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Correlations of IL-6 and IL-10 gene polymorphisms with childhood acute lymphoblastic leukemia

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Abstract. – OBJECTIVE: The aim of this study was to investigate the correlations between interleukin-6 (IL-6) and IL-10 gene polymorphisms with childhood acute lymphoblastic leukemia.

PATIENTS AND METHODS: Specimens were collected from 200 children with acute lymphoblastic leukemia (disease group) and 200 normal children (control group) in our hospital. DNA was extracted from peripheral blood nucleated cells in both groups to detect the gene polymorphisms rs2069830 and rs2069836 of IL-6, as well as rs3024489 and rs3024493 of IL-10. Then, the content of serum IL-6 and IL-10 was determined via enzyme-linked immunosorbent assay (ELISA).

RESULTS: It was found that there were differences in the distribution of alleles of IL-6 gene polymorphism rs2069830 (p=0.000) and IL-10 gene polymorphism rs3024493 (p=0.007) between the disease group and control group. The frequency of T allele of IL-6 gene polymorphism rs2069830 was higher, while that of IL-10 gene polymorphism rs3024493 was lower in the disease group. Besides, the differences in the distribution of genotypes of IL-6 gene polymorphism rs2069830 (p=0.000) and IL-10 gene polymorphism rs3024493 (p=0.000) were also observed between the disease group and control group. Moreover, the disease group had higher frequencies of TT genotype of IL-6 gene polymorphism rs2069830 and TA genotype of IL-10 gene polymorphism rs3024493. The frequencies of dominant model of IL-6 gene polymorphism rs2069830 (p=0.048) and recessive model of IL-10 gene polymorphism rs3024493 (p=0.000) in the disease group were different from those in the control group. In addition, the frequency of CC + CT dominant model of IL-6 gene polymorphism rs2069830 was lower, and the frequency of TA + AA recessive model of IL-10 gene polymorphism rs3024493 was higher in the disease group. There were differences in haplotypes CG (p=0.001), CT (p=0.007), and TG (p=0.000) of IL-6 gene, as well as haplotypes AA (p=0.002) and AT (p=0.005) of IL-10 gene between disease group and control group. Furthermore, the content of IL-6 in the serum was associated with the genotypes of IL-6 gene polymorphism rs2069830 (p<0.05), whereas the children with acute lymphoblastic leukemia carrying CT genotype had remarkably higher content of serum IL-6. The genotypes of IL-6 gene polymorphism rs2069830 was notably related to white blood cell (WBC) (p=0.002), and the WBC level was higher in children with CT genotype. The genotypes of IL-10 gene polymorphism rs3024489 had prominent correlations with platelet (PLT) (p=0.043), and the children with AA genotype had a higher PLT level. In addition, the genotypes of IL-10 gene polymorphism rs3024493 were evidently correlated with hemoglobin, which was significantly higher in children carrying TA genotype.

CONCLUSIONS: The gene polymorphisms of IL-6 and IL-10 are significantly correlated with the susceptibility to and pathogenesis of childhood acute lymphoblastic leukemia.

Key Words:

Gene polymorphism, Childhood acute lymphoblastic leukemia, Interleukin-6, Interleukin-10.

Introduction

Childhood acute lymphoblastic leukemia, one of the major neoplastic diseases that affect children's health, poses a great threat to the lives of children[1,2]. Long-term exposure to aromatic hydrocarbons or other toxic compounds is the leading cause of childhood acute lymphoblastic leukemia in China. Besides, infection, immunity, and familial factors are also important causes of the disease[3]. After acute granulocytes are produced in children, the proliferative capacity of bone marrow cells will be increased, but the hematopoietic ability of the proliferated bone marrow cells will be reduced substantially or lost completely, resulting in insufficient blood cells

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exported to periphery and leading to dramatic decrease in oxygen carrying capacity, coagulant capacity and immune function of erythrocytes in patients[4,5]. In this process, some cytokines, such as interleukin (ILs) and tumor necrosis factors, are related to the changes in the immune state in children with acute lymphoblastic leukemia, which may be involved in the occurrence and development of the disease.

Gene polymorphism refers to a phenomenon in which alleles exhibit differences in various individuals, probably serving as a vital reason for subtle differences in such phenotypes as skin color and bone mineral density among populations[6,7]. Meanwhile, gene polymorphism is one of the crucial causes of increased susceptibility of different populations to a certain kind of disease. For example, gastric cancer is caused by PSCA gene polymorphism[8], and diabetic retinopathy results from eNOS gene polymorphism[9]. It has been proven that the occurrence of childhood acute lymphoblastic leukemia is associated with the polymorphism of multiple genes, including TPA, TPMT, and NUDT15[10]. IL-6 and IL-10, crucial molecules of the IL system, exert pro-inflammatory and anti-inflammatory effects, respectively.

In this paper, therefore, the correlations of IL-6 and IL-10 gene polymorphisms with the susceptibility to childhood acute lymphoblastic leukemia were explored by studying the gene polymorphisms rs2069830 and rs2069836 of IL-6, as well as gene polymorphisms rs3024489 and rs3024493 of IL-10 in acute lymphoblastic leukemia children and healthy children, comparing the haplotypes of the two genes and combining with the expression levels of serum IL-6 and IL-10 and the clinical indexes of the children.

Patients and Methods

General Data

This study was approved by the Ethics Committee of Binzhou Medical University Hospital. Signed written informed consents were obtained from all participants before the study. A total of 200 children with acute lymphoblastic leukemia and 200 healthy children admitted to and treated in our hospital over the past three years were selected as the subjects. Those with acute lymphoblastic leukemia were assigned into disease group, and the healthy subjects were enrolled into control group. The clinical information of the subjects in both groups were collected, including the children's name, hospital admission ID number, age, gender, history of exposure to highly hazardous substances, family history and history of drug allergy. The average age was (4.34±0.87) years old in the control group and (4.12±0.82) years old in disease group. There were no statistically significant differences in the general data, such as age and gender between control group and disease group ($p>0.05$).

Diagnostic criteria for acute lymphoblastic leukemia in disease group: 1) children, 2) patients with an exposure history of benzene and other organic compounds, 3) those with relevant symptoms, such as hemorrhage, anemia and infectious fever, 4) those with enlargement of liver, spleen and lymph node, 5) those with abnormal peripheral blood routine and leukemic cells, and 6) those with blast and immature cells in the bone marrow ≥30%.

Sample Collection and Processing

About 3 mL of peripheral blood samples were drawn from disease group and control group by nurses on duty in the Pediatric Department. After that, the samples were placed in a centrifuge (Beckman Coulter, Miami, FL, USA) within 2 h for centrifugation at 3,000 r/min for 10 min, followed by careful separation of the supernatant and middle layer nucleated cells into new centrifuge tubes. The supernatant was stored in liquid nitrogen to detect the levels of ILs, while the middle-layer nucleated cells were applied to extract genomic deoxyribonucleic acid (DNA).

Extraction of Genomic DNA

The genomic DNA in the peripheral blood of disease group and control group was extracted using blood genomic DNA extraction kit (Tiangen, Beijing, China) in strict accordance with the standards in the kit. Specifically, 200 μL of proteinase K solution was added into the centrifuge tubes according to the sample volume, and the peripheral blood samples and 2 mL of buffer solution GE were added, mixed in a vortex oscillator for 1 min and placed at 65°C for 5 min. Then, the samples were mixed with 2 mL of absolute alcohol and transferred into adsorption columns, into which 2 mL of buffer solution was added for centrifugation at 4000 r/min for 1 min. Later, the buffer solution was added into the adsorption columns and centrifuged. After 200 μL

of elution buffer was added into the adsorption columns, the solution obtained was the genomic DNA of the subjects.

Polymerase Chain Reaction (PCR) Amplification and Analysis of IL-6 and IL-10 Gene Polymorphisms

The regions of gene polymorphisms rs2069830 and rs2069836 of IL-6 and rs3024489 and rs3024493 of IL-10 were amplified separately using a PCR instrument with a total reaction system of 25 μL, including 1 μL of each primer, 0.5 μL of template DNA, 12.5 μL of Taq polymerase and 9.5 μL of dH_2O (Thermo Fisher Scientific, Waltham, MA, USA). PCR conditions: 95°C for 5 min, (94°C for 30 s, 56°C for 40 s and 72°C for 30 s) ×45 cycles, 72°C for 5 min, and incubation at 4°C. The primers for polymorphisms are as follows: polymorphism rs2069830 of IL-6 gene: forward (5'-3'): ACTCACCTCTTCAGAACGAATTG and reverse (5'-3'): CCATCTTTGGAAGGTTCAGGTTG, polymorphism rs2069836 of IL-6 gene: forward (5'-3'): CCTGAACCTTCCAAAGATGGC and reverse (5'-3'): TTCACCAGGCAAGTCTCCTCA, polymorphism rs3024489 of IL-10 gene: forward (5'-3'): CTGCAAGAGACTTCCATCCAG and reverse (5'-3'): AGTGGTATAGACAGGTCTGTTGG, and polymorphism rs3024493 of IL-10 gene: forward (5'-3'): TCTATACCACTTCACAAGTCGGA and reverse (5'-3'): GAATTGCCATTGCACAACTCTTT. GAPDH: forward (5'-3') CTGGGCTACACTGAGCACC, and reverse (5'-3'): AAGTGGTCGTTGAGGGCAATG. The PCR products were sent to Shanghai Biotechnology Co., Ltd. (Shanghai, China) for sequencing, and the gene polymorphisms of IL-6 and IL-10 in the disease group and control group were analyzed.

Detection of Serum IL-6 and IL-10 Levels

The levels of serum IL-6 and IL-10 were measured by means of enzyme-linked immunosorbent assay. The serum samples preserved in liquid nitrogen were thawed slowly, and the levels of serum IL-6 and IL-10 in disease group and control group were determined using the kits (Thermo Fisher Scientific, Waltham, MA, USA) and Luminex 300 system (Luminex Corporation, Austin, TX, USA) according to the instructions of Thermo Fisher Scientific (Invitrogen Corporation, Carlsbad, CA, USA). At last, the average sensitivity of the test was <0.48 pg/mL, and the inter-assay coefficient of variation was 5.1%.

Clinical Correlation Analysis

The indexes of clinical association and disease progression were determined for the subjects in disease group and control group. The peripheral blood was drawn from the children by the nurses on duty, and then, sent to the clinical testing center of the Department of Clinical Laboratory for detection, and morphological changes of the cells were observed through smears. The indexes examined included white blood cell (WBC), platelet (PLT), and hemoglobin (Hb).

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 23.0 software (IBM Corp., Armonk, NY, USA) was employed for statistical analysis. The enumeration data were compared *via* χ^2 test and subjected to Hardy-Weinberg equilibrium test. Haplotypes were analyzed online using SHEsis website, and $p<0.05$ suggested statistically significant differences.

Results

Distribution of Alleles of Gene Polymorphisms rs2069830 and rs2069836 of IL-6 and rs3024489 and rs3024493 of IL-10

The distribution of allele frequencies of gene polymorphisms rs2069830 and rs2069836 of IL-6, as well as rs3024489 and rs3024493 of IL-10, is shown in Table I. There were differences in the distribution of alleles of IL-6 gene polymorphism rs2069830 (p=0.000) and IL-10 gene polymorphism rs3024493 (p=0.007) between the disease group and control group. The frequency of T allele of IL-6 gene polymorphism rs2069830 was higher, while that of IL-10 gene polymorphism rs3024493 was lower in disease group.

Distribution of Genotypes of Gene Polymorphisms rs2069830 and rs2069836 of IL-6 and rs3024489 and rs3024493 of IL-10

The distribution of genotypes of gene polymorphisms rs2069830 and rs2069836 of IL-6, as well as rs3024489 and rs3024493 of IL-10 is shown in Table II. The differences in the distribution of genotypes of IL-6 gene polymorphism rs2069830 (p=0.000) and IL-10 gene polymorphism rs3024493 (p=0.000) were observed be-

Table I. Distribution of alleles of gene polymorphisms rs2069830 and rs2069836 of IL-6 and rs3024489 and rs3024493 of IL-10.

Gene	Polymorphism	Allele	Control group	Disease group	Odds ratio (OR)	95% confidence interval (95% CI)	χ^2	*p*
IL-6	rs2069830	C	210 (0.525)	140 (0.350)	0.48	0.36-0.64	24.88	0.000
		T	190 (0.475)	260 (0.650)				
	rs2069836	G	196 (0.490)	226 (0.565)	1.35	1.02-1.78	4.01	0.085
		T	204 (0.510)	174 (0.435)				
IL-10	rs3024489	C	214 (0.535)	210 (0.525)	1.04	0.78-1.37	0.08	0.776
		A	186 (0.465)	190 (0.475)				
	rs3024493	T	226 (0.565)	188 (0.470)	1.46	1.10-1.93	7.22	0.007
		A	174 (0.435)	212 (0.530)				

tween disease group and control group. In addition, disease group had higher frequencies of TT genotype of IL-6 gene polymorphism rs2069830 and TA genotype of IL-10 gene polymorphism rs3024493.

Analysis on Gene Polymorphisms rs2069830 and rs2069836 of IL-6 and rs3024489 and rs3024493 of IL-10 and Model Analysis

According to the analysis on gene polymorphisms rs2069830 and rs2069836 of IL-6 and rs3024489 and rs3024493 of IL-10, as well as model analysis (Table III), the frequencies of dominant model of IL-6 gene polymorphism rs2069830 (p=0.048) and recessive model of IL-10 gene polymorphism rs3024493 (p=0.000) in the disease group were different from those in control group. Besides, the frequency of CC + CT dominant model of IL-6 gene polymorphism rs2069830 was lower, and that of TA + AA recessive model of IL-10 gene polymorphism rs3024493 was higher in disease group.

Analysis of Haplotypes of Gene Polymorphisms rs2069830 and rs2069836 of IL-6 and rs3024489 and rs3024493 of IL-10

The analysis of haplotypes of gene polymorphisms rs2069830 and rs2069836 of IL-6 and rs3024489 and rs3024493 of IL-10 (Table IV) manifested that there were differences in the haplotypes CG (p=0.001), CT (p=0.007) and TG (p=0.000) of IL-6 gene as well, as the haplotypes AA (p=0.002) and AT (p=0.005) of IL-10 gene between disease group and control group.

Analysis of Correlations of Genotypes of Gene Polymorphisms rs2069830 and rs2069836 of IL-6 and rs3024489 and rs3024493 of IL-10 with Content of Serum IL-6 and IL-10

Based on the analysis of correlations of genotypes of gene polymorphisms rs2069830 and rs2069836 of IL-6 and rs3024489 and rs3024493

Table II. Distribution of genotypes of gene polymorphisms rs2069830 and rs2069836 of IL-6 and rs3024489 and rs3024493 of IL-10.

Gene	Polymorphism	Genotype	Control group	Disease group	χ^2	*p*
IL-6	rs2069830	CC	59 (0.295)	38 (0.190)	25.91	0.000
		CT	92 (0.460)	64 (0.320)		
		TT	49 (0.245)	98 (0.490)		
	rs2069836	GG	42 (0.210)	62 (0.310)	5.53	0.062
		GT	112 (0.560)	102 (0.510)		
		TT	46 (0.230)	36 (0.180)		
IL-10	rs3024489	CC	58 (0.290)	58 (0.290)	0.25	0.879
		CA	98 (0.490)	94 (0.470)		
		AA	44 (0.220)	48 (0.240)		
	rs3024493	TT	61 (0.305)	29 (0.145)	14.74	0.000
		TA	104 (0.520)	130 (0.650)		
		AA	35 (0.175)	41 (0.205)		

Table III. Analyses on gene polymorphisms rs2069830 and rs2069836 of IL-6 and rs3024489 and rs3024493 of IL-10 and model analysis.

	Gene	Polymorphism	Genotype	Control group	Disease group	χ^2	*p*
Dominant model	IL-6	rs2069830	CC + TT	151 (0.755)	102 (0.510)	3.89	0.048
			TT	49 (0.245)	98 (0.490)		
		rs2069836	GG + GT	154 (0.770)	164 (0.820)	0.08	0.777
			TT	46 (0.230)	36 (0.180)		
	IL-10	rs3024489	CC + CA	156 (0.780)	152 (0.760)	2.27	0.132
			AA	44 (0.220)	48 (0.240)		
		rs3024493	TT + TA	165 (0.825)	159 (0.795)	3.08	0.079
			AA	35 (0.175)	41 (0.205)		
Recessive model	IL-6	rs2069830	CC	59 (0.295)	38 (0.190)	1.41	0.235
			GT + TT	141 (0.705)	138 (0.690)		
		rs2069836	GG	42 (0.210)	62 (0.310)	2.68	0.102
			GT + TT	158 (0.790)	138 (0.690)		
	IL-10	rs3024489	CC	58 (0.290)	58 (0.290)	2.65	0.104
			CA + AA	142 (0.710)	142 (0.710)		
		rs3024493	TT	61 (0.305)	29 (0.145)	9.34	0.009
			TA + AA	139 (0.695)	171 (0.855)		
Heterozygous model	IL-6	rs2069830	CC	59 (0.295)	38 (0.190)	3.23	0.199
			CT	92 (0.460)	64 (0.320)		
		rs2069836	GG	42 (0.210)	62 (0.310)	1.51	0.219
			GT	112 (0.560)	102 (0.510)		
	IL-10	rs3024489	CC	58 (0.290)	58 (0.290)	3.31	0.069
			CA	98 (0.490)	94 (0.470)		
		rs3024493	TT	61 (0.305)	29 (0.145)	0.28	0.597
			TA	104 (0.520)	130 (0.650)		
Homozygous model	IL-6	rs2069830	CC	59 (0.295)	38 (0.190)	0.93	0.335
			TT	49 (0.245)	98 (0.490)		
		rs2069836	GG	42 (0.210)	62 (0.310)	1.67	0.196
			TT	46 (0.230)	36 (0.180)		
	IL-10	rs3024489	CC	58 (0.290)	58 (0.290)	0.8	0.371
			AA	44 (0.220)	48 (0.240)		
		rs3024493	TT	61 (0.305)	29 (0.145)	3.29	0.070
			AA	35 (0.175)	41 (0.205)		

of IL-10 with the content of serum IL-6 and IL-10 (Figures 1-4), the content of IL-6 in the serum was associated with the genotypes of IL-6 gene polymorphism rs2069830 ($p<0.05$), where the children with acute lymphoblastic leukemia carrying CT genotype had a remarkably higher level of serum IL-6.

Correlations of Genotypes of Gene Polymorphisms rs2069830 and rs2069836 of IL-6 and rs3024489 and rs3024493 of IL-10 with Clinical Indexes

The correlations of genotypes of gene polymorphisms rs2069830 and rs2069836 of IL-6 and rs3024489 and rs3024493 of IL-10 with clinical

Table IV. Analysis of haplotypes of gene polymorphisms rs2069830 and rs2069836 of IL-6 and rs3024489 and rs3024493 of IL-10.

Gene	Haplotype	Control group	Disease group	OR	95% CI	χ^2	*p*
IL-6	CG	106.93 (0.267)	68.32 (0.171)	0.565	0.401-0.795	10.892	0.001
	CT	103.07 (0.258)	71.68 (0.179)	0.629	0.448-0.884	7.215	0.007
	TG	89.07 (0.223)	157.68 (0.394)	2.272	1.667-3.095	27.585	0.000
	TT	100.93 (0.252)	102.32 (0.256)	1.019	0.741-1.400	0.013	0.910
IL-10	AA	74.11 (0.185)	112.04 (0.280)	1.711	1.226-2.388	10.072	0.002
	AT	111.89 (0.280)	77.96 (0.195)	0.623	0.448-0.867	7.951	0.005
	CA	99.89 (0.250)	99.96 (0.250)	1.001	0.727-1.379	0	0.995
	CT	114.11 (0.285)	110.04 (0.275)	0.951	0.698-1.295	0.103	0.749

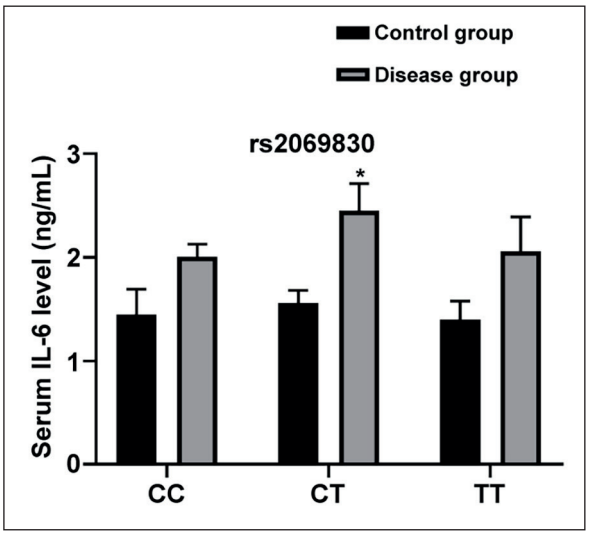

Figure 1. Correlations of genotypes of IL-6 gene polymorphism rs2069830 with serum IL-6 level (*p<0.05 *vs.* CC or TT genotype in disease group and control group).

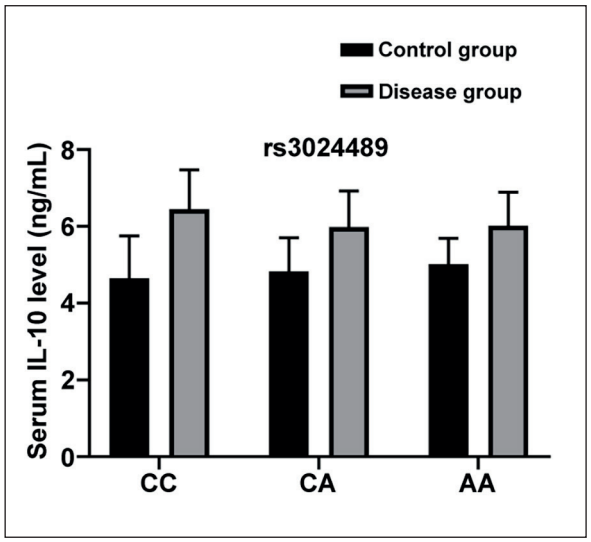

Figure 3. Correlations of genotypes of IL-10 gene polymorphism rs3024489 with serum IL-10 level.

indexes are displayed in Table V. It could be seen that the genotypes of IL-6 gene polymorphism rs2069830 was notably related to WBC (p=0.002), and the WBC level was higher in children with CT genotype. The genotypes of IL-10 gene polymorphism rs3024489 had prominent correlations with PLT (p=0.043), and the children with AA genotype had a higher PLT level. The genotypes of IL-10 gene polymorphism rs3024493 were evidently associated with Hb, which was obviously higher in children carrying TA genotype.

Discussion

Childhood acute lymphoblastic leukemia is a fairly common malignant disease of the hematopoietic system in children. Given the acute onset, the mortality rate of the disease will be high if not treated in time[11,12]. However, the high price of targeted drugs for childhood acute lymphoblastic leukemia brings huge economic burdens to the patients' family and hinders the development of social economy. There is a great majority of lymphocytes with hypofunction in the bone marrow

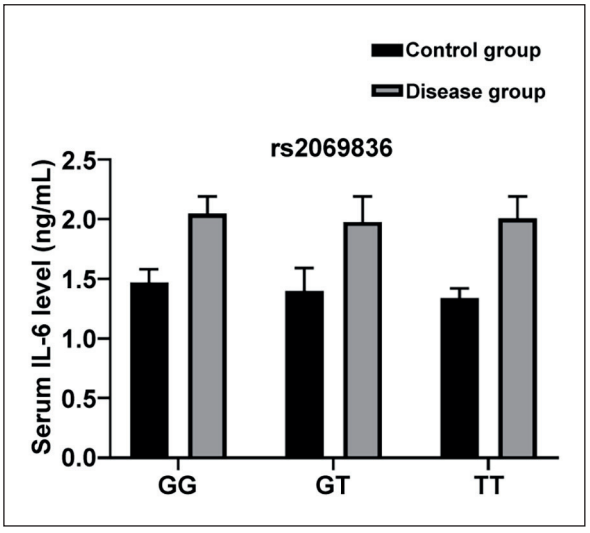

Figure 2. Correlations of genotypes of IL-6 gene polymorphism rs2069836 with serum IL-6 level.

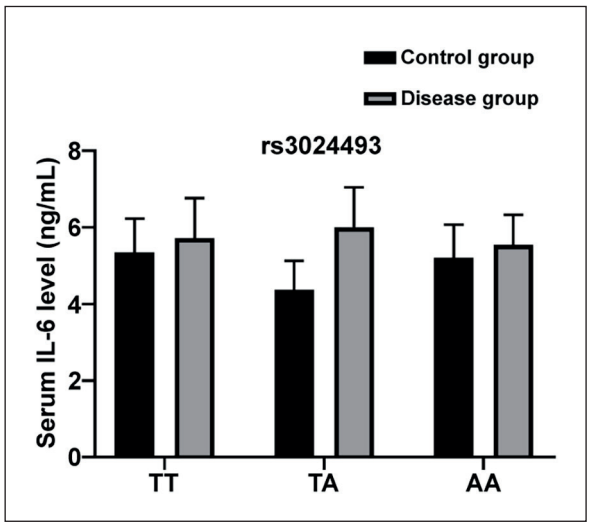

Figure 4. Correlations of genotypes of IL-10 gene polymorphism rs3024493 with serum IL-10 level.

Table V. Correlations of genotypes of gene polymorphisms rs2069830 and rs2069836 of IL-6 and rs3024489 and rs3024493 of IL-10 with clinical indexes.

Gene	Polymorphism	Genotype	WBC (×10⁹/L)			PLT (×10⁹/L)			Hb (g/L)		
			Control group	Disease group	*p*	Control group	Disease group	*p*	Control group	Disease group	*p*
IL-6	rs2069830	CC	7.54	52.13	0.002	231	78	0.372	122	74	0.124
		CT	8.96	69.43		196	89		116	82	
		TT	6.35	46.45		234	103		121	94	
	rs2069836	GG	8.56	51.26	0.263	221	88	0.273	116	92	0.224
		GT	7.45	57.42		202	94		119	78	
		TT	8.52	43.21		219	87		120	82	
IL-10	rs3024489	CC	6.95	44.67	0.125	197	67	0.043	105	87	0.176
		CA	7.94	45.96		185	89		121	91	
		AA	7.44	51.27		235	102		108	84	
	rs3024493	TT	7.12	53.35	0.098	215	88	0.253	105	71	0.031
		TA	6.86	56.41		187	79		121	93	
		AA	8.85	61.54		221	93		102	76	

and peripheral blood in the case of childhood acute lymphoblastic leukemia, which induces systemic immune dysfunction and compromised adaptive immune response, thus reducing their defense against external stimuli[13,14]. Some cytokines can reactivate the immune system and may play important roles in childhood acute lymphoblastic leukemia.

ILs act as vital substances modulating immunity in organisms and have important functions of promoting lymphocyte differentiation and regulating cell proliferation[15], and they probably occupy key positions in acute lymphoblastic leukemia and influence the occurrence and development of the disease. IL-6 participates in the differentiation of lymphocytes and monocytes, stimulates the generation and secretion of antibodies by B lymphocytes, and exerts positive regulatory effects on immunity in organisms. IL-6 gene polymorphism has been indicated to be correlated with lung cancer[16], keloid[17], and obesity of postmenopausal women[18]. As a negative regulatory factor for the immune system, IL-10 is capable of inhibiting the lymphocytes to secret inflammatory factors, decreasing immune responses and coordinating with other cytokines to regulate immune state *in vivo*. Besides, IL-10 gene polymorphism is also associated with the susceptibility to specific diseases, including cardiovascular disease[19] and psoriasis[20]. It was found in this study that the distribution of alleles of IL-6 gene polymorphism rs2069830 (p=0.000) and IL-10 gene polymorphism rs3024493 (p=0.007) exhibited differences between disease group and control group. Disease group had a higher frequency of T allele of IL-6 gene polymorphism rs2069830 and a lower frequency of IL-10 gene polymorphism rs3024493, suggesting that the gene polymorphisms of IL-6 and IL-10 have impacts on the susceptibility to childhood acute lymphoblastic leukemia. Moreover, the distribution of genotypes of IL-6 gene polymorphism rs2069830 (p=0.000) and IL-10 gene polymorphism rs3024493 (p=0.000) in the disease group was different from that in control group, that is, the frequencies of TT genotype of IL-6 gene polymorphism rs2069830 and TA genotype of IL-10 gene polymorphism rs3024493 were higher in the disease group. These results illustrated that the children carrying specific genotypes manifest various degrees of susceptibility to acute lymphoblastic leukemia. In addition, the children with TT genotype of IL-6 gene polymorphism rs2069830 and TA genotype of IL-10 gene polymorphism rs3024493 had increased susceptibility to the disease, so those genotypes should be particularly monitored for high-risk age groups, and the signs of leukemia need to be examined regularly.

The conjoint analysis revealed that there were differences in the frequencies of dominant model of IL-6 gene polymorphism rs2069830 (p=0.048) and recessive model of IL-10 gene polymorphism rs3024493 (p=0.000) between the disease group and control group. The frequency of CC + CT dominant model of IL-6 gene polymorphism rs2069830 was lower, while that of TA + AA recessive model of IL-10 gene polymorphism rs3024493 was higher in the disease group, demonstrating that the two genotypes of the same polymorphism may enhance the susceptibility to childhood acute lymphoblastic leuke-

mia. Moreover, the haplotype analysis revealed the differences in the haplotypes CG (p=0.001), CT (p=0.007) and TG (p=0.000) of IL-6 gene, as well as the haplotypes AA (p=0.002) and AT (p=0.005) of IL-10 gene between disease group and control group. The susceptibility to acute lymphoblastic leukemia may also be changed in children with specific haplotypes of IL-6 and IL-10 genes.

The detection of serum IL-6 and IL-10 levels in the serum showed that the content of serum IL-6 had correlations with the genotypes of IL-6 gene polymorphism rs2069830 (p<0.05), and the children with acute lymphoblastic leukemia carrying CT genotype had a remarkably higher level of serum IL-6, illustrating that IL-6 and IL-10 gene polymorphisms probably influence childhood acute lymphoblastic leukemia by altering the levels of serum IL-6 and IL-10. Meanwhile, it was discovered that the genotypes of IL-6 gene polymorphism rs2069830, IL-10 gene polymorphism rs3024489, and IL-10 gene polymorphism rs3024493 had distinct correlations with WBC (p=0.002), PLT (p=0.043) and Hb, respectively, and the levels of WBC, PLT, and Hb were higher in children with CT genotype, AA genotype and TA genotype, respectively. The above findings elaborated that IL-6 and IL-10 gene polymorphisms can actually influence the clinical indexes, thus affecting the progression of children's disease, and intensive care should be given to the children carrying specific genotypes during the occurrence of acute lymphoblastic leukemia.

Conclusions

The results of this study demonstrated that the gene polymorphisms of IL-6 and IL-10 are significantly correlated with the susceptibility and pathogenesis of childhood acute lymphoblastic leukemia.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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