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Association between interleukin-4 genetic polymorphisms and the risk of cerebral infarction in a population of China.

Hu Wei[1], Gao Feng[2], Wang Pei[1], Wang Gang[1], Zhang Yuelin[1*]

[1]Emergency Surgery, Shaanxi Provincial People's Hospital, Xi'an, PR China

[2]Emergency Department, Shaanxi Provincial Pucheng Hospital, Xi'an, PR China

Abstract

We conducted a case-control study to evaluate the correlation of IL-4 rs2243250 and rs2070874 polymorphisms with the risk of cerebral infarction, and the gene-environmental interaction between IL-4 and environmental factors. A total of 344 patients with cerebral infarction and 360 healthy controls were enrolled in this case-control study. The genotyping of the IL-4 rs2243250 and rs2070874 was performed by Polymerase Chain Reaction (PCR) amplification and single base extension assays in a 384-well plate format on the sequenom MassARRAY platform. By logistic regression analysis, males (OR=1.44, 95% CI=1.07-2.02), creatinine ≥ 1.00 (OR=1.74, 95% CI=1.28-2.38), a history of hypertension (OR=1.64, 95% CI=1.18-2.30) and diabetes mellitus (OR=1.76, 95% CI=1.14-2.73), and high level of HDL-c (OR=2.95, 95% CI=1.46-5.97) were associated with an increased risk of cerebral infarction when compared with the reference group. We observed that the TT (OR=3.32, 95% CI=1.81-6.06) and CT+TT (OR=1.51, 95% CI=1.11-2.06) genotypes of rs2243250 were correlated with a higher risk of cerebral infarction in comparison with the CC genotype. The rs2243250 had interaction with gender and HDL-c in the risk of cerebral infarction. In conclusion, our study suggests that rs2243250 may be considered as a useful biomarker for prediction of the susceptibility of cerebral infarction.

Keywords: Cerebral infarction, IL-4, rs2243250, rs2070874, Polymorphism.

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Introduction

Stroke is the majority cause of death in the elderly, and it causes about 11% of all death worldwide and is the most common reason for adult-acquired disability [1]. Cerebral infarction constitutes about 50% of all stroke cases [2]. Cerebral infarction has a diverse etiology, and several risk factors contribute to the pathogenesis of cerebral infarction, such as long term tobacco smoking and alcohol drinking, lack of exercises, obesity and a history of type 2 diabetes, and adiposity as well [2].

However, the prevalence of cerebral infarction varies across different population worldwide even when they had similar environmental factors, suggesting that genetic factors would play a critical role in the risk of cerebral infarction [3].

Previous studies have reported the association between genetic polymorphisms and risk of cerebral infarction in various populations, *LOX-1*, *Apolipoprotein E4*, *interleukin-10* and transforming growth factor Beta-1 genes [4-7].

Currently, it is reported that a various inflammatory mechanisms contribute to the development of cerebral infarction [8-10]. Several kinds of inflammatory factors, such as tumor necrosis factor (TNF-alpha), interleukin (IL)-1 and IL-6, are produced by cultured brain cells after obtaining various stimuli [10].

Neurones, astrocytes, microglia cells and oligodendrocytes could produce inflammatory mediators, although the cytokine receptors in central nervous system are expressed at a relatively low level [10]. These inflammatory genes are associated with increased risk of ischemic injury through rapid activation of resident cells, production of pro-inflammatory mediators and infiltration of various types of inflammatory cells [11].

IL-4 is a typical cytokine of T helper 2 (Th2) cells, which could inhibit effect on the inflammation, decrease the production of pro-inflammatory cytokines and reduce the destructive enzymes through monocytes [12]. A previous study reported an increased serum levels of IL-4 originated from Th2 cells in patients with stroke in the course of the acute stage [13].

Only a few studies reported the association of IL-4 polymorphisms with the pathogenesis of cerebral infarction [14]. In this study, we conducted a case-control study to evaluate the correlation of IL-4 rs2243250 and rs2070874 polymorphisms with the risk of cerebral infarction, and the

gene-environmental interaction between IL-4 and environmental factors.

Materials and Methods

Subjects

Three hundred and forty-four participants with cerebral infarction were recruited from patients who visited the Shaanxi Provincial People's Hospital between June 2015 and June 2016. The diagnosis of cerebral infarction was confirmed by neurological examination, Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) examinations, based on the diagnostic criteria from World Health Organization. Patients with other causes of cerebrovascular events such as brain trauma, vascular malformation, brain tumors or congenital brain disorders were excluded.

Between June 2015 and June 2014, 360 healthy subjects were selected through a general health check-up of the Shaanxi Provincial People's Hospital, and they are considered as controls. These respondents received CT and MRI, and were confirmed to be free of cerebral infarction.

The exclusion for controls was those with a history of stroke, brain tumors, brain trauma, cardiovascular diseases, autoimmune diseases or any severe diseases. The protocol of this study was approved by the ethics review committee of the Shaanxi Provincial People's Hospital. All respondents voluntary agreed to join in this study and signed informed consents.

The lifestyle characteristics and family history of diseases of respondents were obtained from self-designed questionnaires, including alcohol drinking and tobacco smoking habits, and a history of hypertension and diabetes mellitus.

The clinical variables were collected from medical records, including creatinine, Total Cholesterol (TC), Low Density Lipopolysaccharide Cholesterol (LDL-c), High Density Lipopolysaccharide Cholesterol (HDL-c) and Triglyceride (TG).

The body mass index was defined as the weight divided by the square of the body height. The hypertension was defined as systolic pressure ≥ 140 mmHg and diastolic pressure ≥ 90 mmHg. The type-2 diabetes was defined as fasting plasma glucose ≥ 7.0 mmol/L or two hours after the oral dose a plasma glucose ≥ 11.1 mmol/L by a glucose tolerance test.

The ever drinking was defined as those who drank more than 50 g white wine or 200 g beer per week and lasted for one year. The tobacco smoking was considered as those who smoked more than one cigarette per day and lasted for one year.

The mean ages of patients with cerebral infarction and controls were 58.15 ± 10.45 and 58.47 ± 9.43 years, respectively; the mean BMI values were 23.11 ± 2.01 and 22.45 ± 2.31 kg/m^2, respectively; and the creatinine levels were 0.92 ± 0.26 and 1.02 ± 0.28 mg/dl, respectively.

Genotyping assays

5 ml peripheral platform (Sequenom, San Diego, USA); the sense and antisense primers for genotyping IL-4 rs2243250 and rs2070874 is shown in Table 1. The PCR of IL-4 rs2243250 and rs2070874 was carried out in a 5 μL mixture reaction, and then the SAP and iPLEX reaction was conducted.

The PCR products are then desalted venous blood sample was obtained from each respondent after enrolment. Genomic DNA was isolated from the blood serum through a TIANamp Blood DNA Kit (Tiangen, Beijing, China), and kept at -20°C when use. Genotyping of *IL*-4 rs2243250 and rs2070874 was conducted by Polymerase Chain Reaction (PCR) amplification and single base extension assays. Genotyping of the two SNPs of IL-4 was performed in a 384-well plate format on the sequenom MassARRAY, dispensed to a SpectroCHIP and analyzed with MALDI-TOF MS.

Table 1. *Primers for IL-4 rs2243250 and rs2070874.*

SNPs	Sense (3'-5')	Antisense (3'-5')
rs2243250	AATTCAGGGTCCCTGACACACT	AACCTCCCTTCAAGGTTGTACA
rs2070874	AATTTCTCCTCCAAGAGAGGT	CTGAGAGCATTAGGAGAACA

Statistical analysis

The chi-square test or Fisher's exact test were used for comparison of categorical variables, including demographic and lifestyle variables and allele and genotype frequencies. Student t-test was used to comparison of continued variables, such as clinical variables. Chi-square test with one degree of freedom was used to estimate the Hardy-Weinberg Equilibrium (HWE) for IL-4 rs2243250 and rs2070874 genotype distributions. The association of environmental factors, rs2243250 and rs2070874 polymorphisms with cerebral infarction risk was estimated by unconditional logistic regression analysis and the results were displayed by adjusted Odds Ratio (OR) and 95% Confident Intervals (95% CI). Gene-environmental interaction was performed by Chi-square test. The statistical analyses were performed by SPSS Statistics for Windows, version 20.0 (IBM Corp, Armonk, NY, USA), and all P values were two tailed. The OR (95% CI) was adjusted for potential confounding factors, including gender and age.

Results

By Chi-square test or student t test, we observed significant differences between patients and controls in terms of gender (χ^2=7.61, P=0.006), creatinine (t=13.65, P<0.001), hypertension (χ^2=8.63, P=0.003), diabetes mellitus (χ^2=7.22, P=0.007) and HDL-c (t=1.14, P=0.255) (Table 2). However, no significant differences were found in age, BMI, alcohol

drinking, tobacco smoking, and levels of TC, LDL-c and TG (All P>0.05).

Table 2. Baseline characteristics of study subjects.

Variables	Patients N=344	%	Controls N=360	%	χ^2-test or t-test	P value
Age, year						
<60	200	58.14	211	58.61		
≥ 60	144	41.86	149	41.39	0.02	0.899
Gender						
Females	117	34.01	159	44.17		
Males	227	65.99	201	55.83	7.61	0.006
BMI, kg/m^2						
<24	238	69.19	266	73.89		
≥ 24	106	30.81	94	26.11	1.91	0.167
Creatinine, mg/dl						
<1.00	131	38.08	187	51.94		
≥ 1.00	213	61.92	173	48.06	13.65	<0.001
Alcohol drinking						
Never	154	44.77	179	49.72		
Ever	190	55.23	181	50.28	1.73	0.188
Tobacco smoking						
Never	145	42.15	159	44.17		
Ever	199	57.85	201	55.83	0.29	0.589
Hypertension						
No	221	64.24	268	74.44		
Yes	123	35.76	92	25.56	8.63	0.003
Diabetes mellitus						
No	280	81.4	319	88.61		
Yes	64	18.6	41	11.39	7.22	0.007
TC, mmol/L	4.57 ± 1.04		4.50 ± 1.03		0.79	0.429
LDL-c, mmol/L	2.27 ± 0.42		2.26 ± 0.44		0.31	0.759
HDL-c, mmol/L	1.22 ± 0.25		1.17 ± 0.20		3.14	0.002
TG, mmol/L	2.37 ± 1.16		2.27 ± 1.13		1.14	0.255

TC: Total Cholesterol; LDL-c: Low Density Lipopolysaccharide cholesterol; HDL-c: High Density Lipopolysaccharide cholesterol; TG: Triglyceride.

The CC, CT and TT genotypes frequencies of IL-4 rs2243250 showed significant differences between patients and controls (χ^2=18.93, P<0.001). However, no significant difference was found in the genotype distributions of IL-4 rs2070874 (χ^2=0.81, P=0.67) between the two study groups. The genotype frequencies of IL-4 rs2243250 and rs2070874 were according to the HWE in both patients and controls (Table 3).

The unconditional logistic regression analyses showed that males (OR=1.44, 95% CI=1.07-2.02), creatinine ≥ 1.00 (OR=1.74, 95% CI=1.28-2.38), a history of hypertension (OR=1.64, 95% CI=1.18-2.30) and diabetes mellitus (OR=1.76, 95% CI=1.14-2.73), and high level of HDL-c (OR=2.95, 95% CI=1.46-5.97) were associated with an increased risk of cerebral infarction when compared with the reference group. When compared with the CC genotype, we observed that the TT (OR=3.32, 95% CI=1.81-6.06) and CT

+TT (OR=1.51, 95% CI=1.11-2.06) genotypes of rs2243250 were correlated with a higher risk of cerebral infarction (Table 4). However, rs2070874 polymorphism could not influence the cerebral infarction risk.

Table 3. *Genotype distributions of IL-4 rs2243250 and rs2070874 in study subjects.*

SNP	CAD patients	%	Controls	%	Chi-square	P value	HWE in patients	P value	HWE in controls	P value
rs2243250										
CC	143	41.57	186	51.67						
CT	153	44.48	156	43.33						
TT	48	13.95	18	5	18.93	<0.001	0.47	0.49	4.76	0.06
rs2070874										
TT	135	39.24	151	41.94						
TC	142	41.28	147	40.83						
CC	67	19.48	62	17.22	0.81	0.67	2.62	0.11	3.25	0.08

Note: Adjusted for gender, age, BMI, creatinine, hypertension, diabetes mellitus and HDL-c.

Table 4. *Association between IL-4 rs2243250 and rs2070874 polymorphisms and cerebral infarction risk.*

Variable	B	S.E	Wald	P value	OR (95% CI)
Age ≥ 60, y	0	0.16	0	0.976	0.98 (0.73-1.36)
Males	0.39	0.16	5.78	0.016	1.44 (1.07-2.02)
BMI ≥ 24, kg/m^2	0.19	0.17	1.15	0.284	1.21 (0.86-1.70)
Creatinine ≥ 1.00, mg/dl	0.56	0.16	12.43	0	1.74 (1.28-2.38)
Ever alcohol drinking	0.21	0.16	1.79	0.181	1.21 (0.91-1.68)
Ever tobacco smoking	0.02	0.16	0.02	0.892	1.01 (0.75-1.40)
A history of hypertension	0.5	0.17	8.46	0.004	1.64 (1.18-2.30)
A history of diabetes mellitus	0.57	0.22	6.41	0.011	1.76 (1.14-2.73)
TC, mmol/L	0.06	0.08	0.53	0.467	1.06 (0.91-1.23)
LDL-c, mmol/L	0.09	0.18	0.22	0.637	1.12 (0.78-1.61)
HDL-c, mmol/L	1.04	0.35	8.61	0.003	2.95 (1.46-5.97)
TG, mmol/L	0.07	0.07	1.04	0.308	1.08 (0.94-1.24)
rs2243250					
CC			15.46	0	1.0
CT	0.26	0.17	2.4	0.122	1.29 (0.93-1.79)
TT	1.2	0.31	15.16	0	3.32 (1.81-6.06)
CT+TT	0.41	0.16	6.78	0.009	1.51 (1.11-2.06)
rs2070874					
TT			0.43	0.805	1.0
TC	0.1	0.18	0.29	0.59	1.10 (0.78-1.55)
CC	0.13	0.22	0.32	0.572	1.14 (0.73-1.76)
TC+CC	0.09	0.16	0.31	0.58	1.12 (0.81-1.53)

The gene-environmental interaction was performed in terms of gender, creatinine, hypertension, diabetes mellitus and HDL-c. We observed that the rs2243250 had interaction with gender and HDL-c in the risk of cerebral infarction (Table 5).

Table 5. *Gene-environmental interaction between IL-4 rs2243250 and environmental factors in the risk of cerebral infarction.*

Variables	Patients		χ^2	P value	Controls		χ^2	P value
	CC	TT+CT	CC		TT +CT			
Gender								
Females	48	69			93	66		
Males	95	132	0.02	0.88	93	108	5.31	0.02
Creatinine, mg/dl								
<1.00	55	76			94	93		
≥ 1.00	88	125	0.02	0.9	92	81	0.31	0.58
Hypertension								
No	94	127			135	133		
Yes	49	74	0.24	0.63	51	41	0.7	0.4
Diabetes mellitus								
No	116	164			163	156		
Yes	27	37	0.01	0.91	23	18	0.36	0.55
HDL-c, mmol/L								
<1.10	44	67			59	77		

≥ 1.10	99	134	0.25	0.62	127	97	6.01	0.02

Discussion

Our results investigated the correlation between IL-4 rs2243250 and rs2070874 polymorphisms and the pathogenesis of cerebral infarction. We found that the rs2243250 TT and CT +TT genotypes were correlated with an elevated risk of cerebral infarction in the Chinese population, and rs2243250 polymorphism had an interaction with gender and HDL-c in the risk of this disease.

It has been long accepted that imbalanced T-helper immune responses play an important role in the development of cerebral infarction. IL-4 cytokine is a prototypic member of the T helper (Th2), and contributes a major part in Th1/Th2 cytokine balance regulation. Many experimental studies have reported an association between IL-4 expression and pathogenesis of stroke [15-17]. Zhao has reported that IL-4 expression is secreted by ischemic neurons as an endogenous defense mechanism, which contributes to the regulation of brain clean-up and repair after stroke [16]. Liu et al. have indicated that cytokine IL-4 promotes the long term neurological outcomes after stroke, and the mechanism might be through M2 phenotype induction by microglia/macrophages [17]. Theodorou et al. showed a significant increase in the percentage of IL-4 producing T cells in the ischaemic stroke, compared with the controls [18]. Katsuno have reported that the intracerebral IL-4 is negatively associated with the severity of cerebral diseases, and secretion of IL-4 shows a neuro-protective effect and could be considered as a predictive factor for the outcome of stroke [19].

Single nucleotide polymorphisms mean DNA sequence polymorphisms induced by a single nucleotide variation, such as transversion, insertion or deletion [20]. The IL-4 polymorphisms may influence the expression of cytokine production levels, and thus influence the development of many inflammation-related diseases. Currently, only several studies have reported the association between IL-4 polymorphisms and risk of stroke and cardiovascular diseases [21-25]. Tong et al. performed a study with 100 ischemic stroke and 100 matched healthy controls, and reported that IL-4 VNTR polymorphism was significantly associated with ischemic stroke in the Chinese Uyghur population [21]. Park et al. performed a study with 119 patients with ischaemic stroke, 79 patients with intracerebral haemorrhage and 267 controls in Korean population, and they reported that both the rs2243250 and rs2070874 polymorphisms and their haplotypes were correlated with intracerebral haemorrhage [22]. Marousi et al. performed a study with 290 subjects, and suggested that IL-4 rs2243250 genotype was associated with the recurrences of ischaemic stroke after adjusted for potential confounding factors [24]. Our study also indicated a significant relationship between rs2243250 TT and CT+TT genotypes and increased risk of cerebral infarction in a Chinese population. However, no previous study reported the association of IL-4 rs2243250 and rs2070874 polymorphisms with the cerebral infarction risk in a Chinese population. Therefore, further studies are greatly needed to confirm our findings.

Our study found an interaction of IL-4 rs2243250 with males and HDL-c in the risk of cerebral infarction. Golimbet et al. reported that IL-4 rs2243250 was associated with depression and anxiety in male patients with coronary heart disease, which showed a significant gene-environmental interaction [26]. Ho et al. reported a significant interaction between IL-4 rs2243250 TT genotype and high level of HDL-c in the risk of type 2 diabetes mellitus [27]. These studies suggested that a gene-environment interaction among the IL-4 and males and HDL-c.

Conclusions

Our study suggests that rs2243250 TT and CT+TT genotypes may increase the risk of cerebral infarction when compared with the CC genotype, and rs2243250 could be considered as a useful biomarker for prediction of the susceptibility of cerebral infarction. Further studies with large sample size are necessary to validate our findings.

Disclosure of Conflict of Interest

None.

References

1. Yang G, Wang Y, Zeng Y, Gao GF, Liang X, Zhou M, Wan X, Yu S, Jiang Y, Naghavi M, Vos T, Wang H, Lopez AD, Murray CJ. Rapid health transition in China, 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet 2013; 381: 1987-2015.
2. Lv J, Yu C, Guo Y, Bian Z, Yang L, Chen Y, Tang X, Zhang W, Qian Y, Huang Y, Wang X, Chen J, Chen Z, Qi L, Li L. Adherence to healthy lifestyle and cardiovascular diseases in the Chinese population. J Am Coll Cardiol 2017; 69: 1116-1125.
3. Germans MR, Jaja BNR, de Oliviera Manoel AL, Cohen AH, Macdonald RL. Sex differences in delayed cerebral ischemia after subarachnoid haemorrhage. J Neurosurg 2017; 1-7.
4. Guo X, Xiang Y, Yang H, Yu L, Peng X, Guo R. Association of the LOX-1 rs1050283 polymorphism with risk for atherosclerotic cerebral infarction and its effect on sLOX-1 and LOX-1 expression in a Chinese population. J Atheroscler Thromb 2017; 24: 572-582.
5. Kumar A, Kumar P, Prasad M, Misra S, Kishor Pandit A , Chakravarty K. Association between Apolipoprotein ε4 Gene Polymorphism and Risk of Ischemic Stroke: A Meta-Analysis. Ann Neurosci 2016; 23: 113-121.
6. Kumar P, Yadav AK, Misra S, Kumar A, Chakravarty K, Prasad K. Role of Interleukin-10 (-1082A/G) gene polymorphism with the risk of ischemic stroke: a meta-analysis. Neurol Res 2016; 38: 823-830.
7. Kumar P, Kumar A, Srivastava MK, Misra S, Pandit AK, Prasad K. Association of transforming growth factor

beta-1-509C/T gene polymorphism with ischemic stroke: A meta-analysis. Basic Clin Neurosci 2016; 7: 91-96.

8. Basic Kes V, Simundic AM, Nikolac N, Topic E, Demarin V. Pro-inflammatory and anti-inflammatory cytokines in acute ischemic stroke and their relation to early neurological deficit and stroke outcome. Clin Biochem 2008; 41: 1330-1334.
9. Nayak AR, Kashyap RS, Kabra D, Purohit HJ, Taori GM, Daginawala HF. Time course of inflammatory cytokines in acute ischemic stroke patients and their relation to inter-alfa trypsin inhibitor heavy chain 4 and outcome. Ann Indian Acad Neurol 2012; 15: 181-185.
10. Tuttolomondo A, Di Raimondo D, di Sciacca R, Pinto A, Licata G. Inflammatory cytokines in acute ischemic stroke. Curr Pharm Des 2008; 14: 3574-3589.
11. Jin R, Yang G, Li G. Inflammatory mechanisms in ischemic stroke: role of inflammatory cells. J Leukoc Biol 2010; 87: 779-789.
12. Chomarat P, Vannier E, Dechanet J, Rissoan MC, Banchereau J, Dinarello CA, Miossec P. Balance of IL-1 receptor antagonist/IL-1 beta in rheumatoid synovium and its regulation by IL-4 and IL-10. J Immunol 1995; 154: 1432-1439.
13. Kim HM, Shin HY, Jeong HJ, An HJ, Kim NS, Chae HJ, Kim HR, Song HJ, Kim KY, Baek SH, Cho KH, Moon BS, Lee YM. Reduced IL-2 but elevated IL-4, IL-6, and IgE serum levels in patients with cerebral infarction during the acute stage. J Mol Neurosci 2000; 14: 191-196.
14. Um JY, Kim HM. Polymorphisms of RANTES and IL-4 genes in cerebral infarction. J Mol Neurosci 2009; 37: 1-5.
15. Timmers L, Sluijter JP, van Keulen JK, Hoefer IE, Nederhoff MG, Goumans MJ, Doevendans PA, van Echteld CJ, Joles JA, Quax PH, Piek JJ, Pasterkamp G, de Kleijn DP. Toll-like receptor 4 mediates maladaptive left ventricular remodeling and impairs cardiac function after myocardial infarction. Circ Res 2008; 102: 257-264.
16. Zhao X, Wang H, Sun G, Zhang J, Edwards NJ, Aronowski J. Neuronal Interleukin-4 as a modulator of microglial pathways and ischemic brain damage. J Neurosci 2015; 35: 11281-11291.
17. Liu X, Liu J, Zhao S, H. Z, Cai W, Cai M, Ji X, Leak RK, Gao Y, Chen J, Hu X. Interleukin-4 is essential for microglia/macrophage M2 polarization and long-term recovery after cerebral ischemia. Stroke 2016; 47: 498-504.
18. Theodorou GL, Marousi S, Ellul J, Mougiou A, Theodori E, Mouzaki A, Karakantza M. T helper 1 (Th1)/Th2 cytokine expression shift of peripheral blood CD4+ and CD8+ T cells in patients at the post-acute phase of stroke. Clin Exp Immunol 2008; 152: 456-463.
19. Katsuno M, Yokota H, Yamamoto Y, Teramoto A. Increased regional interleukin-4 during the acute stage of severe intracranial disorders. Neurol Med Chir (Tokyo) 2006; 46: 471-474.
20. Keeling D. Predicting the future: it's not a SNP. J Thromb Haemost 2008; 6: 749-750.
21. Tong YQ, Ye JJ, Wang ZH, Zhang YW, Zhan FX, Guan XH, Geng YJ, Hou SY, Li Y, Cheng JQ, Lu ZX, Liu JF. Association of variable number of tandem repeat polymorphism in the IL-4 gene with ischemic stroke in the Chinese Uyghur population. Genet Mol Res 2013; 12: 2423-2431.
22. Park HJ, Kim MJ, Kang SW, Kim SK, Lee JS, Park HK, Yoo SD, Kim DH, Yun DH, Kim HS, Kim JW, Chung JH, Jeong YS. Association between interleukin-4 gene polymorphisms and intracerebral haemorrhage in Korean population. Int J Immunogenet 2011; 38: 321-325.
23. Tong Y, Cai L, Zhang R, Zhang Y, Liu S, Lin L, Zhao Z, Geng Y, Xu J, Fan H, Zhang J, Mason KA, Cheng J, Lu Z. A novel tailed primers protocol to identify the association of IL-4 and IL-1RN (receptor antagonist) gene variable number of tandem repeats polymorphisms with ischemic stroke in Chinese Han population. Clin Chim Acta 2011; 412: 486-488.
24. Marousi S, Ellul J, Antonacopoulou A, Gogos C, Papathanasopoulos P, Karakantza M. Functional polymorphisms of interleukin 4 and interleukin 10 may predict evolution and functional outcome of an ischaemic stroke. Eur J Neurol 2011; 18: 637-643.
25. Hoppe C, Klitz W, D'Harlingue K, Cheng S, Grow M, Steiner L, Noble J, Adams R, Styles L. SPTiSCAS. Confirmation of an association between the TNF(-308) promoter polymorphism and stroke risk in children with sickle cell anemia. Stroke 2007; 38: 2241-2246.
26. Golimbet VE, Volel BA, Korovaitseva GI, Kasparov SV, Kondratiev NV, Kopylov FY. Association of inflammatory genes with neuroticism, anxiety and depression in male patients with coronary heart disease. Zh Nevrol Psikhiatr Im S S Korsakova 2017; 117: 74-79.
27. Ho KT, Shiau MY, Chang YH, Chen CM, Yang SC, Huang CN. Association of interleukin-4 promoter polymorphisms in Taiwanese patients with type 2 diabetes mellitus. Metabolism 2010; 59: 1717-1722.

*Correspondence to

Zhang Yuelin

Emergency Surgery

Shaanxi Provincial People's Hospital

Xi'an

PR China