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Original Research

The Genetic Association of *MMP-2* Gene Polymorphisms with the Susceptibility to Alzheimer's Disease

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Abstract

Background: A hospital-based case-control study was carried out to elucidate the association of Matrix metalloproteinase-2 (*MMP-2*) gene candidate polymorphisms with the susceptibility to Alzheimer's disease (AD) in the Chinese Han population. **Methods**: A total of 200 AD cases and an equal number of healthy controls were recruited to undergo genotyping of specific loci within the *MMP-2* gene loci (*rs243866*, *rs2285053*, *rs243865*). Logistic regression analysis was applied to examine the association of the genotypes and alleles of *MMP-2* gene polymorphisms with AD after adjusting clinical confounding factors. **Results**: Within AD group, a high proportion of *rs243866* genotype carriers were found, and the difference remained significant despite adjusting for other clinical indicators. Among individuals with the *rs243866 AA* genotype and *rs243865 TT* genotype, the onset age of AD occurred at a younger age. Early-onset AD risk in *rs243866 AA* genotype carriers was 6.528 times higher than those in *GG* genotype carriers, and individuals with *rs243865 TT* genotype faced a 4.048-fold increased risk compared to those with *CC* genotype. **Conclusions**: *MMP-2* gene *rs243866* and *rs243865* polymorphisms were closely associated with the onset age of AD. The presence of *rs243866 AA* genotype emerged as a crucial predictor of AD risk.

Keywords: *MMP-2* gene; single nucleotide polymorphism (SNP); Alzheimer's disease; genetic predisposition

1. Introduction

Alzheimer's disease (AD), also known as senile dementia, is a common neurodegenerative disease [1]. Its primary clinical manifestations include neuropsychiatric symptoms such as progressive memory dysfunction, cognitive impairment, personality change, and language disorder, seriously affecting social, occupational, and life functions [2]. AD is more common in people over 60 years old [3]. The symptoms of AD are relatively insidious and easy to be ignored [4]. Genetic factors are widely recognized as risk factors for AD [5]. Epidemiological studies have underscored a substantial AD risk, 3.5 times higher than that of the general population, among first-degree relatives of AD patients relative to the general population [6]. Most AD cases occur sporadically and coincide with characteristic neuropathological lesions of amyloid plaques accumulation [7]. Given the continued lack of clarity surrounding the etiology and pathogenesis of AD, there is no specific method to reverse and prevent the progression of the disease. Active monitoring and early intervention of susceptible AD population are very important to delay the decline of quality of life [8].

Matrix metalloproteinases (MMP) hold significant importance as proteases that regulate growth and development [9]. Within the nervous system, MMPs are expressed in the nervous system and play a role in regulating myelin turnover, axon generation and angiogenesis [10]. As previously reported by Helbecque *et al.* [11], 6A/6A homozygous of the *MMP-3* polymorphism carriers are at increased risk of dementia. However, ambiguous results are reported in the Japanese, in which no impact of this polymorphism on the risk of AD is determined [12], that might be attributed to racial diversity. Among the MMP family, MMP-2 is one of the most studied and most frequently expressed MMPs in the nervous system [13]. In AD patients, enhanced expression of MMP-2 has been detected in astrocytes surrounding Aβ plaques and brain endothelial cells [14]. Besides, the accumulation of MMP-2 has been tested near the neurofibrillary tangles in the early stage of AD, which is related to the elimination of toxic truncated tau species in AD brains [15]. In AD mice models, MMP-2 is at high expression during the initial stage of the disease, and constitutively expressed with the disease progression [16]. In AD patients, plasma activity of MMP-2 shows positive correlation with mini-mental state examination (MMSE) score, reflecting its diagnostic potential for the earlier detection of AD [17,18].

The *MMP-2* gene is located on chromosome 16q13-21 [19], and it is known that single nucleotide polymorphisms (SNPs) can influence the transcriptional activity and expression of MMP-2 [20,21]. MMP-2 –1575 *G>A* (*rs243866*), MMP-2 –735 *C>T* (*rs2285053*) and MMP-2 –1306 *C>T* (*rs243865*) are common polymorphic loci in the promoter region of *MMP-2* gene [22]. These SNPs could

lead to the dysregulation of MMP-2 [20]. Existing studies have presented the genetic association of *MMP-2* gene SNPs with various human diseases [23]. However, limited study has been conducted to assess the *MMP-2* gene polymorphisms associated with AD so far. Therefore, a hospital-based case-control study was carried out to clarify the relationship of *MMP-2* gene candidate SNPs with AD susceptibility in the Chinese Han population.

2. Materials and Methods

2.1 Study Population

A total of 200 cases subjects who were diagnosed as AD were recruited for this study. An additional 200 AD-free subjects that were matched with case group by age and gender were chosen as the control group. All study subjects belonged to the Chinese Han population and were identified from Science and Technology Innovation Park of the Fourth Affiliated Hospital of Harbin Medical University. Each subject signed a written informed consent, and the study was performed under the approval of the Ethnic Committee of Science and Technology Innovation Park of the Fourth Affiliated Hospital of Harbin Medical University (approval number: 2020-068).

All AD patients were initially diagnosed according to Folstein's Mini Mental State Examination scale (MMSE; scores $\leq$24). And the final diagnosis of AD was made after a detailed neurological examination, including assessment of activities of daily living and neuro-psychological testing according to Clinical Dementia Rating Scale and the Blessed Dementia rating Scale [24]. The exclusion criteria were as follows: (1) presence of severe depression, bipolar disorder, schizophrenia, drug abuse or mental retardation; (2) a history of cerebrovascular disease, hydrocephalus or intracranial tumors within the past 12 months; (3) abnormal thyroid function, severe anemia or abnormal serum vitamin B12 level; (4) cognitive impairment resulting from head trauma or various poisonings; (5) patients with previous history of encephalitis or meningitis; (6) the presence of other neurological diseases that may lead to cognitive impairment, such as epilepsy, Parkinson's disease, Huntington's disease, etc.; (7) patients with a history of malignant tumors within the past 5 years; (8) poorly controlled hypertension and diabetes mellitus, obvious heart, liver, lung and kidney diseases; (9) severe auditory or visual dysfunction, unable to cooperate with various examiners.

The inclusion criteria of the control group were as follows: (1) absence of cognitive impairment, as determined through neuropsychological examination; (2) matching of sex and ag with the patient groups; (3) provision of the informed consent form.

2.2 Collection of Clinical Data

All subjects were labeled in sequence based on the inclusion time, and the patient's age, gender, education level, body mass index (BMI), education, smoking, previous disease history, family history, etc., were recorded using a unified questionnaire. All patients and controls underwent MMSE before enrollment, and were further evaluated according to the examination results and previous neuropsychological data.

2.3 Extraction of DNA

5 mL of peripheral blood was taken intravenously and placed in an anticoagulant tube containing Ethylene Diamine Tetraacetic Acid (EDTA) anticoagulant solution and stored in a refrigerator at –80 °C. The blood sample numbers were consistent with the clinical data labels. Peripheral blood DNA was extracted by blood genomic DNA extraction kit (cat. no. DP318, Tiangen Biotech (Beijing) Co., Ltd., Beijing, China), the numbers were the same as clinical data, and stored at –20 °C for later use. The remaining blood was numbered and stored in a refrigerator at –80 °C.

2.4 SNP Genotyping

Combined application of polymerase chain reaction (PCR) and sanger sequencing were applied for the genotyping of *MMP-2* –1575 *G>A* (*rs243866*), –735 *C>T* (*rs2285053*) and –1306 *C>T* (*rs243865*). First, the Primer Premier 5.0 (PREMIER Biosoft International, Palo Alto, CA, USA). was used for the primer design, and the target gene fragment was amplified by PCR. Subsequent sequencing was performed on an ABI Prism 3100 genetic analyzer (Shanghai Bioengineering Service Co., LTD., Shanghai, China). The location of the variants in the genome and the sequencing results were shown in **Supplementary Figs. 1,2**.

2.5 Statistical Analysis

Prior to data analysis, Hardy-Weinberg equilibrium (HWE) tests for the *MMP-2* gene polymorphism loci in the control group were performed. The statistical analysis was accomplished in SPSS 21.0 software (IBM SPSS, New York, NY, USA). The independent sample *t*-test or one-way analysis of variance (ANOVA) was used to compare continuous variables between two or multiple groups, and the mean value and standard deviation (SD) were used for the recording of the data. Chi-square test was applied to compare categorical variables between groups. Logistic regression was used to analyze the association of the genotypes and alleles of *MMP-2* gene polymorphisms with AD. And the *p* value less than 0.05 was set as the cut-off value of statistical significance.

3. Results

3.1 Demographic Data

The detailed demographic data of the two study groups are presented in Table 1. Both the control and the AD groups included 200 individuals, with an average age of 67.25 $\pm$ 6.95 and 67.16 $\pm$ 7.15 years, respectively. In terms of age, gender, BMI and smoking, no significant difference

was detected ($p > 0.05$). Conversely, in the medical history, more stroke cases were found in the AD group than in the control group ($p < 0.05$). In addition, cases in the AD group appeared to have shorter duration of education time than the controls ($p < 0.05$).

Table 1. Baseline characteristics of the study population.

Items	Control group	AD group	*p* value
Age, year	67.25 ± 6.95	67.16 ± 7.15	0.898
Gender, male/female	66/134	71/129	0.598
BMI, kg/m^2	26.13 ± 4.14	25.35 ± 4.29	0.065
Education, years	12.03 ± 2.06	10.26 ± 2.99	<0.001
Smoker, n (%)	45 (22.50)	48 (24.00)	0.723
Hypertension, n (%)	12 (6.00)	16 (8.00)	0.433
Diabetes, n (%)	11 (5.50)	15 (7.50)	0.417
History of stroke, n (%)	4 (2.00)	12 (6.00)	0.041
Onset age, year	-	66.84 ± 7.18	-
MMSE score	28.43 ± 0.97	19.06 ± 2.78	<0.001

Note: AD, Alzheimer's disease; BMI, Body mass index; MMSE, Mini Mental State Examination scale.

3.2 Genetic Association of MMP-2 Gene Polymorphisms with AD Susceptibility

As displayed in Table 2, the genotype distributions of all three loci of the *MMP-2* gene were in agreement with HWE in the control group. For *MMP-2* gene *rs243866*, a significant difference in the frequency distribution of the *AA* genotype was evident when comparing the case and control groups ($p < 0.05$), a high proportion of *AA* genotype carriers were found in the AD group. And the difference was still significant adjusting for other clinical indicators. Consistently, more cases in the AD group carried *A* allele ($p < 0.05$), but the difference did not reach a significant level after adjusting for other confounding factors ($p > 0.05$). However, we did not find a significant difference in genotype and allele frequencies of both *MMP-2* gene *rs2285053* and *rs243865* polymorphisms between the AD case and control groups ($p > 0.05$).

3.3 Association of MMP-2 Gene Polymorphisms with the Onset Age (Years) of AD Patients

The onset age of different genotype carriers was counted and the results are presented in Table 3. For both *MMP-2* gene *rs243866* and *rs243865* polymorphisms, there was a significant difference in the onset age among cases carrying different genotypes. More precisely, the onset age of cases carrying *rs243866 AA* genotype and *rs243865 TT* genotype was earlier ($p < 0.05$). However, there was no significant difference in the onset age of AD patients with different genotypes of *rs2285053* ($p > 0.05$). Based on these findings, it was concluded that *MMP-2* gene *rs243866* and *rs243865* polymorphisms were closely related to the onset age of AD, *rs243866 AA* genotype and *rs243865 TT* genotype carriers had a later onset age of AD.

3.4 Stratification Analysis by Age

Table 4 presents the stratification results of the relationship between *MMP-2* gene *rs243866* and *rs243865* polymorphisms and AD risk by age. The findings reveal a significant increase in the risk of early-onset AD among *rs243866 AA* genotype carriers, with the risk being 6.528 times higher than *GG* genotype carriers. Likewise, individuals with *rs243865 TT* genotype exhibited a 4.048-fold increased risk compared with *CC* genotype carriers. But the frequency distributions of *rs243866* and *rs243865* polymorphisms were not statistically different between the late-onset AD patients and controls ($p > 0.05$). The findings illustrated that *MMP-2* gene *rs243866* and *rs243865* polymorphisms were related to the susceptibility of early-onset AD.

4. Discussion

Currently, the incidence of AD exhibited a gradual upward trend [25]. The development of AD is influenced by multiple factors, including environmental and genetic factors [26]. One such genetic factor of interest is MMP-2, a brain-enriched protease, which can mediate myelin turnover, axon generation and angiogenesis [10]. Notably, increased MMP-2 has been detected in the neurofibrillary tangles during the early stages of AD, suggesting its involvement in the elimination of toxic truncated tau species [15]. In recent decades, the study potential of gene SNPs in molecular genetics research has gained significant attention [27]. In the current study, three loci including *rs2285053*, *rs243865* and *rs243864* were taken as the study objects to investigate their relationship with AD susceptibility, which were polymorphic in the Chinese Han population. The results revealed that *MMP-2* gene *rs243866* polymorphism was associated with AD susceptibility, and the *AA* genotype carriers may predispose the individuals to AD by acting as the risk factors. In addition, both *rs243866* and *rs243865* polymorphisms were closely related to the onset age of AD. Nonetheless, we did not find any relationship between *MMP-2* gene *rs2285053* SNP and AD emotivity. In addition, based on the detailed demographic information of the present study population, several established modifiable risk factors for AD were demonstrated, including less education and stroke history. Consistently, the results of a country study in the Slovak Republic have presented that low levels of education are related to an increased risk of AD and dementia [28]. Furthermore, a history of stroke is recognized as a contributing factor to the susceptibility of AD [29,30]. Thus, the clinical indicators were adjusted to more accurately present the genetic value of *MMP-2* gene polymorphic loci for AD, it was concluded that *rs243866 AA* genotype was still significantly correlated with AD risk.

MMP-2 has been recognized for its potential to degrade Tau fibrils, activated MMP-2 and phosphorylated tau has been colocalized in neurofibrillary tangles of AD brain [31]. During the early stage of AD, activated MMP-2 has

Table 2. Genotype and allele distributions of *MMP-2* gene polymorphisms in AD patients.

Locus	Genotype frequency (n, %)			*p* value	Adjusted *p* value	Allele frequency (n, %)			*p* value	Adjusted *p* value
	Genotype	Control group	AD group			Allele	Control group	AD group		
rs243866	*GG*	151 (75.50)	139 (69.50)	-						
	GA	43 (21.50)	46 (23.00)	0.535	0.147	*G*	345 (86.25)	324 (81.00)	-	-
	AA	6 (3.00)	15 (7.50)	0.038	0.049	*A*	55 (13.75)	76 (19.00)	0.045	0.316
PHWE		0.186								
rs2285053	*CC*	122 (61.00)	117 (58.50)	-						
	CT	65 (32.50)	63 (31.50)	0.961	0.432	*C*	309 (77.25)	297 (74.25)	-	-
	TT	13 (6.50)	20 (10.00)	0.210	0.289	*T*	91 (22.75)	103 (25.75)	0.322	0.620
PHWE		0.287								
rs243865	*CC*	125 (62.50)	111 (55.50)	-						
	CT	62 (31.00)	67 (33.50)	0.370	0.097	*C*	312 (78.00)	289 (72.25)	-	-
	TT	13 (6.50)	22 (11.00)	0.081	0.340	*T*	88 (22.00)	111 (27.75)	0.060	0.284
PHWE		0.171								

Note: AD, Alzheimer's disease; PHWE, *p* value of Hardy-Weinberg equitibrium.

Table 3. Association of *MMP-2* gene polymorphisms with the onset age (years) of AD patients.

Locus	Genotypes			*p* value
rs243866	*GG*	*GA*	*AA*	
Age, years	68.49 ± 6.28	64.87 ± 7.88	61.87 ± 8.61	<0.001
rs2285053	*CC*	*CT*	*TT*	
Age, years	67.40 ± 6.20	66.59 ± 8.15	67.55 ± 9.07	0.744
rs243865	*CC*	*CT*	*TT*	
Age, years	68.64 ± 6.23	66.88 ± 7.38	60.55 ± 7.24	<0.001

been detected in the entorhinal cortex [15], suggesting a potential early self-protective response in AD patients. Based on our present findings, cases carrying *rs243866 AA* genotype were more susceptible to AD after adjusting other clinical indicators. This susceptibility might be related to the reduced MMP-2 levels and the resulting accumulation of Tau [32]. However, it is worth noting that a recent study reported no significant differences in the genotype and allele distributions between AD patients and health controls from Slovakia, which was inconsistent with our current findings [33]. This inconsistency might be attributed to the differences in the race and age of the included patients. Our study focused on Han Chinese AD patients including those younger than 65 years of age, which differed from the late-onset AD patients from Slovakia in Ocenasova *et al.*'s study [33]. In addition, the significant association between *AA* genotype and AD susceptibility was still obtained in this study after taking into account clinical confounding factors and excluding confounding interference by regression analysis. Thus, the results of the present case-control study presented the genetic association of *MMP-2* gene *rs243866* polymorphism with the susceptibility of AD in the Chinese Han population. Moreover, the stratification analysis results demonstrated that *MMP-2* gene *rs243866* was related to the onset age of AD, and early-onset AD risk in *rs243866 AA* genotype carriers was 6.528 times higher than those in *GG* genotype carriers. It is known that the anti-aging gene Sirtuin 1 (*SIRT1*) is linked to AD and various chronic diseases [34]. It is identified to be a critical regulator of MMP-2 expression, stability, and activity [35,36]. MMP-2 expression and activity are regulated by SIRT1 at posttranslational level [37]. In light of the regulatory role of SIRT1 in MMP-2 expression, the participation of its expression changes in the association between *MMP-2* gene SNPs and AD susceptibility is interesting. It will be meaningful for further exploration in future studies.

Rs243865 is another common SNP in *MMP-2* gene that can influence MMP-2 activity. It causes the *C* to *T* transition at position –1306 in the promoter region of *MMP-2* gene, resulting in decreased MMP-2 activity [38]. Previous reports have indicated that individuals carrying *rs243865 TT* genotype exhibited low activity of MMP-2 relative to those carrying *CC* genotype [39]. In our current study, no significant difference was detected for *MMP-2* gene *rs243865* genotypes between the case and control groups. However, an examination of the relationship of *rs243865* polymorphism with the onset age of AD demonstrated that carriers of the *rs243865 CC* genotype have a later age of onset of AD than those with the *TT* genotype, suggesting a potential protective effect of the *rs243865 CC* against the development of AD. Nevertheless, this difference did not reach a significant level. Consistently, the subtle relationship between *MMP-2* gene *rs243865* polymorphism and AD emotivity has also been presented by Durmanova *et al.* [40] in patients from Slovakia. These findings highlight the potential role of *MMP-2* gene *rs243865* polymorphism in AD occurrence, although conclusive evidence remains elusive. Furthermore, when considering stratification analysis results by age, our results confirm a significant correlation between *MMP-2* gene polymorphism and the onset age of AD. Notably, *rs243865 TT* genotype carriers exhibited a 4.048-fold higher risk of early onset of AD than *CC* genotype carriers. Another SNP in *MMP-2* gene, *rs2285053*, is also analyzed in the present study population, but no clear

Table 4. Stratification analysis of genotype distribution of *MMP-2* gene *rs243866* and *rs243865* polymorphisms by age.

Locus	Genotype	<65 years		OR (95% CI)	*p* value	≥65 years		OR (95% CI)	*p* value
		Control group (n = 68)	AD group (n = 69)			Control group (n = 132)	AD group (n = 131)		
rs243866	*GG*	47 (69.12)	36 (52.17)	-	-	104 (78.79)	103 (78.63)	-	-
	GA	19 (27.94)	23 (33.34)	1.580 (0.749–3.335)	0.228	24 (18.18)	23 (17.56)	0.968 (0.514–1.823)	0.919
	AA	2 (2.94)	10 (14.49)	6.528 (1.346–31.661)	0.010	4 (3.03)	5 (3.81)	1.262 (0.330–4.833)	0.733
rs243865	*CC*	40 (58.82)	28 (40.58)	-	-	85 (64.39)	83 (63.36)	-	-
	CT	22 (32.35)	24 (34.78)	1.558 (0.734–3.311)	0.247	40 (30.30)	43 (32.82)	1.101 (0.650–1.863)	0.720
	TT	6 (8.82)	17 (24.64)	4.048 (1.418–11.550)	0.007	7 (5.30)	5 (3.82)	0.731 (0.223–2.397)	0.604

Note: AD, Alzheimer's disease; OR, odds ratio; 95% CI, 95% confidence interval.

correlation was identified in both the development and onset age of AD. In the current study, only polymorphic loci in the promoter region of *MMP-2* gene were included, variants in the gene coding region were not included. It is the limitation of the study, which is interesting for further study.

5. Conclusions

In conclusion, the present findings underscore a significant association between *MMP-2* gene *rs243866* polymorphism and AD onset age and risk. The presence of the r*s243866 AA* genotype emerges as a significant predictor of AD risk, offering valuable insights for the early detection of AD. furthermore, our findings emphasize a distinct correlation between *MMP-2* gene *rs243865* polymorphisms and the onset age of AD.

Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Author Contributions

LNL and LRL contributed to the study conception and design. Material preparation, data collection and analysis were performed by LNL, LRL, YTL, TYZ and WTZ. The first draft of the manuscript was written by LNL and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Each subject signed a written informed consent, and the study was performed under the approval of the Ethnic Committee of Science and Technology Innovation Park of the Fourth Affiliated Hospital of Harbin Medical University (approval number: 2020-068).

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.jin2303052.

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