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Association between the rs189037 single nucleotide polymorphism in the *ATM* gene promoter and cognitive impairment

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ABSTRACT. The aim of this study was to explore the existence of a relationship between the rs189037 single nucleotide polymorphism (SNP) of the ataxia telangiectasia mutated (*ATM*) gene and cognitive impairment in the elderly (aged 60 years and above). In a cohort, 505 residents of Suinung City were consecutively recruited and their cognitive function was measured using a 30-point Mini-Mental State Examination (MMSE). The subjects were divided into cognitive impairment group and control group on the basis of MMSE scores. Presence of the rs189037 SNP variant was examined using polymerase chain reaction-restriction fragment length polymorphism. The prevalence rates of cognitive impairment were 32.7% in the whole

sample. The genotype frequencies of the rs189037 polymorphism were 33.5% (CC), 50.7% (CT), and 15.8% (TT); the C and T allele frequencies were 58.8 and 41.2%, respectively. No significant differences in the frequency distributions of the CC, CT and TT genotypes were observed between cognitively impaired and control groups. We found that the rs189037 SNP was not directly correlated with cognitive impairment among the elderly Chinese Han population.

Key words: Ataxia telangiectasia mutated gene; rs189037; Cognitive impairment; Single nucleotide polymorphism

INTRODUCTION

The number of older adults with cognitive impairment is expected to rise dramatically due to the aging population (Brookmeyer and Gray, 2000). Cognitive impairment causes a significant financial burden to society; the total worldwide societal cost of dementia was estimated to be US$315 billion for 29.3 million demented individuals in 2005, and the cost had increased to US$422 billion in 2009, based on a dementia population of 34.4 million persons, including US$142 billion for informal care (34%) (Wimo et al., 2010). Furthermore, dementia, a severe cognitive impairment, affects approximately 7% of the general population older than 65 years, and 30% of people older than 80 years (O'Brien et al., 2003). Accumulated evidence from epidemiological research strongly supports roles for lifestyle and cardiovascular risk factors in the pathogenesis and development of cognitive impairment (Qiu et al., 2010). These factors include increasing age, low education, smoking, living alone, poor living conditions (Cervilla et al., 2000; Frisoni et al., 2000; Verghese et al., 2003; Tervo et al., 2004), and vascular-related diseases such as hyperlipidemia, hypertension, heart disease, diabetes mellitus, and cerebrovascular disease or stroke (Elias et al., 1997; Kilander et al., 1998; Kivipelto et al., 2001; Ballard et al., 2003).

To date, four genes associated with Alzheimer's disease have been identified: amyloid precursor protein (*APP*) (Goate et al., 1991), *apoE* (Strittmatter et al., 1993), *PS1* (Sherrington et al., 1995), and *PS2* (Levy-Lahad et al., 1995); these are located on chromosomes 21, 19, 14, and 1, respectively. Ataxia telangiectasia mutated (*ATM*) is the gene mutated in the genetic disorder ataxia telangiectasia, symptoms of which include progressive neurological degeneration, immunodeficiency, high cancer incidence, extreme sensitivity to ionizing radiation, ischemic heart disease, and premature aging (Li and Swift, 2000). The *ATM* gene plays roles in antioxidant elevation, telomere protection, and regulation of insulin-like growth factor receptor 1 expression, and its mutation might result in elevated plasma cholesterol and triglyceride levels, insulin resistance, and impaired glucose tolerance in patients with ataxia telangiectasia (Badalian and Kalininal, 1976; Ristow, 2004). In addition, the antioxidant capability is weakened and the level of reactive oxygen species and oxidative stress are increased in knockout mice lacking the *ATM* gene (Wu et al., 2005). These parameters are known as major contributors to the pathogenesis of senescence and to the development of atherosclerosis risk factors. In turn, atherosclerosis risk factors such as smoking, hypercholesterolemia, diabetes mellitus, and hypertension are also associated with cognitive impairment (Herbig et al., 2006; Mercer et al., 2010).

It is well known that promoters play a major role in the control of gene expression, and the *ATM* promoter region is the primary regulator of *ATM* gene transcription and expression. In our previous studies, we identified a single nucleotide polymorphism (SNP), rs189037, that is located in the promoter region of *ATM* and is associated with human longevity and coronary stenosis (Chen et al., 2010; Li et al., 2011). Therefore, based on the evidence mentioned above, we carried out a preliminary experiment to examine whether there was an association between the SNP rs189037 in the *ATM* gene promoter and cognitive impairment.

MATERIAL AND METHODS

Setting and subjects

We recruited 554 participants consecutively from eight villages in the Yongxing county of Suining City, Sichuan, China, between October and December 2011. The inclusion criteria were: 1) 60 years of age and above; 2) prior residence in the trial areas for at least 6 months; and 3) available to and capable of giving informed consent. We excluded those subjects who had mental diseases, trauma, or mental retardation, did not complete the 30-item Mini-Mental State Examination (MMSE), or had no blood specimen for genotype detection and laboratory testing. The trial protocol was approved by the Institutional Review Boards at the West China Hospital and was conducted according to the Helsinki Declaration II. Full informed consent (by signature or thumbprint) was obtained from all trial participants. Trained personnel visited all study participants at local neighborhood committees for data collection, e.g., anthropometric measurements and the collection of a blood specimen. Sociodemographic characteristics and lifestyle habits were collected by using a general questionnaire.

Assessment of cognitive impairment

The MMSE is a major method to screen cognitive function, and covers components of orientation, attention, calculation, language, and recall (Crum et al., 1993). A total maximal score on the MMSE is 30 points and a score of less than 18 points is generally considered to indicate cognitive impairment (Katzman et al., 1988). To minimize error and assure reliability, we 1) reviewed the MMSE scoring systems outlined in a short booklet and a video; 2) observed a geriatrician performing the MMSE assessment (on residents not part of our study); and 3) obtained supervision when performing the MMSE. The MMSE test was thereafter applied to the consented study subjects. In our study, the subjects were divided into cognitive impairment group ($\leq$17 points) and control group (>17 points) on the basis of MMSE scores.

Genotype detection

Genomic DNA was isolated from whole blood drawn from the antecubital vein, using Blood Genomic extraction kits (DP319, TianGen, Beijing, China) according to standard procedures. Genotyping of the SNP rs189037 was carried out by a polymerase chain reaction (PCR)-restriction fragment length polymorphism detection method. The forward and

reverse primers were 5'-GCTGCTTGGCGTTGCTT-3' and 5'-CATGCGATTGGCGGTCTG G-3', respectively (Chen et al., 2010). The PCR cycling conditions used were as follows: an initial denaturation step at 94°C for 3 min, followed by 30 cycles of denaturation at 94°C for 30 s, annealing for 30 s at 55°C, and elongation for 30 s at 72°C, with a final extension of 5 min at 72°C. The amplified PCR products were digested with *Sac*II (TaKaRa, Dalian, China) at 37°C overnight and resolved on a 10% polyacrylamide gel and stained with silver nitrate.

Assessment of covariates

The baseline examination included information on gender, age (years), MMSE score, educational level (illiteracy, primary school, secondary school and above), fasting plasma glucose (FPG, mM), systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), triglycerides (mM), total cholesterol (mM), low-density lipoprotein cholesterol (mM), high-density lipoprotein cholesterol (mM), serum uric acid (UA, mM), body mass index (BMI, kg/m^2), alcoholism, and histories of smoking, stroke, diabetes mellitus, hypertension, and coronary heart disease. Right arm blood pressure was measured in the sitting or recumbent positions twice to the nearest 2 mmHg using a standard mercury sphygmomanometer by trained physicians. SBP and DBP were calculated by the mean value of the two measurements. BMI was calculated as body weight (in kg) divided by the square of height (in meters). FPG, lipid/lipoprotein levels, and UA were determined by technicians in the laboratory of Suining City People's Hospital. The other covariates were collected by using a general questionnaire.

Statistical analysis

All of the statistical analyses for this study were performed with the SPSS for Windows software package, version 19.5 (SPSS Inc., Chicago, IL, USA). the Pearson chi-square or the Fisher exact test (where an expected cell count was <5) was conducted to assess whether the genotypic frequencies conformed to Hardy-Weinberg equilibrium, and to compare the genotypic and allelic frequencies between cognitive impairment and control groups (MMSE cut-off point = 18). Multiple-logistic regression models were used to adjust for factors associated with cognitive function. A P value <0.05 was considered to be the criterion of statistical significance and all of the P values were two-sided.

RESULTS

Baseline characteristics of cognitive impairment

Of 554 participants, 49 were excluded for no blood specimen for genotyping and laboratory testing (41), incomplete MMSE test (5), or for mental diseases or retardation (3). As a result, a total of 505 participants were included in the present study (225 men and 280 women). The mean age was 70.80 ± 6.74 years (range, 60-90 years). The total prevalence rate of cognitive impairment (MMSE scores <18) was 32.7% in the whole sample. The prevalence rate among men was 15.6%, while it was 46.4% among women; the difference was statistically significant (P < 0.001). The basic characteristics of the main demographic and clinical characteristics with cognitive impairment are presented in Table 1.

Table 1. Baseline characteristics according to cognitive impairment (N = 505, means ± standard deviation).

Characteristics	Cognitive		Wilcoxon or χ^2	P value
	Impairment (N = 165)	Normal (N = 340)		
Age (years)	73.84 ± 7.12	69.32 ± 6.03	75366.0	0.000
Gender (male/female, N)	35/130	190/150	54.05	0.000
Score on MMSE	13.04 ± 3.32	23.97 ± 3.60	13695.0	0.000
BMI (kg/m^2)	22.32 ± 3.26	22.48 ± 3.18	39473.5	0.464
SBP (mmHg)	153.28 ± 25.13	150.74 ± 23.46	84135.0	0.340
DBP (mmHg)	91.94 ± 15.45	91.95 ± 15.21	85143.5	0.767
FPG (mM)	6.21 ± 2.85	5.81 ± 2.08	83406.0	0.089
TG (mM)	1.50 ± 1.22	1.37 ± 0.82	85263.5	0.623
TC (mM)	5.00 ± 0.98	5.00 ± 0.90	41229.0	0.737
HDL-C (mM)	1.83 ± 0.32	1.84 ± 0.33	85556.5	0.763
LDL-C (mM)	2.50 ± 0.74	2.52 ± 0.73	40806.5	0.542
UA (mM)	282.68 ± 71.89	285.36 ± 68.39	41063.5	0.658
Educational levels (N)				
Illiteracy	142/165	148/340		
Primary school	21/165	157/340	82.76	0.000
Secondary school and above	2/165	35/340		
Alcoholic habits (%)	45 (27.3)	130 (38.2)	5.90	0.015
Smoking habits (%)	15 (9.1)	106 (31.2)	29.74	0.000
DM (%)	12 (7.3)	10 (2.9)	5.00	0.025
History of stroke (%)	2 (1.2)	5 (1.5)	0.05	0.816
Hypertension (%)	52 (31.5)	80 (23.5)	3.67	0.055
CHD (%)	10 (6.1)	18 (5.3)	0.12	0.724
Genotype				
CC (%)	49 (29.7)	120 (35.3)		
CT (%)	89 (53.9)	167 (49.1)	1.59	0.451
TT (%)	27 (16.4)	53 (15.6)		

Baseline characteristics were compared between those with and without prevalent cognitive impairment. Statistical analyses were performed using the Pearson chi-square or the Fisher exact test (where an expected cell count was <5) for categorical variables and the unpaired Student *t*-test for continuous variables. In the testing, a P value <0.05 was considered to be statistically significant. MMSE = Mini-Mental State Examination; BMI = body mass index; FPG = fasting plasma glucose; HDL-C = high-density lipoprotein cholesterol; LDL-C: = low-density lipoprotein cholesterol; SBP = systolic blood pressure; DBP = diastolic blood pressure; TG = triglycerides; TC = total cholesterol; UA = uric acid; DM = diabetes mellitus; CHD = coronary heart disease.

SNP rs189037 genotyping

The PCR amplification products of rs189037 are shown in Figure 1A; the products were digested by *Sac*II, resolved by 10% polyacrylamide gel electrophoresis, and stained with silver nitrate. Three fragments of 46, 116, and 125 bp were generated when the CC genotype was present, while two fragments of 125 and 162 bp were generated when the TT genotype was present, and four fragments of 46, 116, 125, and 162 bp were generated when the heterozygous CT genotype was present (Figure 1B).

Association between the SNP rs189037 and cognitive function

The genotypic frequencies of the SNP rs189037 in the promoter region of the *ATM* gene were 33.5% CC, 50.7% CT, and 15.8% TT in the whole sample. C and T allele frequencies were 58.8 and 41.2%, respectively. We observed that the genotypic and allelic frequencies of the SNP rs189037 had no significant difference between the cognitively impaired and control groups (Table 2). Demographic and clinical characteristics grouped by SNP rs189037 are presented in Table 3.

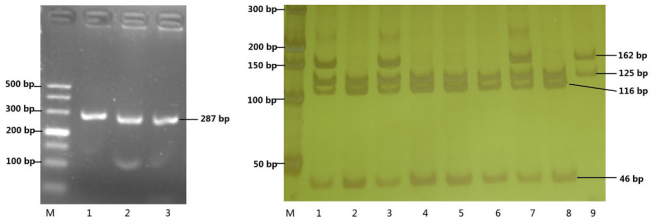

Figure 1. PCR amplification products (**A**) and polymerase chain reaction-restriction fragment length polymorphism genotyping results (**B**) of the rs189037 polymorphism. *Lane M*: marker; *lanes 1*, *3*, and *7* in (B) represent the CT genotype; *lanes 2*, *4*, *5*, *6*, and *8* represent the CC genotype; while *lane 9* represents the TT genotype.

Table 2. Association between SNP rs189037 and cognitive function [case (%)].

		Cognitive		χ^2	P
		Impairment [N = 165 (%)]	Normal [N = 340 (%)]		
Genotypes [N (%)]	CC	49 (29.7)	120 (35.3)	1.592	0.451
	CT	89 (53.9)	167 (49.1)		
	TT	27 (16.4)	53 (15.6)		
Dominant model	CC	49 (29.7)	120 (35.3)	1.563	0.211
	CT+TT	116 (70.3)	220 (64.7)		
Recessive model	TT	27 (16.4)	53 (15.6)	0.050	0.823
	CC+CT	138 (83.6)	287 (84.4)		
Alleles	C	187 (56.7)	407 (59.9)	0.931	0.335
	T	143 (43.3)	273 (40.1)		

Dominant model: CC *vs* CT+TT; recessive model: TT *vs* CC+CT. SNP = single nucleotide polymorphism.

Table 3. Baseline characteristics according to genotype (N = 505, means ± standard deviation).

Characteristics	CC	CT	TT	Wilcoxon or χ^2	P value
Age (years)	70.76 ± 6.82	70.82 ± 6.78	70.81 ± 6.55	0.047	0.977
Gender (male/female, N)	74/95	109/147	42/38	2.490	0.288
Score on MMSE	20.72 ± 6.32	20.18 ± 6.01	20.41 ± 6.67	1.083	0.582
BMI (kg/m^2)	22.52 ± 3.14	22.31 ± 3.23	22.64 ± 3.27	0.510	0.775
SBP (mmHg)	154.43 ± 26.48	149.59 ± 22.05	151.84 ± 24.33	2.651	0.266
DBP (mmHg)	92.86 ± 16.92	91.00 ± 13.98	93.01 ± 15.56	2.185	0.335
FPG (mM)	5.71 ± 1.8	6.05 ± 2.67	6.09 ± 2.33	0.118	0.943
TG (mM)	1.38 ± 0.85	1.49 ± 1.09	1.25 ± 0.74	3.582	0.167
TC (mM)	4.92 ± 0.86	1.49 ± 1.09	1.25 ± 0.74	2.424	0.298
HDL-C (mM)	1.82 ± 0.29	1.86 ± 0.35	1.82 ± 0.30	0.553	0.758
LDL-C (mM)	2.44 ± 0.68	2.53 ± 0.78	2.61 ± 0.68	2.846	0.241
UA (mM)	278.39 ± 64.72	285.41 ± 69.54	294.39 ± 78.17	2.524	0.283
Alcoholic habits (%)	57 (33.7)	88 (34.4)	30 (37.5)	0.359	0.836
Smoking habits (%)	31 (18.3)	67 (26.2)	23 (28.8)	4.621	0.099
Educational levels (N)					
Illiteracy	100/169	146/256	44/80		
Primary school	53/169	97/256	28/80	5.016	0.286
Secondary school and above	16/169	13/256	8/80		
DM (%)	5 (3.0)	13 (5.1)	4 (5.0)	1.192	0.551
History of stroke (%)	1 (0.6)	3 (1.2)	3 (3.8)	4.137	0.126
Hypertension (%)	53 (31.4)	59 (23.0)	20 (25.0)	3.709	0.157
CHD (%)	9 (5.3)	17 (6.6)	2 (2.5)	2.019	0.364
Cognitive Impairment (%)	49 (29.0)	89 (34.8)	27 (33.7)	1.592	0.451

Baseline characteristics were compared between different genotypes using the χ^2 or the Fisher exact test (where an expected cell count was <5) for categorical variables and the unpaired Student *t*-test for continuous variables. In the testing, a P value <0.05 was considered to be statistically significant. MMSE = Mini-Mental State Examination; BMI = body mass index; FPG = fasting plasma glucose; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure; DBP = diastolic blood pressure; TG = triglycerides; TC = total cholesterol; UA = uric acid; DM = diabetes mellitus; CHD = coronary heart disease.

Multiple-logistic regression analyses were used to adjust for factors associated with cognitive function. The results showed that age, gender, and education levels were factors that impacted cognitive dysfunction ($P < 0.05$). However, genotypes of the polymorphism rs189037 were not significant factors of cognitive impairment ($P > 0.05$; Table 4).

Table 4. Risk factors for cognitive function in multiple logistic regression analysis.

Characteristics	β	SE	P	OR	95%CI
Age	0.119	0.019	0.000	1.127	1.085-1.170
Gender	1.146	0.276	0.000	3.144	1.831-5.399
Educational level	-1.254	0.270	0.000	0.285	0.168-0.484
Genotype			0.269		
CT*	0.324	0.254	0.201	1.383	0.841-2.275
TT*	0.510	0.347	0.142	1.665	0.844-3.287
Constant	-7.062	1.817	0.000	0.001	

*The CC genotype was taken as the control group. SE = standard error; OR = odds ratio; CI = confidence interval. Dummy variables were assigned for gender: male = 0, female = 1. Dummy variables were assigned for educational levels: illiteracy = 0, primary school = 1, secondary school and above = 2.

DISCUSSION

Cognitive impairment is a multi-factorial condition, which is influenced both by genetic and demographic factors, and, importantly, by modifiable environmental factors. Recent long-term population-based studies have suggested that vascular risk factors and vascular-related diseases were risk factors for vascular dementia, and also have an important role in the pathogenesis of cognitive impairment (Tervo et al., 2004). The present study showed that elderly people living in rural areas have a high prevalence of cognitive impairment (32.7%). This might have been observed because we included mild cognitive impairment participants. The prevalence of cognitive impairment in women (46.4%) was three times as high as that in men (15.6%), which is consistent with previous studies (Andersen et al., 1999). There were no significant differences of the frequency distributions of the CC, CT, and TT genotypes of the SNP rs189037 between the cognitively impaired and control groups. Furthermore, multiple-logistic regression analysis showed that genotypes of the SNP rs189037 had no effect on cognitive impairment. Accordingly, the present study indicated that there is no relationship between the SNP rs189037 in the promoter region of the *ATM* gene and cognitive impairment.

However, numerous studies have found that the *ATM* gene was related to risk factors of cognitive dysfunction (Chen et al., 2010; Li et al., 2011). In previous studies, we observed a significant association between the CT genotype of the polymorphism rs189037 and longevity, and individuals with the CT heterozygote genotype had the potential to live longer (Chen et al., 2010). In subsequent experiments, we found that the TT genotype was associated with less severe coronary stenosis, indicating that the TT genotype was a protective factor for coronary heart disease (Li et al., 2011). In addition, *ATM* heterozygosity in *ApoE* null mice promotes atherosclerosis and multiple features of metabolic syndrome, including hypertension, hypercholesterolemia, hepatic steatosis, glucose intolerance, and alterations in lipid metabolism (Mercer et al., 2012). Coronary and aortic atherosclerosis and its associated diseases have also been observed in *ATM*-deficient mice (Herbig et al., 2006), suggesting that a decreased expression level of the *ATM* gene is a risk factor for vascular diseases.

There are some probable explanations for the negative results of the present study: 1) the development of cognitive dysfunction is the result of both genetic and environmental

factors, and the effect of the SNP rs189037 might be not robust enough to be detected; 2) all of the participants in this study lived in rural areas and the majority took part in physical activities almost every day, which is a protective factor for cognitive impairment (Laurin et al., 2001), which may modify the clinical expression of cognitive impairment; 3) the sample size was limited. The number of TT genotype carriers was only 80, which might weaken statistical efficacy. We noticed that the CT genotype in the cognitive impaired group was more frequent than in the normal group (53.9 *vs* 49.1%), although this did not reach a statistical difference. If the sample size was expanded, a statistically significant difference might be observed. In addition, only the Han population was included in our study; thus, this does not imply that the negative result is applicable to other races. For example, the incidence of a polymorphism in the *PS1* gene, which is related to Alzheimer's disease, was different in different races (Wragg et al., 1996).

In conclusion, in the present study we did not find an association between the SNP rs189037 and cognitive impairment in a Chinese Han elderly population from rural areas. Several limitations exist in this study, including the limited sample size and other potential confounders, such as nutrition and socio-economic status. Multi-ethnic and different regional studies with a larger sample size are needed in the future to confirm and expand this result.

Conflicts of interest

The authors declare no conflict of interest.

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