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Cytokines Interleukin 4 (IL-4) and Interleukin 10 (IL-10) Gene Polymorphisms as Potential Host Susceptibility Factors in Virus-Induced Encephalitis

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Background: This study aimed to analyze and explore the relationship between the cytokines IL-4 and IL-10 in relation to gene polymorphism and their respective effects on the susceptibility to virus-induced encephalitis.

Material/Methods: From January 2012 to June 2013, 112 patients with virus-induced encephalitis (the case group and 109 healthy individuals (the control group) were recruited for the purposes of this study. The functional variations that IL-4 and IL-10 genes exhibit were detected through the use of a function analysis and selection tool for single-nucleotide polymorphisms (FASTSNP). The genotypes of IL-4 were rs2227283 and IL-4 rs2227288, and the genotypes of IL-10 were rs1800871 and IL-10 rs1800872. These genotypes were respectively assessed using direct sequencing.

Results: IL-4 rs2227283 and IL-10 rs1800871 have no correlation in with risk of virus-induced encephalitis (both $P>0.05$) GA and AA genotypes were related to IL-4 rs2227288 and GT, while TT and GT + TT genotypes were related to IL-10 rs1800872. These were highlighted as being risk factors in virus-induced encephalitis (all $P<0.05$). However, the duration of fever, white blood cell (WBC) count, C-reactive protein (CRP), neutrophils, and lymphocytes and monocytes of virus-induced encephalitis patients with IL-4 rs2227288 and IL-10 rs1800872 all displayed significant differences (all $P<0.05$). Frequencies of GAGT and CAGT haplotypes were evaluated and deemed to be of statistical significance and subsequently were highlighted as being risk factors in virus-induced encephalitis (all $P<0.05$).

Conclusions: IL-4 rs2227288 and IL-10 rs1800872 may contribute to an increased risk for virus-induced encephalitis. Through use of direct sequencing, we showed that genotypes of IL-4 rs2227288 and IL-10 rs1800872 may have particular host susceptibility to virus-induced encephalitis.

MeSH Keywords: Encephalitis, Arbovirus • Microbial Sensitivity Tests • Transcription Factor TFIIIA

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Background

Virus-induced encephalitis is a life-threatening disorder characterized by inflammation of brain tissue. The inflammation associated with brain parenchyma is linked to and a consequence of viral infections [1–3]. Virus-induced encephalitis is associated with misdiagnosis and delays in recognition, which may have devastating consequences for patients [4]. Additionally, the efficacy of therapies is highly time-dependent due to high morbidity and mortality rates [5,6]. Enterovirus is the main etiological agents of virus-induced encephalitis, followed by mumps, rubella, and Japanese encephalitis virus. However, the lack of unified guidelines in the assessment and management of the illness is a serious limitation [2,7]. The most common symptoms and neurological signs of virus-induced encephalitis are fever, reduced consciousness, seizures, and focal neurological deficits [8–10]. Patients with virus-induced encephalitis suffer from various degrees of renal damage [11]. Additionally, virus-induced encephalitis may cause serious brain damage and bleeding; therefore, prompt diagnosis and early treatment are crucial to prevent the disease from developing, and delayed treatment often results in poor prognosis [1]. In patients who are able to survive the virus-induced encephalitis, impairments of neurologic defect and cognitive, emotional, and behavioral function impairments are common [12]. However, chronic encephalitis has been reported as being uncommon, possibly owing to its viral origins, which may result in the disease being exhibited in patients that have compromised immunity, as well as in healthy individuals [13]. Thus, difficulties are faced in correctly diagnosing patients and subsequently providing prompt therapies for individuals with virus-induced encephalitis [14]. Consequently, it is important to further explore the details and mechanisms involved. At present, increasing numbers of scientific and clinical studies are being initiated to further understand virus-induced encephalitis.

Interleukin 4 (IL-4) and interleukin 10 (IL-10), are 2 cytokines that have been found to have strong links to encephalitis [15–17]. It has been suggested that IL-4 is crucial to the induction of the naive helper T (Th0) cells differentiating to type 2 helper T (Th2) cells [18,19]. IL-4 is known to have 2 different receptor complexes: the IL-4Rα chain and the γc chain [20]. IL-4 has a role in maintaining physiological balance and repairing tissues [21]. Moreover, IL-4 has exhibited in anti-inflammatory functions. IL-4 derived by activated CD4+ T cells can promote allergic responses [20,22,23]. Additionally, IL-10 is a cytokine produced by T cells, B cells, and macrophages, exhibiting a role in anti-inflammation and immunosuppression [24–26]. Virus-induced encephalitis is reported to respond to IL-10 [27]. IL-4 and IL-10 gene polymorphisms have been widely investigated in inflammatory diseases, such as asthma, chronic polyarthritis, rhinovirus bronchiolitis, and type 2 diabetes mellitus (T2DM) [28–31]. Patients previously diagnosed with virus-induced encephalitis formed the basis of the experimental exploration of this study. The IL-4 and IL-10 gene polymorphisms and their correlation to virus-induced encephalitis susceptibility, through direct sequencing, were analyzed during the study.

Material and Methods

Ethic statement

The Ethics Committee of Taizhou Municipal Hospital approved the study. All subjects were given official consent documents that were subsequently agreed upon and signed by all.

Study subjects

Between January 2012 and June 2013, 112 patients (63 males and 49 females) with a mean age of 39.89±15.98 years ranging from 14 to 78 years, participated in the study. All subjects had been previously diagnosed with virus-induced encephalitis and were evaluated during the study as a case group. The control group consisted of 109 healthy individuals. The inclusion criteria were as follows: (1) Patients previously diagnosed with symptoms such as fever of varying degrees, disorders of consciousness, seizure, meningeal irritation sign, pyramidal sign, and intracranial hypertension detected by computed tomography (CT) head scan, electroencephalogram (EEG), and cerebrospinal fluid (CSF), which corresponded to the seventh edition of the diagnostic criteria regarding virus-induced encephalitis [32]; (2) Positive results were detected using reverse transcription-polymerase chain reaction (RT-PCR) of encephalitis virus nucleic acid in the stool of subjects as well as cerebrospinal fluid (CSF) samples. The exclusion criteria were as follows: (1) patients who had experienced mumps, meningo-encephalitis, epidemic encephalitis B, or herpes simplex encephalitis; and (2) Patients that exhibited abnormalities detected by brain CT or magnetic resonance imaging (MRI)

Blood sampling and DNA extraction

Peripheral venous blood samples (3 ml) were collected from healthy individuals as well as virus-induced encephalitis patients in the acute phase (5-day duration) with empty stomachs. The general conditions, signs, symptoms, and other accessory examinations of virus-induced encephalitis patients were recorded within 13 to 20 days from clinical observation to admission. The blood samples (3 ml) were placed in tubes with ethylenediamine tetraacetic acid (EDTA)-K2 and shaken. DNA was extracted using the improved potassium iodide method.

Single-nucleotide polymorphism (SNP) selection and sequencing

Using HapMap database, the genomic data was downloaded. The following methods were used: (1) literature review; (2) Tag

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Table 1. Primer sequences for IL-4 rs2243283/rs2243288 and IL-10 rs1800871/rs1800872.

Gene	SNP	Primer sequence
IL-4	rs2243283	Forward 5'-GGCTGAAAGGGGGAAAGCAT-3'
		Reverse 5'-CCTTGCCGCCAGTCTTTCAT-3'
	rs2243288	Forward 5'-CAGTCATGCAGAAGGCCCAGTA-3'
		Reverse 5'-GGCCAGCAGGTTTTGCCTATTT-3'
IL-10	rs1800871	Forward 5'-TCCCAAGCAGCCCTTCCATT-3'
	rsl800872	Reverse 5'-CCAAATTCTCAGTTGGCACTGG-3'

SNP – single nucleotide polymorphism; F – forward; R – reverse.

Table 2. Baseline characteristics of subjects between the case and control groups.

	Case group	Control group	t/χ^2	*P*
Age	39.89±15.98	40.70±14.52	0.059	0.953
Gender			0.259	0.611
Male	63	65		
Female	49	44		
WBC count (ρ/mg·L^{-1})	6.95±0.88	4.55±0.83	20.845	<0.001
CRP (10^9/L)	9.12±0.49	5.05±0.21	79.870	<0.001
Neutrophils ($\times10^9$)	9.38±2.22	3.88±1.97	19.462	<0.001
Lymphocyte ($\times10^9$)	5.49±1.04	2.37±0.62	26.997	<0.001
Monocyte ($\times10^9$)	3.70±0.33	0.58±0.15	90.064	<0.001

WBC – white blood cell; CRP – C-reactive protein.

SNP selection; and (3) functional variations in IL-4 and IL-10 genes detected by function analysis and selection tool for single-nucleotide polymorphisms (FASTSNP). After selection, IL-4 rs2243283/rs2243288 and IL-10 rs1800871/rsl800872 were eligible for further study.

SNPs detection

The PCR primers were designed by Primer Premier 5.0 and synthesized by Shanghai Sangon BioTech Co., Ltd. (Shanghai, China). The forward and reverse primers of IL-4 and IL-10 gene polymorphisms are shown in Table 1 and IL-10 rs1800871/rsl800872 shared a pair of primers. The total volume of PCR reaction system was 50 μl, including 0.5 μl of DNA template, 5 μl of forward primer and reverse primer, respectively, 25 μl of PCR-pfu mix enzyme, and 14.5 μl of water. After DNA was dissolved, 5-μl samples (concentration >0.1 μg/μl) were assessed using an ultraviolet spectrophotometer on the basis of the ratio (260/280) of the range between 1.8 to 2.1. The PCR reaction conditions were as follows: pre-denaturation at 94°C for 45 s, annealing at 60°C for 45 s, extension at 72°C for 45 s, 39 cycles, and extension at 72°C for 5 min by proper adjustment of annealing temperature according to primer synthesis report.

A total of 1.5 μl of PCR product was detected with 1.0% agarose gel using electrophoresis. The gel was transferred and photographs were taken with an ultraviolet analyzer for observational purposes. Selected PCR product was sequenced in Beijing ZhongKe Xilin Biotechnology Co., Ltd. to determine the genotypes of IL-4 rs2243283, IL-4 rs2243288, IL-10 rs1800871, and IL-10 rsl800872.

Statistical methods

SPSS 19.0 software was used for data analysis. The Hardy-Weinberg equilibrium (HWE) detection was performed for genotype distribution analysis. Measurement data are shown as mean ± standard deviation and compared by *t* test and categorical data are presented as percentage and rate and were examined by the χ^2 test or Fisher's exact test. The odds ratio and 95% confidence intervals were estimated using non-conditional logistic regression analysis. Haplotype analysis of IL-4 and IL-10 genes was performed using Shesis software.

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Table 3. The observed and expected values of the frequencies of IL-4 rs2243283/rs2243288 and IL-10 rs1800871/rs1800872 in the case and control groups.

SNP	Genotype	Case group				Control group			
		E	O	χ^2	*P*	E	O	χ^2	*P*
IL-4 rs2243283				1.613	0.204			3.033	0.082
	CG	34	31			40	35		
	CC	56	62			52	61		
	GG	22	19			17	13		
IL-4 rs2243288				0.033	0.856			2.248	0.134
	GG	27	27			50	53		
	GA	56	55			48	41		
	AA	29	30			11	15		
IL-10 rs1800871				0.447	0.504			3.499	0.061
	GG	20	18			24	19		
	GA	54	58			54	64		
	AA	38	36			31	26		
IL-10 rs1800872				0.557	0.456			2.133	0.144
	GG	8	7			15	19		
	GT	45	48			51	44		
	TT	59	57			43	46		

SNP – single nucleotide polymorphism; E – expected values; O – observed values.

Results

Baseline characteristics of subjects between the case and control groups

There was no significant difference in age and sex of subjects between the case and control groups ($P>0.05$). However, remarkable differences were found in the number of white blood cells (WBC), C-reactive protein (CRP), neutrophils, lymphocytes, and monocytes between the 2 groups (all $P<0.05$, Table 2).

HWE detection in the case and control groups

Genotype frequencies of IL-4 rs2243283/rs2243288 and IL-10 rs1800871/rs1800872 were tested by HWE method. The observed and expected values of each genotype in the case and control groups were compared and chi-square analysis demonstrated no statistically significant difference ($P>0.05$) in the distribution of observed number and the expected number of each genotype in the 2 groups. This allowed for the achievement of genetic balance with group representation (Table 3).

Genotype distributions and allele frequencies in the case and control groups

As shown in Table 4, IL-4 rs2227283 and IL-10 rs1800871 gene polymorphisms were not associated with the risk of virus-induced encephalitis (both $P>0.05$); however, GA, AA, and GA + AA genotypes in IL-4 rs2227288, and GT, TT, and GT + TT genotypes in IL-10 rs1800872, A allele in IL-4 rs2227288, and T allele in IL-10 rs1800872 were risk factors for virus-induced encephalitis (all $P<0.05$).

Correlation of IL-4 and IL-10 genes with the clinical features of patients in the case group

The sex and age of virus-induced encephalitis patients with different genotypes in IL-4 rs2227283/rs2227288 and IL-10 rs1800871/rs1800872 polymorphisms showed no statistically significant difference (all $P>0.05$). There were no clear differences in the duration of fever, CRP, WBCs, neutrophils, lymphocytes, and monocytes in virus-induced encephalitis patients with IL-4 rs2227283 genotype and IL-10 rs1800871 (all $P>0.05$). However, the duration of fever, CRP, WBCs, neutrophils, lymphocytes, and monocytes of virus-induced encephalitis patients with different genotypes in IL-4 rs2227288 and IL-10 rs1800872 showed significant differences (all $P<0.05$, Table 5).

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Table 4. Distributions of genotype and allele frequencies of IL-4 rs2243283/rs2243288 and IL-10 rs1800871/rs1800872 in the case and control groups.

SNP	Genotype	Case group (n=112)		Control group (n=109)		χ^2	OR (95%CI)	*P*
IL-4 rs2243283	CC	31	(27.68)	35	(32.11)	Ref.		
	CG	62	(55.36)	61	(55.96)	0.203	1.148 (0.630~2.089)	0.652
	GG	19	(16.96)	13	(11.93)	1.327	1.650 (0.702~3.882)	0.249
	CG + GG	81	(72.32)	74	(67.89)	0.518	1.236 (0.693~2.201)	0.472
	C	124	(55.36)	131	(60.09)	Ref.		
	G	100	(44.64)	87	(39.91)	1.015	1.214 (0.832~1.772)	0.314
IL-4 rs2243288	GG	27	(24.11)	53	(48.62)	Ref.		
	GA	55	(49.11)	41	(37.62)	9.719	2.633 (1.423~4.872)	0.002
	AA	30	(26.79)	15	(13.76)	12.579	3.926 (1.810~8.514)	0.001
	GA + AA	85	(75.89)	56	(51.38)	14.376	2.980 (1.679~5.286)	< 0.001
	G	109	(48.66)	147	(67.43)	Ref.		
	A	115	(51.34)	71	(32.57)	15.971	2.184 (1.485~3.213)	< 0.001
IL-10 rs1800871	GG	18	(16.07)	19	(17.43)	Ref.		
	GA	58	(51.93)	64	(58.72)	0.014	0.957 (0.458~1.998)	0.906
	AA	36	(32.61)	26	(23.85)	0.829	1.462 (0.645~3.3.14)	0.363
	GA + AA	94	(83.93)	90	(82.57)	0.073	1.103 (0.543~2.235)	0.787
	G	94	(41.96)	102	(46.79)	Ref.		
	A	130	(58.04)	116	(53.21)	1.042	1.216 (0.835~1.771)	0.307
IL-10 rs1800872	GG	7	(6.25)	19	(17.43)	Ref.	1 (Ref.)	
	GT	48	(42.86)	44	(40.37)	5.194	2.961 (1.135~7.722)	0.023
	TT	57	(50.89)	46	(42.20)	6.706	3.363 (1.301~8.696)	0.010
	GT + TT	105	(93.75)	90	(82.57)	6.788	3.202 (1.287~7.969)	0.010
	G	62	(27.68)	82	(37.61)	Ref.	1 (Ref.)	
	T	162	(72.32)	136	(62.39)	4.966	1.575 (1.055~2.353)	0.026

SNP – single nucleotide polymorphism; OR – odd ratio; CI – confidence interval; Ref. – reference.

Haplotype analysis in the case and control groups

Haplotypes of IL-4 rs2227283/rs2227288 and IL-10 rs1800871/rs1800872 are shown in Table 6, which were analyzed by using the Shesis software (haplotypes with the frequency under 0.05 in these 2 groups were excluded). The results revealed that the frequencies of haplotypes (CAAT, GAGT, GAAT, CAGT, and CGGT) showed statistical significance (all $P<0.05$) as the risk factors for virus-induced encephalitis, while the frequencies of several other haplotypes (CGAG, CGGG, GGAG, GGGT, CGAT, and CGAG) showed no significant differences between the 2 groups (all $P>0.05$).

Discussion

During the evaluation of the correlation between encephalitis and other viral infections at similar time points, impairments of the central nervous system and associated inflammation were observed (CNS).

When virus-induced encephalitis was correlated with viral infections, the central nervous system (CNS) also shows associated impairment and inflammation [3,33,34]. Virus-induced encephalitis affected approximately 7.5 people out of every 100 000, with considerable morbidity and mortality rates and displaying an increased risk for development of seizures in approximately 22% of patients [35]. This being said it was of considerable importance that the mechanisms in which

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Table 5. Comparison of IL-4 and IL-10 genes with the clinical features in the case group.

SNP	Genotype	Gender		Age	Duration of fever	CRP (10^9/L)	WBC count (ρ/mg·L-1)	Neutrophils	Lymphocyte	Monocyte
		Male	Female							
IL-4 rs2243283	CG	18	13	41.10± 17.09	2.57± 0.41	9.03± 0.50	6.80± 0.93	8.95± 2.14	5.35± 1.03	3.64± 0.32
	CC	33	29	38.39± 15.67	2.68± 0.43	9.18± 0.49	7.04± 0.87	9.65± 2.29	5.59± 1.07	3.74± 0.35
	GG	12	7	42.84± 15.38	2.59± 0.38	9.06± 0.46	6.87± 0.81	9.21± 2.07	5.40± 0.97	3.67± 0.31
IL-4 rs2243288	GG	14	13	37.37± 12.64	2.12± 0.26	8.51± 0.25	5.91± 0.67	6.52± 1.14	4.12± 0.58	3.29± 0.12
	GA	32	23	41.78± 15.94	2.61± 0.13*	9.09± 0.20*	6.88± 0.23*	9.28± 0.73*	5.51± 0.36*	3.67± 0.3*
	AA	17	13	38.70± 18.63	3.14± 0.26*	9.71± 0.25*	7.99± 0.56*	12.14± 1.07*	6.69± 0.58*	4.14± 0.16*
IL-10 rs1800871	GG	9	9	42.11± 16.33	2.74± 0.32	9.24± 0.41	7.20± 0.67	10.02± 1.91	5.72± 0.79	3.79± 0.30
	GA	33	27	38.21± 16.05	2.68± 0.45	9.17± 0.52	7.05± 0.92	9.64± 2.33	5.63± 1.09	3.75± 0.35
	AA	21	15	41.5± 15.84	2.51± 0.39	9.07± 0.44	6.86± 0.78	9.17± 2.04	5.38± 0.92	3.67± 0.29
IL-10 rs1800872	GG	4	3	37.43± 17.24	1.75± 0.20	8.15± 0.15	4.97± 0.62	4.97± 1.03	3.30± 0.45	3.13± 0.07
	GT	32	16	41.21± 15.51	2.40± 0.15#	8.80± 0.19#	6.51± 0.28#	8.03± 0.96#	4.87± 0.46#	3.47± 0.13#
	TT	27	30	39.09± 16.42	2.94± 0.29#	9.50± 0.30#	7.56± 0.61#	11.06± 1.40#	6.28± 0.61#	3.97± 0.23#

SNP – single nucleotide polymorphism; CRP – C-reactive protein; WBC – white blood cell.

Table 6. Haplotype analysis of rs2243283, rs2243288, rs1800871 and rs1800872 in the case and control groups.

Haplotype				Case group (n=112)	Control group (n=109)	*P*	OR	95% CI
rs2243283	rs2243288	rs1800871	rs1800872					
C	A	A	T	16 (0.149)	8 (0.071)	0.031	1.997	1.056~3.777
C	G	A	G	11 (0.100)	13 (0.119)	0.269	0.713	0.390~1.302
G	A	G	T	6 (0.051)	1 (0.014)	0.049	3.409	0.933~12.462
C	G	G	G	8 (0.073)	6 (0.056)	0.728	1.146	0.532~2.469
G	G	A	G	8 (0.073)	4 (0.041)	0.259	1.619	0.697~3.760
G	A	A	T	13 (0.112)	5 (0.045)	0.025	2.350	1.091~5.062
G	G	G	T	5 (0.042)	8 (0.069)	0.112	0.511	0.220~1.186
C	G	A	T	16 (0.146)	19 (0.171)	0.18	0.703	0.419~1.179
C	A	G	T	23 (0.202)	7 (0.063)	<0.001	3.296	1.738~6.253
C	G	A	G	11 (0.100)	13 (0.102)	0.269	0.713	0.390~1.302
C	G	G	T	2 (0.022)	16 (0.143)	<0.001	0.115	0.044~0.305

OR – odd ratio; CI – confidence interval.

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virus-induced encephalitis work were further explored and understood. Moreover, the diagnosis of encephalopathy can be achieved on the basis of higher serum thyroperoxidase antibody titer (including antithyroglobulin antibodies and antithyroid peroxidase antibody) and clinical manifestations such as brain MRI abnormalities, fever, headache, and stroke. [36]. Anti-thyroid antibodies also play significant roles in the pathogenesis of encephalopathy [14].

Using direct sequencing, our study determined the genotypes of IL-4 rs2243283, IL-4 rs2243288, IL-10 rs1800871, and IL-10 rsl800872 and analyzed the correlation of IL-4 and IL-10 gene polymorphisms with the susceptibility to virus-induced encephalitis, suggesting that IL-4 rs2227288 and IL-10 rs1800872 might enhance the risk for virus-induced encephalitis. Previous studies have suggested that IL-4 and IL-10 were 2 cytokines that have a relationship to encephalitis [15–17,37]. Initially, we found during this study that the A allele, and GA, AA, and GA + AA genotypes in IL-4 rs2227288 were risk factors for virus-induced encephalitis. According to Anovazzi et al., there were strong relationships between the alleles, genotypes, and haplotypes of IL-4 gene polymorphisms and chronic periodontitis [38]. It was suggested that the IL-4-590 T/T and IL-4-33 T/T genotypes were potentially correlated with resistance to therapy in hepatitis C virus patients, and the CT/TT genotypes of IL-4 C-589T was correlated with wheezing without actually having a cold in African Americans infants [39,40]. The etiology of systemic lupus erythematosus (SLE) and elevated risk for SLE were revealed as having correlations with IL-4 gene in a previous study [41], and another study indicated that the IL-4-590 C/T polymorphisms might participate in controlling parasitemia and the result could affect the severity of malaria [42]. Promoter polymorphisms of IL-4, an immune-regulatory Th2 cytokine, were proposed as being related to T2DM and might play a role in the susceptibility to T2DM [43]. Furthermore, IL-4 polymorphisms potentially contribute to evaluation of severity of rheumatoid arthritis (RA), and IL-4-590 promoter polymorphism might be correlated with elevated risk and increased activity of RA [44]. An SNP of IL-4 rs2243250 was demonstrated as being correlated with increased risk of development of *Clostridium difficile* infection in patients with inflammatory bowel disease [45].

We found that T allele, and GT, TT, and GT + TT genotypes in IL-10 rs1800872 were risk factors for virus-induced encephalitis. Attempts to control the subsequent inflammation and decreased tissue destruction were of particular importance to CNS infections, including virus-induced encephalitis, as well as the regulation IL-10 expressions, could possibly diminish the tissue damage in acute encephalitis [37]. IL-10 rs1800872 polymorphism might be a risk factor for colorectal cancer development in European populations and the A/C allele of IL-10 rs1800872 might raise the risk for RA [46,47]. Previous studies have revealed that polymorphisms in IL-10-592C/A (rs1800872) were associated with risk of acute myeloid leukemia and enhanced the likelihood of early-onset preeclampsia [48,49]. IL10-592C/A polymorphisms were correlated with risk factors of coronary heart disease (CHD). Additionally, the A allele may be a risk factor for CHD [50]. Polymorphisms of IL-10 rs1800872 were recorded in order to draw links and data-related correlations with the increased production of IL-10 protein in peritoneal fluid (PF) in endometriosis patients [51]. Furthermore, haplotypes of IL10-rs1800872 had significant correlation with the increase of risk for early pregnancy loss [52].

Conclusions

In conclusion, IL-4 rs2227288 and IL-10 rs1800872 may lead to increased risk in relation to virus-induced encephalitis. This being said, the sample size of this study was relatively small and the range of research should be extended for future research in this particular area. It remains unknown in our study whether IL-4 rs2227288 and IL-10 rs1800872 gene polymorphisms affect the levels of IL-4 and IL-10 and subsequently participate in the pathogenesis of encephalopathy. Further prospective studies should be performed to provide stronger evidence of the underlying mechanisms of IL-4 rs2227288 and IL-10 rs1800872 gene polymorphisms in virus-induced encephalitis.

Conflicts of interest

None.

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