired vision and hearing, language, mental disabilities or other severe diseases; (c) failure to obtain a blood sample. A total of 1,860 participants were enrolled, of whom 206 participants failed to complete the Chinese version of the Mini-Mental State Examination (CMMSE) and Activities of Daily Living (ADL), and 38 participants could not provide a blood sample. Finally, a total of 1,616 individuals were included in this survey, with a completion rate of 86.88%. The flow diagram is shown in Figure 1.

We conducted neuropsychological and general physical examinations. Relevant information with questionnaires, including basic demographic characteristics, a series of tests such as the Geriatric Depression Scale (GDS), Mini-Mental State Examination (MMSE), and ADL, was obtained through a face-to-face interview. Smoking was defined as smoking at least one cigarette per day for ≥ 6 months, including current and former smokers. Alcohol drinking was defined as drinking at least 50 ml per week, at least once a day, for a period of more than one year, including current and former drinkers. Depression was measured using the GDS, with a total score ranging from 0 to 30.

Fasting plasma glucose was assessed using fasting venous blood. Non-alcoholic fatty liver disease (NAFLD) was diagnosed by professional doctors with reference to abdominal ultrasonography results. Anthropometric data, including height, weight, and body mass index (calculated as the weight [kg]/height ([m^2])], were collected.

This study was approved by the Institutional Review Committee of Ningxia Medical University (grant No. 2015-151; grant No. 2018-115). Written informed consent was obtained from each subject prior to the investigation and blood sample request.

2.2. MCI testing

MCI was diagnosed by combining CMMSE and ADL. MCI criteria were (a) ADL < 22 with < 2 items scoring ≥ 3 points and (b) conforming to CMMSE scores.

ADL consists of 14 scoring items, divided into two dimensions, namely instrumental activity of daily living (IADL) and basic activity of daily living (BADL). IADL consists of eight entries with a total score of 32. BADL consists of six entries with a total score of 24. Each item can score 0–4 points, where 1 is normal and 2–4 points represent different degrees of damage. The higher the scale score, the more serious the damage degree. The possible obtainable score is 14–56 points.

MMSE is one of the most influential cognitive impairment screening test tools among the elderly. CMMSE was modified by the sociocultural difference of Chinese people for MMSE. A total of 30 points is the maximal score, and a higher score indicates a higher level of cognitive function. MMSE scores are closely related to educational level, and cut-off scores were adjusted according to the educational level as follows: ≤ 17 for illiterate individuals, ≤ 20 for those with elementary school education, and ≤ 24 for those with middle school education or above.[6,7]

2.3. Single-nucleotide polymorphisms genotyping

Eight polymorphisms of *ABCA1* gene were selected only based on GWAS results for patients with dementia (http://snp4disease.mpi-bn.mpg.de/).

Genomic DNA was extracted from 1,616 blood samples using Wizard® Genomic DNA purification Kit (Promega Corporation, WI, USA) according to the manufacturer's instructions. The purity and concentration of extracted DNA were quantified by spectrophotometer, and quality was detected by agarose gel electrophoresis. The primer was designed using genotyping tools and the MassARRAY Assay Design software of Agena Bioscience. The forward primers

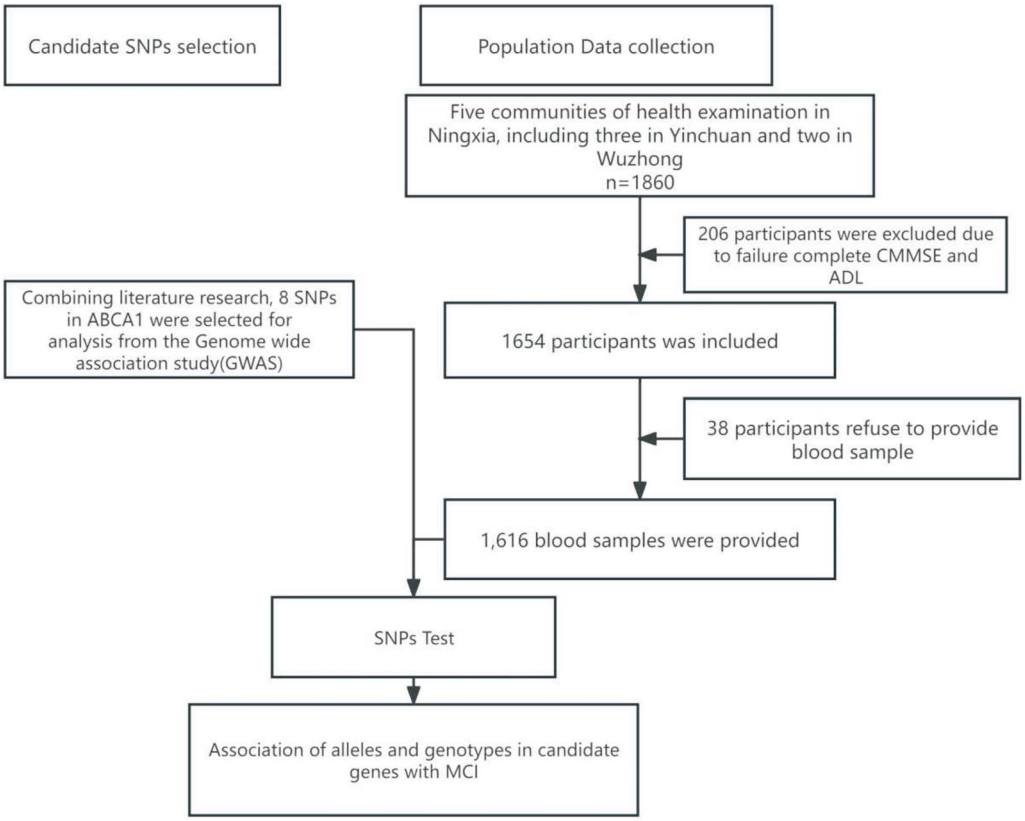

Figure 1. Flow chart of study. A total of 1,860 participants from the Health Examination were enrolled in the study, of whom 206 failed to complete the CMMSE and ADL, 38 were unable to provide a blood sample, finally a total of 1,616 individuals were included in this survey with a completion rate of 86.88%.

and the reverse primers are shown in Table 1.

Single-nucleotide polymorphisms (SNPs) were genotyped using matrix-assisted laser desorption/ionization time of flight and TYPER 4.0 software (Agena Bioscience).

2.4. Statistical analysis

SPSS 25.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. Categorical variables were represented as number of cases and percentage (%). Basic demographic variables, frequencies of alleles, and genotypes for *ABCA1* polymorphic sites between MCI and controls were analyzed by Chi-square test or Fisher exact test. Bonferroni multiple comparison analysis was used to understand subgroup differences among different genotype groups.

Hardy-Weinberg equilibrium was performed for each polymorphism by SNPStats software (https://www.snpstats.net/start.htm). The genotyping association between SNPs and MCI, was analyzed by SNPStats software, and odds ratios and 95% confidence intervals (CIs) for each model were calculated. Akaike Information Criterion (AIC) was used to select the optimal genetic model. The model with the smallest AIC value was considered the optimal model.

The logistic regression model was adjusted by age, sex, marriage, education level, NAFLD, and alcohol drinking. A $p \leq 0.05$ was considered statistically significant.

3. Results

3.1. Demographic characteristics of the study population

A total of 1,654 Hui nationality subjects were included in this study: 1,376 patients in the control group and 278 patients in the MCI group. The male age was 64.74 ± 4.752 years (mean $\pm$ standard deviation [SD]), and the female age was 62.77 ± 4.818 years. Finally, 278 participants with MCI were identified. Demographic characteristics are shown in Table 2. There were significant differences between control and MCI groups in age, sex, education, marital status, NAFLD,

Table 1
PCR primers for SNPs.

SNPs	Forward primers	Reverse primers
rs10512338	5′-ACGTTGGATGAACACCCCCCAAGAAAAGAC-3′	5′-ACGTTGGATGGAGTGACATGACTCACTAAG-3′
rs12350560	5′-ACGTTGGATGAACTGTGAATCAAGGCAGGG-3′	5′-ACGTTGGATGCAAAGGCTTTCTTTCTCGTG-3′
rs2065412	5′-ACGTTGGATGGTGATTAACAGCACTCAGGCG-3′	5′-ACGTTGGATGGGGATAAGTGCTCTAGAGAC-3′
rs2066715	5′-ACGTTGGATGGACAACCTGTTTGAGAGTCC-3′	5′-ACGTTGGATGAGAGGAAGGTGTCAAACAGC-3′
rs2230808	5′-ACGTTGGATGAGACAGCGGTTTACCTTGAC-3′	5′-ACGTTGGATGCTGCAGATCGATTTCTCAAC-3′
rs2482424	5′-ACGTTGGATGTCTGCCCTCTATGATAAGCC-3′	5′-ACGTTGGATGAGGGATTGATGGAATCTGGC-3′
rs4149268	5′-ACGTTGGATGTCAGCTCTCAGACATAGAGG-3′	5′-ACGTTGGATGTGTGCCCAGCCCACTTCAT-3′
rs4149271	5′-ACGTTGGATGTTGCCCATTGCCTCTTTTAC-3′	5′-ACGTTGGATGAGAGTTTAAACCAGACTCAG-3′

Table 2
Baseline characteristics of the study population.

Characteristics	Total	MCI	Controls	χ^2	*p* value
Age, n (%)				10.315	0.006
≤ 60	472 (28.5%)	68 (24.5%)	404 (29.4%)		
61–65	623 (37.7%)	93 (33.5%)	530 (38.5%)		
≥ 66	559 (33.8%)	117 (42.1%)	442 (32.1%)		
Sex, n (%)				34.227	< 0.001
Male	800 (48.4%)	90 (32.4%)	710 (51.6%)		
Female	854 (51.6%)	188 (67.6%)	666 (48.4%)		
Education, n (%)				6.448	0.040
Illiterate	965 (58.3%)	180 (64.7%)	785 (57.0%)		
Primary	417 (25.2%)	55 (19.8%)	362 (26.3%)		
Junior or above	272 (16.4%)	43 (15.5%)	229 (16.6%)		
Marital status, n (%)				4.439	0.035
Once	1608 (97.2%)	265 (95.3%)	1343 (97.6%)		
More than once	46 (2.8%)	13 (4.7%)	33 (2.4%)		
Solitary, n (%)				0.730	0.393
No	1469 (88.8%)	251 (90.3%)	1218 (88.5%)		
Yes	185 (11.2%)	27 (9.7%)	158 (11.5%)		
Normoglycemia, n (%)				0.663	0.416
No	848 (62.4%)	140 (64.8%)	708 (61.9%)		
Yes	512 (37.6%)	76 (35.2%)	436 (38.1%)		
NAFLD, n (%)				4.373	0.037
No	994 (76.8%)	165 (82.5%)	829 (75.7%)		
Yes	301 (23.2%)	35 (17.5%)	266 (24.3%)		
Depression, n (%)				1.853	0.173
No	1456 (88.0%)	238 (85.6%)	1218 (88.5%)		
Yes	198 (12.0%)	40 (14.4%)	158 (11.5%)		
BMI, n (%)				5.314	0.070
BMI < 24	548 (40.2%)	87 (40.7%)	461 (40.2%)		
24 ≤ BMI < 28	576 (42.3%)	79 (36.9%)	497 (43.3%)		
BMI ≥ 28	238 (17.5%)	48 (22.4%)	190 (16.6%)		
Smoking, n (%)				2.203	0.138
No	1557 (94.1%)	267 (96.0%)	1290 (93.8%)		
Yes	97 (5.9%)	11 (4.0%)	86 (6.3%)		
Drinking, n (%)				8.333	0.004
No	1635 (98.9%)	271 (96.9%)	1364 (99.1%)		
Yes	19 (1.1%)	7 (3.1%)	12 (0.9%)		

Notes: Normoglycemia: If the level was 3.9–6.1 mmol/L, it was judged as yes, otherwise was judged as no.
NAFLD: non-alcoholic fatty liver disease; BMI: body mass index.

and alcohol drinking ($p < 0.05$). In the MCI group, 67.6% of patients were female, while 48.4% of patients were female among controls. Moreover, 64.7% of patients were illiterate in the MCI group, and 57.0% of patients were illiterate among controls.

3.2. Associations of ABCA1 polymorphisms with MCI

Hardy-Weinberg equilibrium test results showed that *p*-values of rs10512338, rs12350560, and rs4149271 in MCI patients and controls were < 0.05, and correlation analysis was not included. There were significant differences between MCI patients and controls for allele and genotype frequencies of rs4149268, respectively ($p = 0.007$; $p = 0.025$).

The optimal genetic inheritance model of rs4149268 was log-additive. A significant association was observed for rs4149268 with log-additive, codominant, and dominant models. Codominant model results suggested that TT increased the risk of developing MCI 1.63 times compared to CC (95% CI: 1.03–2.56) and CT increased the risk of developing MCI 1.37 times compared to CC (95% CI: 1.04–1.80). Dominant model results suggested that CT-TT increased the risk of developing MCI 1.41 times compared with CC (95% CI: 1.09–1.83). A significant association still remained after adjustment for age, sex, marital status, education, NAFLD, and alcohol drinking with log-additive, codominant, and dominant models. Results are shown in Table 3.

3.3. Logistic regression of the correlation between ABCA1 polymorphism and MCI

In Table 4, the risk of MCI among subjects aged ≥ 66 years was 2.097 times higher than that in those aged < 60 years (95% CI: 1.481–2.968). Additionally, females were 2.656 times more likely to develop MCI than males (95% CI: 1.940–3.636). TT or CT significantly increased the risk of MCI than CC for *ABCA1* rs4149268.

4. Discussion

This study investigated the relationship between MCI and *ABCA1*

Table 3
Association of *ABCA1* polymorphisms with MCI.

SNPs	Group	Allele frequency n (%)		Genotype frequency n (%)			*p* value		Model inheritance	OR (95% CI)
		C	T	CC	CT	TT	Allele	Genotype		
rs2065412	MCI (n = 272)	51 (9.4)	493 (90.6)	3 (1.1)	45 (16.5)	224 (82.4)	0.729	0.941	Codominant	0.95 (0.67-1.35) [a]
	Controls (n = 1339)	264 (9.9)	2414 (90.1)	17 (1.3)	230 (17.2)	1092 (81.6)				0.86 (0.25-2.96) [a]
									Dominant [b]	**0.95 (0.67-1.33)** [a]
										1.11 (0.74-1.66) [c]
									Recessive	0.87 (0.25-2.98) [a]
									Over dominant	0.96 (0.67-1.36) [a]
									Log-additive [b]	**0.95 (0.69-1.29)** [a]
										1.12 (0.78-1.61) [c]
rs2066715	MCI (n = 273)	359 (65.8)	187 (34.2)	118 (43.2)	123 (45.1)	32 (11.7)	0.242	0.401	Codominant	0.83 (0.63-1.10) [a]
	Controls (n = 1339)	1690 (63.1)	988 (36.9)	520 (38.8)	650 (48.5)	169 (12.6)				0.83 (0.54-1.28) [a]
									Dominant [b]	**0.83 (0.64-1.09)** [a]
										0.77 (0.57-1.06) [c]
									Recessive	0.92 (0.61-1.37) [a]
									Over dominant	0.87 (0.67-1.13) [a]
									Log-additive	0.89 (0.73-1.08) [a]
rs2230808	MCI (n = 275)	353 (64.2)	197 (35.8)	109 (39.6)	135 (49.1)	31 (11.3)	0.452	0.165	Codominant	1.28 (0.97-1.69) [a]
	Controls (n = 1337)	1761 (65.9)	913 (34.1)	594 (44.4)	573 (42.9)	170 (12.7)				0.99 (0.64-1.53) [a]
									Dominant	1.22 (0.93-1.59) [a]
									Recessive	0.87 (0.58-1.31) [a]
									Over dominant [b]	**1.29 (0.99-1.67)** [a]
										1.04 (0.76-1.42) [c]
									Log-additive	1.07 (0.89-1.30) [a]
rs2482424	MCI (n = 276)	488 (88.4)	64 (11.6)	217 (78.6)	54 (19.6)	5 (1.8)	0.293	0.503	Codominant	0.82 (0.60-1.14) [a]
	Controls (n = 1340)	2325 (86.8)	355 (13.2)	1010 (75.4)	305 (22.8)	25 (1.9)				0.93 (0.35-2.46) [a]
									Dominant [b]	**0.83 (0.61-1.14)** [a]
										0.83 (0.58-1.21) [c]
									Recessive	0.97 (0.37-2.56) [a]
									Over dominant [b]	**0.83 (0.60-1.14)** [a]
										0.82 (0.56-1.21) [c]
									Log-additive	0.86 (0.65-1.14) [a]
rs4149268	MCI (n = 274)	368 (67.2)	180 (32.8)	123 (44.9)	122 (44.5)	29 (10.6)	0.007	0.025	Codominant	1.37 (1.04-1.80) [a]
	Controls (n = 1342)	1956 (72.9)	728 (27.1)	718 (53.5)	520 (38.7)	104 (7.7)		< 0.05 [d]		1.63 (1.03-2.56) [a]
								< 0.05 [e]	Dominant	1.41 (1.09-1.83) [a]
								> 0.05 [f]	Recessive	1.41 (0.91-2.17) [a]
									Over dominant	1.27 (0.98-1.65) [a]
									Log-additive [b]	**1.31 (1.08-1.59)** [a]
										1.37 (1.08-1.73) [c]

Note: Due to poor DNA quality of some blood samples, some loci were not genotyped correctly, so the sample size of loci involved in calculating genotype and allele distribution frequency was lower than the total blood sample size.
a = Unadjusted regression model.
b = Identifies the best genetic inheritance model.
c = Adjusted regression model.
d, e, f = Subgroup differences between CC and CT (d), CC and TT (e), CT and TT (f) by Bonferroni multiple comparison analysis ($p < 0.05$).

Table 4
Logistic regression of the correlation between *ABCA1* polymorphism and MCI.

Variable	*B*	S.E.	*p* value	OR (95% CI)
Age (≤ 60)			< 0.001	
Age (61–65)	0.232	0.178	0.192	1.262 (0.890–1.789)
Age (≥ 66)	0.741	0.209	< 0.001	2.097 (1.481–2.968)
Sex (Female)	0.977	0.160	< 0.001	2.656 (1.940–3.636)
Education (Illiterate)			0.136	
Education (Primary)	-0.098	0.176	0.578	0.907 (0.642–1.281)
Education (Junior or above)	0.347	0.209	0.096	1.415 (0.940–2.129)
rs4149268 (CC)			0.018	
rs4149268 (CT)	0.308	0.143	0.031	1.361 (1.029–1.801)
rs4149268 (TT)	0.566	0.237	0.017	1.761 (1.108–2.800)

locus, involving 1,654 elderly subjects. *ABCA1* rs4149268 was an independent risk factor for MCI after controlling for age, sex, education, marital status, NAFLD, and alcohol drinking. TT and CT were associated with a higher risk of MCI than CC.

The prevalence of MCI was 16.8%, which was different from that in other regions of China. MCI prevalence was 14.2% in Guangzhou (age ≥ 65 years),[8] and 21.3% in Hebei (age ≥ 60 years).[9] This was consistent with the results of a meta-analysis on the prevalence and distribution trends of MCI among the elderly population in China, and the prevalence of MCI among the elderly population in different provinces was significantly different. The discrepancies might be due to the differences in the MCI screening scale and the study population. The MCI screening scale used in this study was CMMSE. It was modified by the sociocultural difference of Chinese people for MMSE, which is more suitable for Chinese people.

ABCA1 was involved in cholesterol reversal by transporting intracellular cholesterol and phospholipids to apolipoprotein A1, which was the precursor of high density lipoprotein (HDL) on the cell surface. They bind to extracellular apolipoproteins to form incipient HDL-C. This is the first step in the reverse cholesterol transport mechanism, which transports cholesterol and phospholipids from peripheral cells back to the liver, participating in cholesterol homeostasis via *ABCA1*. A previous observational study showed that a 50% increase in *ABCA1*-mediated cholesterol efflux led to a 30% increase in HDL-C concentration, resulting in a 50% reduction in the incidence of coronary artery disease.[10] *ABCA1*-mediated cholesterol efflux capacity was 30% less in patients with MCI compared with cognitively healthy controls, and the capacity of cerebrospinal fluid to facilitate *ABCA1*-mediated cholesterol efflux was impaired in patients with MCI. Our results showed that TT or CT significantly increased the risk of MCI than CC for *ABCA1* rs4149268. And, analysis results of 4948 healthy eastern Asians from the ALFA Allele Frequency project showed that the frequency of C allele was higher than that of T (C = 0.681 > T = 0.319), which was consistent with our results (C = 0.672 > T = 0.328). Additionally, rs4149268 was found to correlate with lipid levels in recent genome-wide studies, which might be related to *ABCA1*-mediated reduced levels of extracellular cholesterol and cerebrospinal fluid. It might indirectly suggest that TT or CT increases the risk of MCI.

An American study of genome-wide scan results of AD showed no relationship between *ABCA1* rs2482424 and AD. Similarly, our results did not find a relationship with MCI.[11] Previously reported studies demonstrated that rs2230808 was associated with susceptibility to AD.[12] However, in our study, no association with MCI was found. Geographic differences in the population of these subjects, differences in clinical characteristics, and differences in the detection rates of different genes in AD and MCI might partially explain these inconsistent results. Currently, it is known that genes related to AD include β-amyloid precursor protein (*APP*), presenilin-1, presenilin-2, apolipoprotein Ee4 and Sortilin receptor 1 genes. However, the detection rate of *APP*, presenilin-1, and presenilin-2 mutations in MCI was much lower than that in AD,[13] which also confirms our hypothesis that differences in the detection rates of different genes in AD and MCI might lead to inconsistent results.

Our analysis of risk factors showed that age and sex were the risk factors for the occurrence of MCI, which was consistent with previous research results.[14] The risk of MCI increases with age,[15] and women are at higher risk than men.[14] The regression analysis of education was inconsistent with the previous analysis showing that education level was a protective factor for MCI, and the higher the education level, the lower the risk of MCI.[1,9] The discrepancies might be caused by regional education levels. In this study, the general education level of the population was low, representing a pyramid phenomenon of education level. The higher the education level, the fewer the number of people. Furthermore, higher education level was found to be a protective factor for amnestic MCI and not all MCI subtypes.[16] Therefore, the relationship between education level and MCI should be interpreted with caution.

There were some limitations in this study. First, this study only mentioned the association of *ABCA1* gene polymorphisms with MCI. There were still many unmeasured genetic factors and environmental factors that were not considered. We could not estimate all the potential risk factors for MCI completely. Second, a large number of samples from multiple regions are needed in the future to investigate the relationship between the two and confirm our findings.

5. Conclusion

In conclusion, a genetic association of *ABCA1* with MCI was shown. Our results suggested that rs4149268 of gene *ABCA1* was significantly correlated with MCI in a Chinese population, but the underlying mechanism remains puzzling. These results still have practical implications for the prevention of MCI. As the pre-onset stage of AD, early intervention in MCI is crucial for controlling this neurodegenerative disease in the future. Obtaining SNP information from the peripheral blood of MCI patients is noninvasive and cost effective for predicting the transformation of MCI to AD.

Ethics approval and consent to participate

This study was approved by the Institutional Review Committee of Ningxia Medical University (grant No. 2015-151; grant No. 2018-115). All subjects gave their informed consent prior to their inclusion in the present study. All methods and procedures were carried out in accordance with relevant guidelines and regulations.

Disclosure of conflicts of interest

The authors declared no conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Authors' contribution

Yu Liu contributed to the data analysis, literature search and

writing – the original draft. Jia-Wei Duan and Zhiqin Hai contributed to literature search and data analysis. Zhizhong Wang and Shulan He contributed to conceptualization, data collection, writing – Review &editing and supervision.

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