Int J Clin Exp Pathol 2017;10(2):2127-2134
www.ijcep.com /ISSN:1936-2625/IJCEP0042526

Original Article

Association of IL-1α, IL-1β, IL-18 and IL-33 genetic variants with the risk of Alzheimer disease in a Chinese population

Qiansheng Zhang[1*], Zhiqiang Yao[2*], Liping Xu[3], Xiaobing Cheng[1], Tao Cui[1]

[1]Department of Neurosurgery, The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, Henan, China; [2]Department of Interventional Radiology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan, China; Department of Neurosurgery, Zhujiang Hospital, Guangzhou 510282, Guangdong, China; [3]Department of Gastroenterology, The First People's Hospital of Luoyang, Luoyang 471000, Henan, China. [*]Equal contributors.

Received October 21, 2016; Accepted October 27, 2016; Epub February 1, 2017; Published February 15, 2017

Abstract: Alzheimer's disease is chronic neurodegenerative disease. The development of Alzheimer's disease is associated with immunologic mechanism, including interleukin-1. IL-1 is an important inflammatory cytokines for inducing inflammatory response and the defense response. In the currently study, we performed a study to investigate the correlation between the role of IL-1α rs1800587, IL-1β rs1143627, IL-18 rs187238 and IL-33 rs11792633 and rs7044343 genetic polymorphisms and risk of Alzheimer's disease, and gene-environmental interaction for the risk of this disease. A total of 227 patients with Alzheimer's disease and 227 controls were included into our study between March 2013 and March 2015. Polymerase chain reaction (PCR)-restriction fragment length polymorphism method was taken to genotype the IL-1α rs1800587, IL-1β rs1143627, IL-18 rs187238 and IL-33 rs11792633 and rs7044343. Individuals carrying with the CT genotype of IL-1α rs1800587 had a higher risk of Alzheimer's disease when compared with those carrying the CC genotype (OR=1.96, 95% CI=1.15-3.38). In dominant model, the CT+TT genotype of IL-1α rs1800587 was associated with an increased risk of Alzheimer's disease in comparison with the CC genotype (OR=1.91, 95% CI=1.15-3.23). For the IL-33 rs11792633, we observed that the TT genotype was significant related to a lower risk of Alzheimer's disease when compared with the CC genotype (OR=0.33, 95% CI=0.19-0.58). Moreover, the IL-33 rs11792633 was significant associated with a reduced risk of Alzheimer's disease in dominant (OR=0.54, 95% CI=0.35-0.85) and recessive (OR=0.42, 95% CI=0.26-0.66) models. However, no significant association was reported between IL-1β rs1143627, IL-18 rs187238 and IL-33 rs7044343 and risk of Alzheimer's disease. A significant interaction was found between family history of Alzheimer's disease and IL-1α rs1800587 (Correlation coefficient=0.068, P=0.03) and IL-33 rs11792633 (Correlation coefficient=0.091, P=0.01) polymorphisms in the risk of Alzheimer's disease. In conclusion, our study suggests that the IL-1α SNP rs1800587 and IL-33 rs7044343 could influence the susceptibility to Alzheimer's disease.

Keywords: IL-1α, IL-1β, IL-18, IL-33, polymorphism, Alzheimer's disease

Introduction

Alzheimer's disease is chronic neurodegenerative disease, and the occurrence of this disease develops slowly, but it becomes deteriorate over time [1]. It is reported that about one to two percentage of population with age above 65 years develop Alzheimer's disease [2]. It is estimated that about 30% of population would develop this disease [3]. Many environmental and genetic factors contribute to the development of Alzheimer's disease. The environmental factors include age, brain trauma, long term consumption of alcohol drinking and tobacco smoking, lack of exercise, poor nutrition, lonely and depression. However, about 58% of patients with Alzheimer's disease would be attributed to heritability factors [4-6]. Moreover, not all patients would develop Alzheimer's disease even when they are exposure to similar risk factors of this disease, which indicate that the genetic factors may have a critical role in the pathogenesis of this disease. Previous molecular epidemiologic studies have indicated that many genetic factors are associated with the risk of occurrence of Alzheimer's disease,

Table 1. Forward and reverse primers for IL-1α rs1800587, IL-1β rs1143627, IL-18 rs187238 and IL-33 rs11792633 and rs7044343

SNPs	Forward	Reverse
IL-1α rs1800587	ACGTTGGATGTGGAGAAGAGGCAG	ACGTTGGATGGGCCACAAGGATTAT
IL-1β rs1143627	AGCTTGGATGATTCTCAGCCTCCTAC	ACGTTGGATGCCTCGAAGAGGTTGT
IL-18 rs187238	AGCTTGGATGACAGAGCCAACTTAC	AGCTTGGATGGCAGAGGATACGACC
IL-33 rs11792633	ACGTTGGATGAGACTGATATCCTGTT	ACGTTGGATGAGTCAGCATCACTGGC
IL-33 rs7044343	ACGTTGGATGGAGAGTTGTGAATGG	ACGTTGGATGTTGGGTGACACTATGAG

such as cytochrome P450 family 19 subfamily A member 1 gene, ATP binding cassette subfamily B member 1 gene, apolipoprotein E gene, clusterin gene, nuclear receptor-γ gene, inositol hexakisphosphate kinase 3 gene and translocase of outer mitochondrial membrane 40 gene [7-13].

Previous studies have shown that the inflammation plays an important role in the individual's immune response and neural immune response, and thus contributes to the development of nervous system degenerative disease [14]. The development of Alzheimer's disease is associated with immunologic mechanism, including interleukin-1, IL-8, IL-6 and tumor necrosis factor-α (TNF-α) and macroglobulin-α. Genotype polymorphisms of encoding these cytokines could influence the biological activity of cytokines for the pathogenesis of Alzheimer's disease through regulation of gene transcription, translation and the secretion process [1, 15]. IL-1 is an important inflammatory cytokines for inducing inflammatory response and the defense response [1]. IL-1 could promote neuron synthesis and perform amyloid precursor protein-β, facilitate the deposition of amyloid protein, active astrocytes, and promote the release of many inflammatory factors and nerve activity [16]. IL-18 and IL-33 are two new family members of IL-1. IL-18 is an important regulatory factor for innate and adaptive immune response, which is involved in the early pathogenesis of Alzheimer's disease [15, 17]. IL-33 is a nuclear transcription factor to regulate the transcription process and reduce the generation of cells [18]. The genotype polymorphisms of IL-1, IL-18 and IL-33 could influence the expression of protein, and thus they could contribute to the development of diseases. In the currently study, we performed a study to investigate the correlation between IL-1α rs1800587, IL-1β rs1143627, IL-18 rs187238 and IL-33 rs11792633 and rs7044343 genetic polymorphisms and risk of Alzheimer's disease, and gene-environmental interaction for the development of this disease.

Material and methods

Each patient signed a written inform consent for the study objectives before participating into our study. The performance of the study protocol obtained the permission from the Ethics committee of the First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology.

Subjects

A total of 227 patients with Alzheimer's disease were included into our study between March 2013 and March 2015 at The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology. The diagnosis of Alzheimer's disease was according to the NINCDS-ADRDA criteria proposed by the Department of Health and Human Services Task Force on Alzheimer's disease (McKhann et al., 1984), and diagnosed by a neurologist. The inclusion criteria for Alzheimer's disease were as follows: (1) Mini-mental Status examination (MMSE) value less than threshold value; Hamilton depression scale value <7; and Hachinski value ≤4. The exclusion criteria were those having myocardial infarction, heart failure, stroke, diabetes, atherosclerosis and auto-immune disease. The mean age of included patients was 70.50±6.43 years. There were 102 males and 125 females in patients with Alzheimer's disease.

Between March 2013 and March 2015, a total of 227 control subjects were collected from the department of gastroenterology, orthopedics, dermatology and respiratory departments. The controls were matched with patients by sex and age (±5 years). All the controls were confirmed to be without Alzheimer's disease. Controls with a history of myocardial infarction, heart failure, stroke, diabetes, atherosclerosis and

Table 2. Baseline information of patients with Alzheimer's disease and controls

Variables	Patients (%)	Controls (%)	χ^2 or t values	P
Sex				
Male	102 (44.93)	102 (44.93)	0.00	1.00
Female	125 (55.07)	125 (55.07)		
Age, year	70.50±6.43	71.20±6.60	1.14	0.13
BMI, kg/m^2				
≤24	153 (67.40)	150 (66.08)		
>24	74 (32.60)	77 (33.92)	0.09	0.77
Brain trauma				
No	14 (6.17)	6 (2.64)		
Yes	213 (93.83)	221 (97.36)	3.35	0.07
Tobacco smoking				
No	156 (68.72)	151 (66.52)		
Yes	71 (31.28)	76 (33.48)	0.25	0.62
Alcohol drinking				
No	146 (64.32)	158 (69.60)		
Yes	81 (35.68)	69 (30.40)	1.43	0.23
Family history of Alzheimer's disease				
No	197 (86.78)	223 (98.24)		
Yes	30 (13.22)	4 (1.76)	21.49	<0.001
TC, mmol/L	5.36±0.72	5.22±0.75	2.03	0.02
TG, mmol/L	1.89±1.23	1.91±1.25	0.17	0.43
LDL-c, mmol/L	2.51±0.87	2.47±0.90	0.48	0.32
HDL-c, mmol/L	1.35±0.44	1.31±0.46	0.95	0.17

auto-immune disease were excluded from our study. The mean age of included patients was 71.20±6.60 years. There were 102 males and 125 females in patients with controls, respectively.

The baseline and clinical characteristics of included subjects were shown in **Table 1**. The demographic characteristics of Alzheimer's disease patients and control subjects were collected by a structured questionnaire, including sex, age, brain trauma, body mass index (BMI), family history of Alzheimer's disease, tobacco smoking, and alcohol drinking. The clinical characteristics were obtained from medical records, including total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-c) and high density lipoprotein cholesterol (HDL-c).

DNA extraction and genotyping analysis

Each subject gave his 5 ml peripheral blood (5 mL), and the collected blood sample was stored in tubes with 5% ethylenediaminetetraacetic acid (EDTA) at -20°C. The DNA was extracted from the blood sample with the QIAamp DNA MAX Kit (Qiagen, Hilden, Germany), according to instructions. Polymerase chain reaction (PCR)-restriction fragment length polymorphism method was used to genotype the IL-1α rs1800587, IL-1β rs1143627, IL-18 rs187238 and IL-33 rs11792633 and rs7044343. The forward and reverse primers for IL-1α rs1800587, IL-1β rs1143627, IL-18 rs187238 and IL-33 rs11792633 and rs7044343 were shown in **Table 1**. The PCR amplification was done in a 25-μL reaction mixture, and this mixture contained 20 pmol each primer, 0.25 mM 4×dNTPs, 2.0 mM $MgCl_2$, 2.5 μL 10X buffer and 0.5 μL DNA as well as 1.25 U Taq DNA polymerase. The PCR amplification reaction was done as follows: initial denaturation at 95°C for 60 seconds; 30 cycles of denaturation at 96°C for 45 seconds, annealing at 66°C for 45 seconds, extension at 72°C for 60 seconds; and a final extension at 72°C for 5 minutes. The PCR products of IL-1α rs1800587, IL-1β rs1143627, IL-18 rs187238 and IL-33 rs11792633 and rs7044343 were determined by 3% agarose gel electrophoresis and EB staining.

Statistical analysis

The categorical variables were expressed as frequencies (N) and percentages (%) of total, and the continuous variables were described as mean ± standard deviation. The differences of the categorical and continuous variables between the two investigated groups were compared using the Chi-square test or stu-

Table 3. Genotype distributions and Hardy-Weinberg equilibrium in the two investigated groups

Genotype	Patients (%)	Controls (%)	χ^2	*P* value	HWE in patients		HWE in controls	
					χ^2	P	χ^2	P
IL-1α rs1800587								
CC	175 (77.09)	196 (86.34)						
CT	49 (21.59)	28 (12.33)						
TT	4 (1.76)	3 (1.32)	7.06	0.03	0.07	0.79	2.74	0.10
IL-1β rs1143627								
TT	61 (26.87)	74 (32.60)						
CT	112 (49.34)	107 (47.14)						
CC	54 (23.79)	46 (20.26)	2.01	0.37	0.03	0.85	0.41	0.52
IL-18 rs187238								
GG	177 (77.97)	161 (70.93)						
GC	47 (20.70)	62 (27.31)						
CC	3 (1.32)	3 (1.32)	2.82	0.24	0.004	0.95	1.21	0.27
IL-33 rs11792633								
CC	75 (33.04)	48 (21.15)						
CT	114 (50.22)	105 (46.26)						
TT	38 (16.74)	74 (32.60)	17.87	<0.001	0.23	0.63	0.89	0.35
IL-33 rs7044343								
TT	79 (34.80)	76 (33.48)						
TC	111 (48.90)	101 (44.49)						
CC	37 (16.30)	49 (21.59)	2.20	0.33	0.04	0.85	1.97	0.16

dent's t-test. Whether the genotype frequencies were departure from Hardy-Weinberg equilibrium (HWE) was analyzed by Chi-square goodness of fit test. The correlation between the IL-1α rs1800587, IL-1β rs1143627, IL-18 rs187238 and IL-33 rs11792633 and rs7044343 polymorphisms and risk of Alzheimer's disease was analyzed using multiple variable logistic regression analysis, and the results were described using the odds ratios (OR) and their 95% confidence intervals (95% CI). Three genetic models were taken to analyze, including co-dominant, dominant and recessive models. The gene-environmental interaction was performed using Spearman correlation analysis. All the analysis was done using SPSS Statistics for Windows, Version 17.0. (SPSS Inc., Chicago, USA) *P* value less than 0.05 was considered as statistical significance.

Results

The demographic and clinical variables of patients with Alzheimer's disease and controls were shown in **Table 2**. When comparing with the controls, we observed that patients with Alzheimer's disease were apt to have a family history of Alzheimer's disease (χ^2=21.49, P<0.001) and have higher level of TC (t=2.03, P=0.02). However, there were no significant differences were found between patients with Alzheimer's disease and controls in terms of sex (χ^2=0.00, P=1.00), age (t=1.14, P=0.13), BMI (χ^2=0.09, P=0.77), brain trauma (χ^2=3.35, P=0.07), tobacco smoking (χ^2=0.25, P=0.62), alcohol drinking (χ^2=1.43, P=0.23), and levels of TG (t=0.17, P=0.43), LDL-c (t=0.48, P=0.32) and HDL-c (t=0.95, P=0.17).

The genotype distributions of IL-1α rs1800587, IL-1β rs1143627, IL-18 rs187238 and IL-33 rs11792633 and rs7044343 were shown in **Table 3**. Comparison with the controls, we observed significant differences in the genotype distributions of IL-1α rs1800587 (χ^2=7.06, P=0.03) and IL-33 rs11792633 (χ^2=17.87, P<0.001) between patients with Alzheimer's disease and controls. However, no significant differences were observed in IL-1β rs1143627 (χ^2=2.01, P=0.37), IL-18 rs187238 (χ^2=2.82, P=0.24) and IL-33 rs11792633 (χ^2=2.20,

Table 4. Multiple regression analysis between IL-1α rs1800587, IL-1β rs1143627, IL-18 rs187238 and IL-33 rs11792633 and rs7044343 and risk of Alzheimer's disease

Genotype	Patients (%)	Controls (%)	Multiple logistic regression analysis	
			OR (95% CI)[1]	P
IL-1α rs1800587				
Co-dominant				
CC	174 (76.65)	197 (86.78)	1.0 (Ref.)	
CT	49 (21.59)	27 (11.89)	1.96 (1.15-3.38)	0.01
TT	4 (1.76)	3 (1.32)	1.12 (0.21-6.11)	0.87
Dominant				
CC	174 (76.65)	197 (86.78)	1.0 (Ref.)	
CT+TT	53 (23.35)	30 (13.22)	1.91 (1.15-3.23)	0.01
Recessive				
CC+CT	223 (98.24)	224 (98.68)	1.0 (Ref.)	
TT	4 (1.76)	3 (1.32)	1.34 (0.22-9.24)	0.70
IL-1β rs1143627				
Co-dominant				
TT	61 (26.87)	74 (32.6)	1.0 (Ref.)	
CT	112 (49.34)	107 (47.14)	1.27 (0.81-2.00)	0.28
CC	54 (23.79)	46 (20.26)	1.42 (0.82-2.47)	0.18
Dominant				
TT	61 (26.87)	74 (32.6)	1.0 (Ref.)	
CT+CC	166 (73.13)	153 (67.4)	1.32 (0.86-2.01)	0.18
Recessive				
TT+CT	173 (76.21)	181 (79.74)	1.0 (Ref.)	
CC	54 (23.79)	46 (20.26)	1.23 (0.77-1.97)	0.36
IL-18 rs187238				
Co-dominant				
GG	177 (77.97)	161 (70.93)	1.0 (Ref.)	
GC	47 (20.7)	62 (27.31)	0.69 (0.44-1.09)	0.09
CC	3 (1.32)	4 (1.32)	0.68 (0.10-4.10)	0.62
Dominant				
GG	177 (77.97)	161 (70.93)	1.0 (Ref.)	
GC+CC	50 (22.02)	66 (28.63)	0.69 (0.44-1.08)	0.09
Recessive				
GG+GC	224 (98.67)	223 (98.24)	1.0 (Ref.)	
CC	3 (1.32)	4 (1.32)	0.75 (0.11-4.47)	0.70
IL-33 rs11792633				
Co-dominant				
CC	75 (33.04)	48 (21.14)	1.0 (Ref.)	
CT	114 (50.22)	105 (46.26)	0.69 (0.43-1.11)	0.11
TT	38 (16.74)	74 (32.6)	0.33 (0.19-0.58)	<0.001
Dominant				
CC	75 (33.04)	48 (21.14)	1.0 (Ref.)	
CT+TT	152 (66.96)	179 (78.86)	0.54 (0.35-0.85)	0.004
Recessive				
CC+CT	189 (83.26)	153 (67.4)	1.0 (Ref.)	
TT	38 (16.74)	74 (32.6)	0.42 (0.26-0.66)	<0.001

P=0.33) genotype distributions between the two studied groups.

The correlation between IL-1α rs1800587, IL-1β rs1143627, IL-18 rs187238 and IL-33 rs11792633 and rs7044343 and risk of Alzheimer's disease were described in **Table 4**. For IL-1α rs1800587, individuals carrying with the CT genotype had a higher risk of Alzheimer's disease when compared with those carrying the CC genotype (OR=1.96, 95% CI=1.15-3.38). In dominant model, the CT+TT genotype of IL-1α rs1800587 was associated with an increased risk of Alzheimer's disease in comparison with the CC genotype (OR=1.91, 95% CI=1.15-3.23). For the IL-33 rs11792633, we observed that the TT genotype was significant related to a lower risk of Alzheimer's disease when compared with the CC genotype (OR=0.33, 95% CI=0.19-0.58). Moreover, the IL-33 rs11792633 was significant associated with a reduced risk of Alzheimer's disease in dominant (OR=0.54, 95% CI=0.35-0.85) and recessive (OR=0.42, 95% CI=0.26-0.66) models. However, no significant association was reported between IL-1β rs1143627, IL-18 rs187238 and IL-33 rs7044343 and risk of Alzheimer's disease.

The gene-environmental interaction analysis found a significant interaction between family history of Alzheimer's disease and IL-1α rs1800587 (Correlation coefficient=0.068,

IL-33 rs7044343				
Co-dominant				
TT	79 (34.80)	76 (33.48)	1.0 (Ref.)	
TC	111 (48.90)	101 (44.49)	1.06 (0.68-1.63)	0.79
CC	37 (16.30)	49 (21.59)	0.73 (0.41-1.28)	0.24
Dominant				
TT	79 (34.80)	76 (33.48)	1.0 (Ref.)	
TC+CC	148 (65.20)	150 (66.08)	0.95 (0.63-1.43)	0.79
Recessive				
TT+TC	190 (83.70)	177 (77.97)	1.0 (Ref.)	
CC	37 (16.30)	49 (21.59)	0.70 (0.42-1.16)	0.14

[1]Adjusted for family history of Alzheimer's disease and TC.

Table 5. Gene-environmental interaction between IL-1α rs1800587 and IL-33 rs11792633 polymorphisms and environmental factors in the risk of Alzheimer's disease

Variables	IL-1α rs1800587		IL-33 rs11792633	
	Correlation coefficient	*P* value	Correlation coefficient	*P* value
BMI	0.032	0.41	0.040	0.13
Brain trauma	0.027	0.52	0.023	0.64
Tobacco smoking	0.019	0.67	0.027	0.61
Alcohol drinking	0.022	0.55	0.037	0.22
Family history of Alzheimer's disease	0.068	0.03	0.091	0.01
TC, mmol/L	0.041	0.24	0.031	0.45
TG, mmol/L	0.037	0.17	0.028	0.58
LDL-c, mmol/L	0.039	0.19	0.030	0.51
HDL-c, mmol/L	0.032	0.28	0.035	0.36

P=0.03) and IL-33 rs11792633 (Correlation coefficient=0.091, P=0.01) polymorphisms in the risk of Alzheimer's disease (**Table 5**). However, no other gene-environmental interactions were observed.

Discussion

Currently, the candidate gene approach is often used to screen for and identify genes associated with disease susceptibility and the development/progression of diseases. The replacement, deletion, or insertion of a single nucleotide within the genome, otherwise known as single nucleotide polymorphism, is known to be essential in regulating and modifying protein expression, and can contribute to individual disease susceptibility. In the present study, we performed a 1:1 matched case-control study to investigate the possible correlation between IL-1α, IL-1β, IL-18 and IL-33 gene polymorphisms and risk of Alzheimer's disease. Our study has found that the IL-1α rs1800587 and IL-33 rs11792633 polymorphisms contribute to the development of Alzheimer's disease in a Chinese population.

The main pathological changes of Alzheimer's disease are accompanied by activation of glial cells, and the activated glial cells are related with high expression of IL-1, IL-6 and IL-8. These inflammation factors could promote the death of neurons and increase the pathological changes of Alzheimer's disease through initiation of immunologic cascade [19]. The IL-1 and its family members, such as IL-18 and IL-33, are associated with the development of Alzheimer's disease. Therefore, the Alzheimer's disease is a chronic inflammatory disease. IL-1 gene can induce inflammatory reaction and the body defense reaction, and can regulate multiple effect proinflammatory factor in immune inflammation mechanism. IL-1 consists of three homologous proteins, including IL-1α, IL-1β and IL-1Rα. These proteins were located at 2q12~q21, which consists of IL-1 gene cluster. Genetic polymorphisms were observed in the three genes.

Currently, several studies have indicated that the association between IL-1 gene polymorphisms and risk of nervous system diseases, such as brain abscess, acute stroke, astrocytes and neuropsychiatric symptoms [20-23]. Currently, many studies have reported the association between IL-1 gene polymorphisms and development of Alzheimer's disease, but the results are inconsistent [24-28]. Hua et al. (2012), Li et al. (2013) and Tian et al. (2014) reported that IL-1α SNP rs1800587 was associated with the development of Alzhei-

mer's disease [24, 26, 28]. A recent meta-analysis indicated that IL-1α SNP rs1800587 was only associated with the risk of Alzheimer's disease in Caucasians, but not in Asians [29]. The results of our study are partly associated with previous results.

Only three previous studies revealed an association between IL-33 polymorphism and risk of Alzheimer's disease [28, 30, 31]. Three studies have indicated that the IL-33 rs7044343 polymorphisms reduce the susceptibility to Alzheimer's disease, and our results are in line with previous studies. Moreover, we found that IL-1α SNP rs1800587 and IL-33 rs7044343 polymorphisms have interaction with family history of Alzheimer's disease in the risk of this disease, which suggest that the IL-1α SNP rs1800587 and IL-33 rs7044343 genetic variations are hereditary molecular factors.

One limitation should be pay attention to. The investigated subjects were recruited from only one place and hospital in China. This would not be sufficiently representative of other populations and cause selection bias in this study. In conclusion, our study suggests that the IL-1α SNP rs1800587 and IL-33 rs7044343 could influence the susceptibility to Alzheimer's disease. Further studies with more sample size are greatly required to confirm the findings of our study.

Acknowledgements

We thank for the great supports and funding from the First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology.

Disclosure of conflict of interest

None.

Address correspondence to: Tao Cui, Department of Neurosurgery, The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, No.636 Guanlin Road, Luoyang 471003, Henan, China. E-mail: suyuepanyp@163.com

References

[1] Su F, Bai F and Zhang Z. Inflammatory cytokines and Alzheimer's disease: a review from the perspective of genetic polymorphisms. Neurosci Bull 2016; 32: 469-480.

[2] Campion D, Dumanchin C, Hannequin D, Dubois B, Belliard S, Puel M, Thomas-Anterion C, Michon A, Martin C, Charbonnier F, Raux G, Camuzat A, Penet C, Mesnage V, Martinez M, Clerget-Darpoux F, Brice A and Frebourg T. Early-onset autosomal dominant Alzheimer disease: prevalence, genetic heterogeneity, and mutation spectrum. Am J Hum Genet 1999; 65: 664-670.

[3] Hebert LE, Scherr PA, Bienias JL, Bennett DA and Evans DA. Alzheimer disease in the US population: prevalence estimates using the 2000 census. Arch Neurol 2003; 60: 1119-1122.

[4] Scheltens P, Blennow K, Breteler MM, de Strooper B, Frisoni GB, Salloway S and Van der Flier WM. Alzheimer's disease. Lancet 2016; 388: 505-517.

[5] Gatz M, Reynolds CA, Fratiglioni L, Johansson B, Mortimer JA, Berg S, Fiske A and Pedersen NL. Role of genes and environments for explaining Alzheimer disease. Arch Gen Psychiatry 2006; 63: 168-174.

[6] Tosto G and Reitz C. Genomics of Alzheimer's disease: value of high-throughput genomic technologies to dissect its etiology. Mol Cell Probes 2016; 30: 397-403.

[7] Cai R, Han J, Sun J, Huang R, Tian S, Shen Y, Dong X, Xia W and Wang S. Plasma clusterin and the CLU gene rs11136000 variant are associated with mild cognitive impairment in type 2 diabetic patients. Front Aging Neurosci 2016; 8: 179.

[8] Crocco P, Saiardi A, Wilson MS, Maletta R, Bruni AC, Passarino G and Rose G. Contribution of polymorphic variation of inositol hexakisphosphate kinase 3 (IP6K3) gene promoter to the susceptibility to late onset Alzheimer's disease. Biochim Biophys Acta 2016; 1862: 1766-1773.

[9] Geng S, Wang Y, Sun Y, Li J, Yin H, Zeng Z, Yang X, Zhang Y and Wang Y. Gene- gene interaction between CYP2J2 and PPAR -γ gene on late-onset Alzheimer's disease in the eastern Chinese Han population. Behav Brain Res 2016; [Epub ahead of print].

[10] Huang H, Zhao J, Xu B, Ma X, Dai Q, Li T, Xue F and Chen B. The TOMM40 gene rs2075650 polymorphism contributes to Alzheimer's disease in Caucasian, and Asian populations. Neurosci Lett 2016; 628: 142-146.

[11] Ruiz M, Arias I, Rolon G, Hernandez E, Garavito P and Silvera-Redondo C. APOE gene polymorphism analysis in Barranquilla, Colombia. Biomedica 2016; 36: 52-58.

[12] Zheng J, Yan H, Shi L, Kong Y, Zhao Y, Xie L, Li J, Huang M and Zhao S. The CYP19A1 rs3751592 variant confers susceptibility to Alzheimer disease in the Chinese Han population. Medicine (Baltimore) 2016; 95: e4742.

[13] Zhong X, Liu MY, Sun XH and Wei MJ. Association between ABCB1 polymorphisms and haplotypes and Alzheimer's disease: a meta-analysis. Sci Rep 2016; 6: 32708.
[14] Li Y, Wang J, Sheng JG, Liu L, Barger SW, Jones RA, Van Eldik LJ, Mrak RE and Griffin WS. S100 beta increases levels of beta-amyloid precursor protein and its encoding mRNA in rat neuronal cultures. J Neurochem 1998; 71: 1421-1428.
[15] Olsen I and Singhrao SK. Inflammasome Involvement in Alzheimer's disease. J Alzheimers Dis 2016; 54: 45-53.
[16] Sheng JG, Griffin WS, Royston MC and Mrak RE. Distribution of interleukin-1-immunoreactive microglia in cerebral cortical layers: implications for neuritic plaque formation in Alzheimer's disease. Neuropathol Appl Neurobiol 1998; 24: 278-283.
[17] O'Bryant SE, Lista S, Rissman RA, Edwards M, Zhang F, Hall J, Zetterberg H, Lovestone S, Gupta V, Graff-Radford N, Martins R, Jeromin A, Waring S, Oh E, Kling M, Baker LD and Hampel H. Comparing biological markers of Alzheimer's disease across blood fraction and platforms: comparing apples to oranges. Alzheimers Dement (Amst) 2016; 3: 27-34.
[18] Teh PP, Vasanthakumar A and Kallies A. Development and function of effector regulatory T cells. Prog Mol Biol Transl Sci 2015; 136: 155-174.
[19] Mrak RE and Griffin WS. Glia and their cytokines in progression of neurodegeneration. Neurobiol Aging 2005; 26: 349-354.
[20] Moynagh PN. The interleukin-1 signalling pathway in astrocytes: a key contributor to inflammation in the brain. J Anat 2005; 207: 265-269.
[21] Gromadzka G and Członkowska A. Influence of IL-1RN intron 2 variable number of tandem repeats (VNTR) polymorphism on the age at onset of neuropsychiatric symptoms in Wilson's disease. Int J Neurosci. 2011; 121: 8-15.
[22] Mishra P, Prasad KN, Singh K, Bajpai A, Sahu RN and Ojha BK. Tumor necrosis factor-alpha and interleukin-1beta gene polymorphisms and risk of brain abscess in North Indian population. Cytokine 2015; 75: 159-164.
[23] Rezk NA and Mohamad HS. Influence of interleukin-1 gene cluster polymorphisms on the susceptibility and outcomes of acute stroke in Egyptian patients. Cell Biochem Biophys 2015; 71: 637-647.
[24] Li BH, Zhang LL, Yin YW, Pi Y, Guo L, Yang QW, Gao CY, Fang CQ, Wang JZ, Xiang J, Li JC. Association between interleukin-1α C(-889)T polymorphism and Alzheimer's disease: a meta-analysis including 12,817 subjects. J Neural Transm (Vienna) 2013; 120: 497-506.
[25] Yuan H, Xia Q, Ge P and Wu S. Genetic polymorphism of interleukin 1beta-511C/T and susceptibility to sporadic Alzheimer's disease: a meta-analysis. Mol Biol Rep 2013; 40: 1827-1834.
[26] Hua Y, Zhao H, Kong Y and Lu X. Meta-analysis of the association between the interleukin-1A -889C/T polymorphism and Alzheimer's disease. J Neurosci Res 2012; 90: 1681-1692.
[27] Qin X, Peng Q, Zeng Z, Chen Z, Lin L, Deng Y, Huang X, Xu J, Wu H, Huang S, Li S and Zhao J. Interleukin-1A-889C/T polymorphism and risk of Alzheimer's disease: a meta-analysis based on 32 case-control studies. J Neurol 2012; 259: 1519-1529.
[28] Tian M, Deng YY, Hou DR, Li W, Feng X and Yu Z. Association of IL-1, IL-18, and IL-33 gene polymorphisms with late-onset Alzheimer's disease in a Hunan Han Chinese population. Brain Res 2014; 1596: 136-145.
[29] Qin X, Peng Q, Zeng Z, Chen Z, Lin L, Deng Y, Huang X, Xu J, Wu H, Huang S, Li S, Zhao J. Interleukin-1A -889C/T polymorphism and risk of Alzheimer's disease: a meta-analysis based on 32 case-control studie. J Neurol 2012; 259: 1519-1529.
[30] Chapuis J, Hot D, Hansmannel F, Kerdraon O, Ferreira S, Hubans C, Maurage CA, Huot L, Bensemain F, Laumet G, Ayral AM, Fievet N, Hauw JJ, DeKosky ST, Lemoine Y, Iwatsubo T, Wavrant-Devrièze F, Dartigues JF, Tzourio C, Buée L, Pasquier F, Berr C, Mann D, Lendon C, Alpérovitch A, Kamboh MI, Amouyel P and Lambert JC. Transcriptomic and genetic studies identify IL-33 as a candidate gene for Alzheimer's disease. Mol Psychiatry 2009; 14: 1004-1016.
[31] Yu JT, Song JH, Wang ND, Wu ZC, Zhang Q, Zhang N, Zhang W, Xuan SY and Tan L. Implication of IL-33 gene polymorphism in Chinese patients with Alzheimer's disease. Neurobiol Aging 2012; 33: 1014, e11-4.