Int J Clin Exp Pathol 2017;10(9):10134-10139
www.ijcep.com /ISSN:1936-2625/IJCEP0017046

Original Article

Association between *ACE* gene polymorphisms and Alzheimer's disease in Han population in Hebei Peninsula

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Received September 29, 2015; Accepted October 28, 2015; Epub September 1, 2017; Published September 15, 2017

Abstract: Purpose: This study aimed to detect the association between angiotensin I converting enzyme (*ACE*) gene polymorphisms (rs4343 and rs1800764) and Alzheimer's disease (AD) in Han population in Hebei Peninsular. Methods: We recruited 113 AD patients and 142 healthy individuals in this case-control study. Differences of genotypes, alleles and haplotypes in two groups were analyzed by chi-square test. Besides, odds ratios (ORs) and 95% confidence intervals (CIs) were used to represent the relative risk of AD. At last, the analyses of linkage disequilibrium and haplotypes were done with HaploView software. Results: In the analyses of genotypes and alleles of *ACE* polymorphisms (rs4343 and rs1800764) in AD, no obvious association was found between genotypes and alleles of rs4343 with the susceptibility of AD. In rs1800764 polymorphism, only C allele had significant association with AD susceptibility (*P*=0.035, OR=1.473, 95% CI=1.027-2.111), which suggested that rs1800764 C allele is the susceptible allele of AD. Linkage disequilibrium analysis between rs4343 and rs1800764 polymorphisms indicated there existed 3 haplotypes (A-T, A-C and G-C). A-C haplotype might associate with the susceptibility of AD (*P*=0.023, OR=2.591, 95% CI=1.111-6.043). Conclusion: Rs4343 polymorphism of *ACE* gene had no relationship with AD risk. C allele of rs1800764 could increase the susceptibility of AD. A-C haplotype of rs4343 and rs1800764 polymorphisms might increase the risk of AD, and the ORs was 2.591.

Keywords: Angiotensin I converting enzyme (*ACE*), Alzheimer's disease (AD), polymorphisms, haplotype

Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disease with a concealed onset and progressive development. It is characterized by comprehensive dementia in clinic, such as dysmnesia, aphasia, apraxia, agnosia, changes of personality and behavior and etc. With the loss of bodily functions and the neglect of family and society, the AD patients often go to dying. Due to the increase of aging population, the incidence of AD has an growing trend [1, 2]. It is one of the most costly diseases in developed country [3]. AD is a complex disease affected by genetic and environmental factors, but the main cause of the AD risk is believed to be genetic factors [4-10]. However, the pathogenesis of AD has not been clear.

Some studies have pointed out that Angiotensin I converting enzyme (*ACE*) gene is associated with AD risk [11-15]. *ACE* gene is located in chromosome 17q23.3, including 26 exons. *ACE* gene is closely associated with the production and degradation of amyloid-β which relate to the development of AD. Many single nucleotide polymorphisms (SNPs) of *ACE* gene were involved in various diseases [16-18]. The single *Alu* insertion/deletion (I/D) is the staple polymorphism of *ACE* gene [19, 20]. Recent years, two SNPs rs4343 and rs1800764 of *ACE* gene have been found associated with the occurrence of many diseases including AD [21, 22]. Nevertheless, the association between *ACE* gene and AD susceptibility is still not clear, and there is scarcely research focused on the two SNPs in Han population in China.

As we all know, the distribution of SNPs genotypes exist region difference. In order to certify the association between *ACE* gene and AD sus-

Table 1. Distributions of genetypes and alleles of rs4343 and rs1800764 in AD patient group and control group

SNP	Cases n=113 (%)	Controls n=142 (%)	χ^2	*P* value	OR (95% CI)
Genotype					
rs4343A/G					
AA	53 (46.9)	72 (50.7)	-	-	1
AG	39 (34.5)	53 (37.3)	0.000	0.999	1.000 (0.580-1.724)
GG	21 (18.6)	17 (12.0)	1.945	0.163	1.678 (0.808-3.487)
rs1800764C/T					
TT	39 (34.5)	65 (45.8)	-	-	1
CT	51 (45.1)	58 (40.8)	1.882	0.170	1.466 (0.848-2.532)
CC	23 (20.4)	19 (13.4)	3.3649	0.056	2.018 (0.976-4.169)
Allele					
rs4343A/G					
A	145 (64.2)	197 (69.4)	-	-	1
G	81 (35.8)	87 (30.6)	1.545	0.214	1.265 (0.873-1.833)
rs1800764C/T					
T	129 (57.1)	188 (66.2)	-	-	1
C	97 (42.9)	96 (33.8)	4.448	0.035	1.473 (1.027-2.111)

Table 2. Haplotype analysis of alleles of rs4343 and rs1800764

Haplotype locus1-locus2	Cases (n=226)	Controls (n=284)	χ^2	*P* value	OR (95% CI)
A-T	129 (57.1)	188 (66.2)	-	-	1
A-C	16 (7.1)	9 (3.2)	5.154	0.023	2.591 (1.111-6.043)
G-C	81 (35.8)	87 (30.6)	2.529	0.112	1.357 (0.931-1.977)

Note: locus1, rs4343; locus2, rs1800764.

ceptibility, we carried out the case-control study. In this study we analyzed the differences of genotypes and alleles of the *ACE* SNPs (rs4343 and rs1800764) in China Han population. Afterwards, haplotypes of rs4343 and rs1800764 polymorphisms were analyzed.

Materials and methods

Objects

A total of 113 diagnosed AD patients (aged 52-81 years old, 63 males and 50 females) were enrolled from the outpatients and inpatients of Grade 3 A Class hospitals in five cities in Hebei. 142 healthy subjects (aged 54-79 years old, 77 males and 65 females) who were matched with patients in age, gender and community were recruited as controls. AD patients had been diagnosed by 2 doctors using the combination of clinical data and check means. Diagnoses were in correspondence with the American diagnostic criteria of neurology, aphasis and apoplexy-senile dementia as well as the other criteria of NINCDS-ADRDA. There were no such situations such as memory deterioration, diabetes, diseases of heart and nervous system in controls. This study had been approved by the Ethics Committees of Hebei province, and all the participants had signed informed consent.

DNA extraction

5 ml peripheral venous blood from every fasting participant was anticoagulated with EDTA and preserved in -20°C fridge. The blood was undergone the operation of hypotonicity separation for white blood cells. Genome DNA was extracted with potassium iodide method, and dissolved in TE solution.

Polymerase chain reaction (PCR) amplification

PCR primers were referenced previous studies [21, 23]. Total volume of PCR system was 50 μl using general constituents. PCR procedures were as the following: 2 min initial denaturation at 94°C, following 30 cycles of 60 s denaturation at 94°C, 45 s annealing at 58°C and 50 s extension at 72°C, and 5 min final extension at 72°C. PCR products were sequenced by Sangon Biotech (Shanghai, China).

Statistical method

SPSS 18.0 software was used for statistical calculation. Differences of genotypes and alleles of rs4343 and rs1800764 between case and control groups were examined with χ^2 test, and had statistical significance when $P<0.05$. Haploview software was adopted to analyze linkage disequilibrium and haplotypes. PLINK1.07 was applied to do Hardy-Weinberg equilibrium (HWE) examination. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to represent the relative risk of AD.

Results

Analysis of the objects

Distributions of ages (t=0.12, *P*=0.870) and genders (χ^2=0.63, *P*=0.963) in two groups had no significant differences. Genotypes and alleles distributions in control group were corresponding with HWE showed that the goodness of fit was well at each locus (*P*>0.05), which suggested that the controls were in balanced states and had good representative.

Genotype and allele analyses of rs4343 and rs1800764

Distributions of genotypes and alleles of rs4343 and rs1800764 were listed in **Table 1**. We found that the genotypes and alleles of rs4343 had no significant relation with AD susceptibility. For rs1800764, only C allele could increase the AD susceptibility (*P*=0.035, OR=1.473, 95% CI=1.027-2.111). There were no association between the genotypes of rs1800764 and the susceptibility of AD.

Linkage disequilibrium and haplotype analyses between rs4343 and rs1800764

Linkage disequilibrium between rs4343 and rs1800764 polymorphisms was analyzed by Haploview software. The result indicated that the high linkage disequilibrium was existed between rs4343 and rs1800764 (D'=1, r^2= 0.633). Therefore, we analyzed the association of haplotypes with AD susceptibility (**Table 2**). Compared with A-T haplotype, the A-C haplotype maybe increase the susceptibility of AD (*P*=0.023, OR=2.591, 95% CI=1.111-6.043), and G-C haplotype had no correlation with AD. So we suggested that A-C is the susceptible haplotype for AD.

Discussion

As the common chronic neurodegenerative disease which will leads to death, AD is closely associated with age. Incidence of AD is rose obviously after 65 years old [24]. But not all of the old people are suffering the risk of AD, there exist individual difference. The difference was determined by various factors, including genetic and environmental factors. Previous studies indicated that AD is a complex disease. *ACE* gene is one of the factors which could affect the occurrence of AD [25-28].

ACE gene encodes an enzyme catalyzing the conversion of angiotensin I which is a part of renin-angiotensin system. Multiple variants of the gene could change the function of ACE enzyme, leading to the disorder of blood pressure. Thus, it will cause the occurrence of variety disease including AD [29]. Except the widely studied single *AIu* insertion/deletion (I/D) polymorphism of *ACE* gene, rs4343 and rs1800764 also become the focal points in the recent years. Rs4343 is a synonymous mutation, locate at exon 17 of *ACE* gene. Rs1800764 is located in the promoter of the *ACE* gene with a transition of C allele to T allele. Previous studies indicated that the two SNPs were correlated with the occurrence and development of many diseases [30-33]. The two polymorphisms maybe correlate with AD, but the relationship between them was unclear. So we performed this study to explore the association between *ACE* polymorphisms and AD susceptibility in Chinese Han population.

In this case-control study, we found that genotypes and alleles of rs 4343 SNP had no significant association with the susceptibility of AD. That was accordance with previous studies [22, 34]. But Ning et al. indicated that rs4343 polymorphism was significantly associated with AD susceptibility [12]. For rs1800764 polymorphism, no significant association between the genotypes of the SNP and AD susceptibility was found. C allele of rs1800764 was significantly associated with the risk of AD, and increased the AD risk about 1.473 times compared with T allele. A study executed by Corneveaux et al. suggested that C allele of rs1800764 was decreased the risk of AD [35], that result was different from our study. Another study focused on diabetes was get the similar results which found out that rs1800764 C allele could increased the diabetes risk [36]. There are many factors resulting in the above differences. On the one hand, AD is caused by different factors. On the other hand, the polymorphisms are affected by many factors from genetic background, region to race. Besides, the criteria for sample selection are different, and the samples may do not possess comprehensive representativeness. In order to certify the pathogenesis of AD we analyzed the linkage disequilibrium of rs4343 and rs1800764 polymorphisms of *ACE* gene. We found that there existed 3 haplotypes between the two SNPs. Afterwards, the correlation between the haplo-

types and the susceptibility of AD was detected. The results manifested that the distribution of A-C haplotype is significantly higher in case group than that in control group, demonstrated a positive association with AD risk. Based on the above results, we suggested that when the linkage disequilibrium was existed between the SNPs, the functions of the single SNPs may be changed.

Although we obtained a meaningful result, there also had many limitations in this study. First, the sample size is small. Second, the results were not adjusted by other factors. It was insufficient to certify the etiology of AD. As such, a well designed study which contained a multiple center and a larger sample size is needed, so as to receive an exact evidence to certify the AD etiology. Then the study could supply useful method for the prevention and treatment of AD, thereby reducing the AD morbidity.

Disclosure of conflict of interest

None.

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