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Correlations of IL-1 and IL-6 Gene polymorphisms with hypertrophic cardiomyopathy

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Abstract

The purpose of this study was to explore the correlations of interleukin-1 (IL-1) and IL-6 gene polymorphisms with hypertrophic cardiomyopathy (HCM). A total of 200 patients with HCM were enrolled as disease group, and 200 healthy individuals were included as control group. Peripheral blood was collected from all subjects in both disease and control groups. Gene polymorphisms and serum expression levels of IL-1 and IL-6 were detected, and conjoint analysis was performed based on results of cardiac color Doppler ultrasound examination. The allele distribution of IL-1 rs1878320 showed a difference between disease and control groups (P=0.000). The frequency of the allele T was lower in disease group. The genotype distribution of IL-1 rs1878320 (P=0.001) and IL-6 rs1474347 (P=0.000) in disease group was different from that in control. The frequency of TC genotype of IL-1 rs1878320 was lower in disease group, and that of CA genotype of IL-6 rs1474347 was higher in disease group. There was a difference in the distribution of the dominant model of IL-6 rs1474347 between disease and control groups (P=0.021), and the frequency of CC + CA in the dominant model was 171 (0.855). The frequency of AC haplotype of IL-1 gene was overtly higher in disease group (P=0.000), while the frequency of AT haplotype was lower in disease group (P=0.000). The IL-1 rs1516792 polymorphism had an association with serum IL-1 level (P<0.05), the IL-1 level was notably increased in the patients with the genotype AA, and it was higher in disease group. The polymorphism of rs1878320 locus in IL-1 gene was correlated with interventricular septal (IVS) (P=0.047), and IVS was reduced in the patients with TC genotype. The polymorphism of rs1516792 locus in IL-1 gene was distinctly related to left ventricular outflow tract (LVOT) (P=0.041), and LVOT was lowered in the patients with GG genotype. The IL-6 rs2069831 polymorphism was associated with left ventricular ejection fraction (LVEF) (P=0.035), and LVEF declined in the patients with TT genotype. The IL-1 and IL-6 gene polymorphisms are correlated with the susceptibility and progression of HCM.

Keywords: Gene polymorphism, Hypertrophic cardiomyopathy, IL-1, IL-6

1. Introduction

Hypertrophic cardiomyopathy (HCM) is one of the important causes of sudden cardiac death in young and middle-aged people [1,2]. Most patients with HCM suffer from pathological changes of unknown causes, including asymmetrical and uneven thickening of the ventricular wall, resulting in a sharp decrease in blood volume in the heart and insufficient cardiac ejection, and further enhancing systole and inducing sudden death [3]. The development of HCM is mainly associated with gene mutations and other family genetic factors, most of which are genes related to structural proteins encoding sarcomere [4]. Besides, inflammatory and immune responses may participate in the pathogenesis of HCM, and the changes in the expression of various cytokines including SGLT1 and interleukin-18 (IL-18) [5] promote the progression of heart disease and aggravate the condition. As important biological media promoting inflammation and immunity, IL-1 and IL-6 can facilitate the differentiation of various immune cells, repress apoptosis and accelerate the development of HCM.

Genetic polymorphisms affect the susceptibility and progression of various diseases, such as metastatic muscle disease [6], which mainly control the changes of the same allele in different populations, leading to different susceptibility of these populations to various diseases, and potentially affecting their progression. They are important factors in monitoring and controlling the development of diseases [7,8]. HCM has been proven to be affected by the polymorphism of multiple genes like angiotensin-converting enzyme-related genes [9] and TLR4 [10]. IL-1 and IL-6 are important pro-inflammatory and pro-immune substances, that play a vital role in HCM, but the relationships of their polymorphisms with the disease have not been reported.

In this study, therefore, the associations of IL-1 and IL-6 gene polymorphisms with HCM were investigated by analyzing the polymorphisms of the loci rs1516792

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and rs1878320 in IL-1 gene and the loci rs1474347 and rs2069831 in IL-6 gene in HCM patients and healthy people, statistically analyzing the frequency of alleles and genotypes of the subjects, and analyzing the distribution of haplotype, based on such clinical data as the results of cardiac color Doppler ultrasound examination.

2. Materials and methods

2.1. General data

A total of 200 patients with HCM (disease group) and 200 healthy individuals (control group) in our hospital were selected as subjects. The general data such as name, gender and age and clinical data like incidence, treatment method, disease history, family history and drug allergy history in each group were collected. The mean age was (37.11±5.24) years old in disease group and (36.28±4.28) years old in control group. There were no significant differences in such general data as age and gender between disease group and control group. This study was approved by the Ethics Committee of Hainan West Central Hospital. Signed written informed consents were obtained from all participants before the study.

Inclusion criteria for patients with HCM in disease group: 1) patients who were mainly young adults with family history, 2) those with clinical symptoms like palpitation, paroxysmal dyspnea and chest pain, 3) those with signs such as a ratio of ventricular septal hypertrophy to left ventricular free wall thickness >1.5 cm, small ventricular cavity and ventricular outflow tract stenosis on ultrasonic cardiograms, 4) those with cardiac hypertrophy based on cardiac magnetic resonance imaging (MRI) results, and 5) those with hypertrophic cardiomyocytes found via myocardial biopsy

2.2. Methods

2.2.1. Sample collection and treatment

Peripheral blood (10 mL) was collected from subjects in disease group and control group by undergraduate nurses, sent to the clinical lab within 2 h, and centrifuged at 3500 rpm for 10 min to separate and severally transfer the middle karyocyte layer and the upper serum to new centrifuge tubes for genomic deoxyribonucleic acid (DNA) extraction and further detection.

2.2.2. Extraction of genomic DNA

Genomic DNA was extracted from the peripheral blood of 400 subjects in disease group and control group using a blood genomic DNA extraction kit (TIANGEN, Beijing, China) in strict accordance with the standard operations of the kit: proteinase K solution (200 μL, determined based on the sample volume), peripheral blood samples of disease group and control group and buffer GE (about 200 μL) were successively added to the centrifuge tube, mixed using a vortex oscillator for 1 min and let stand at 65°C for 5 min. Thereafter, the samples were added with 2 mL of absolute ethanol, mixed and transferred to an adsorption column. Then, 2 mL of buffer was added to the adsorption column, and centrifuged at 3500 rpm for 1 min. Next, buffer was added to the adsorption column and centrifuged. After that, 200 μL of elution buffer was added to the adsorption column, and the resulting solution was the genomic DNA of disease group and control group.

2.2.3. Polymerase chain reaction (PCR) amplification and IL-1 and IL-6 gene polymorphism analysis

The polymorphic regions of loci rs1516792 and rs1878320 in IL-1 gene and rs1474347 and rs2069831 in IL-6 gene were amplified using a PCR instrument. The total PCR reaction system was 25 μL in volume, containing 1 μL of forward primer, 1 μL of reverse primer, 0.5 μL of template DNA, 12.5 μL of Taq enzyme and 9.5 μL of deionized water. The PCR conditions: 95°C for 5 min, 40 cycles of 95°C for 30 s, 56°C for 45 s, and 72°C for 35 s, and 72°C for 5 min. The polymorphic site primers: polymorphism region of IL-1 rs1516792: forward primer (5'→3') ACTCACCTCTTCAGAACGAATTG, reverse primer (5'→3') CCATCTTTGGAAGGTTCAGGTTG, polymorphism region of IL-1 rs1878320: forward primer (5'→3') CCTGAACCTTCCAAAGATG, reverse primer (5'→3') TTCACCAGGCAAGTCTCCTCA. IL-6 rs1474347 polymorphism region: forward primer (5'→3') CTGCAAGAGACTTCCATCCAG, reverse primer (5'→3') AGTGGTATAGACAGGTCTGTTGG. IL-6 rs2069831 polymorphism region: forward primer (5'→3') TCTATACCACTTCACAAGTCGGA, reverse primer (5'→3') GAATTGCCATTGCACAACTCTTT. The products of PCR were sent to Hangzhou Biotechnology Co., Ltd. (Hangzhou, China) for sequencing, and the polymorphisms of IL-1 and IL-6 loci in disease group and control group were obtained via analysis.

2.2.4. Measurement of serum IL-1 and IL-6 levels in disease group and control group

The levels of IL-1 and IL-6 in peripheral blood in disease group and control group were measured through enzyme-linked immunosorbent assay using a IL-1 assay kit and a IL-6 assay kit (R&D, Minneapolis, MN, USA) in strict accordance with the instructions of the kits. Three replicates were set for each well. After the assay was completed, the absorbance value was read at a wavelength of 450 nm using a microplate reader (Bio-Rad, Hercules, CA, USA), and the levels of IL-1 and IL-6 in disease group and control group were obtained after conversion based on standard curves.

2.3. Echocardiography in disease group and control group

Cardiac color Doppler ultrasound examination was adopted to detect such indicators as interventricular septal (IVS) thickness, left ventricular outflow tract (LVOT) width and left ventricular ejection fraction (LVEF) of the heart in disease group and control group.

2.4. Statistical analysis

Statistical Product and Service Solutions (SPSS) 23.0 software (IBM, Armonk, NY, USA) was used for statistical analysis. χ^2 test was employed for comparison among enumeration data, and the Hardy-Weinberg equilibrium test was performed. Haplotype analysis was conducted online using the SHEsis website. GraphPad Prism 8.0 (La Jolla, CA, USA) was utilized for plotting. $P<0.05$ suggested that the difference was statistically significant.

3. Results

3.1. Allele distribution of IL-1 rs1516792 and rs1878320 and IL-6 rs1474347 and rs2069831

The allele distribution of the loci rs1516792 and rs1878320 in IL-1 gene and rs1474347 and rs2069831 in

IL-6 gene (Table 1) revealed that the allele distribution of IL-1 rs1878320 was different between disease group and control group (P=0.000): the frequency of T allele was lower in disease group than that in control group.

3.2. Genotype distribution of IL-1 rs1516792 and rs1878320 and IL-6 rs1474347 and rs2069831

The genotype distribution of the loci rs1516792 and rs1878320 in IL-1 gene and rs1474347 and rs2069831 in IL-6 gene (Table 2) showed that there was a difference in the genotype distribution of IL-1 rs1878320 (P=0.001) and IL-6 rs1474347 (P=0.000) between disease group and control group: the frequency of TC genotype of IL-1 rs1878320 was lower in disease group than that in control group, and that of CA genotype of IL-6 rs1474347 was higher in disease group than that in control group.

3.3. Polymorphism analysis of IL-1 rs1516792 and rs1878320 and IL-6 rs1474347 and rs2069831

The polymorphism analysis of IL-1 rs1516792 and rs1878320 and IL-6 rs1474347 and rs2069831 was shown in Table 3. A difference was detected in the distribution of the dominant model of IL-6 rs1474347 between disease group and control group (P=0.021): the frequency of CC + CA in the dominant model was 171 (0.855).

3.4. Haplotype analysis of IL-1 rs1516792 and rs1878320 and IL-6 rs1474347 and rs2069831

Based on the haplotype analysis of IL-1 rs1516792 and rs1878320 and IL-6 rs1474347 and rs2069831 (Table 4), the frequency of AC haplotype of IL-1 gene was overtly higher in disease group than that in control group (P=0.000), while the frequency of AT haplotype was lower in disease group than that in control group (P=0.000).

3.5. Correlations of genotypes of IL-1 rs1516792 and rs1878320 and IL-6 rs1474347 and rs2069831 with serum IL-1 and IL-6 levels

The correlations of genotypes of IL-1 rs1516792 and rs1878320 and IL-6 rs1474347 and rs2069831 with serum IL-1 and IL-6 levels were displayed in Figure 1-4. The polymorphism of IL-1 rs1516792 was associated with serum IL-1 level (P<0.05), the IL-1 level was notably increased in the patients carrying AA genotype, and it was higher in disease group than that in control group.

3.6. Correlations of genotypes of IL-1 rs1516792 and rs1878320 and IL-6 rs1474347 and rs2069831 with echocardiographic indexes

The relations of genotypes of IL-1 rs1516792 and

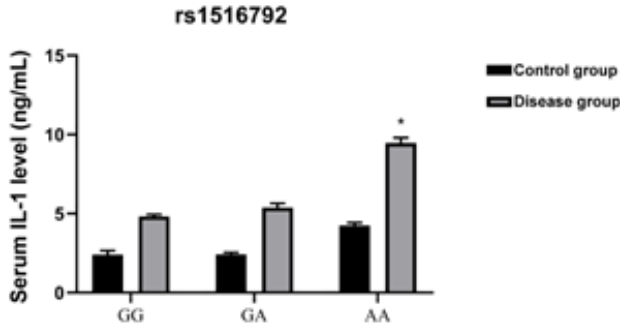

Fig. 1. Relationship between IL-1 rs1516792 genotype and serum IL-1 level (*p<0.05 *vs.* GG and GA genotypes in disease group and control group).

Table 1. Allele distribution of IL-1 rs1516792 and rs1878320 and IL-6 rs1474347 and rs2069831.

Gene	Locus	Allele	Control group	Disease group	OR	95% CI	χ^2	p
IL-1	rs1516792	G	180 (0.450)	165 (0.412)	1.16	0.88-1.54	1.14	0.284
		A	220 (0.550)	235 (0.588)				
	rs1878320	T	201 (0.502)	151 (0.378)	1.66	1.25-2.20	12.68	0.000
		C	199 (0.497)	249 (0.623)				
IL-6	rs1474347	C	194 (0.485)	204 (0.510)	0.92	0.68-1.19	0.55	0.479
		A	206 (0.515)	196 (0.490)				
	rs2069831	C	210 (0.525)	225 (0.562)	1.16	0.88-1.53	1.13	0.287
		T	190 (0.475)	175 (0.438)				

Table 2. Genotype distribution of IL-1 rs1516792 and rs1878320 and IL-6 rs1474347 and rs2069831.

Gene	Locus	Genotype	Control group	Disease group	OR	95% CI	χ^2	p
IL-1	rs1516792	GG	35 (0.175)	41 (0.205)	1.13	0.98-1.34	7.61	0.022
		GA	110 (0.550)	83 (0.415)				
		AA	55 (0.275)	76 (0.380)				
	rs1878320	TT	48 (0.240)	31 (0.155)	0.87	0.54-1.21	13.55	0.001
		TC	105 (0.525)	89 (0.445)				
		CC	47 (0.235)	80 (0.400)				
IL-6	rs1474347	CC	46 (0.230)	33 (0.165)	0.99	0.76-1.14	14.07	0.000
		CA	102 (0.510)	138 (0.690)				
		AA	52 (0.260)	29 (0.145)				
	rs2069831	CC	50 (0.250)	51 (0.255)	1.02	0.76-1.45	3.79	0.156
		CT	110 (0.550)	123 (0.615)				
		TT	40 (0.200)	26 (0.130)				

Table 3. Polymorphism analysis of IL-1 rs1516792 and rs1878320 and IL-6 rs1474347 and rs2069831.

	Gene	Locus	Genotype	Control group	Disease group	χ^2	*p*
Dominant model	IL-1	rs1516792	GG + GA	145 (0.725)	124 (0.620)	4.7	0.095
			AA	55 (0.275)	76 (0.380)		
		rs1878320	TT + TC	153 (0.765)	120 (0.600)	3.35	0.187
			CC	47 (0.235)	80 (0.400)		
	IL-6	rs1474347	CC + CA	148 (0.740)	171 (0.855)	7.68	0.021
			AA	52 (0.260)	29 (0.145)		
		rs2069831	CC + CT	160 (0.800)	174 (0.870)	1.14	0.566
			TT	40 (0.200)	26 (0.130)		
Recessive model	IL-1	rs1516792	GG	35 (0.175)	41 (0.205)	4.64	0.098
			GA + AA	165 (0.825)	159 (0.795)		
		rs1878320	TT	48 (0.240)	31 (0.155)	1.64	0.440
			TC + CC	152 (0.760)	169 (0.845)		
	IL-6	rs1474347	CC	46 (0.230)	33 (0.165)	3.45	0.140
			CA + AA	154 (0.770)	167 (0.835)		
		rs2069831	CC	50 (0.250)	51 (0.255)	4.27	0.118
			CT + TT	150 (0.725)	149 (0.745)		
Hybrid model	IL-1	rs1516792	GG	35 (0.175)	41 (0.205)	1.31	0.519
			GA	110 (0.550)	83 (0.415)		
		rs1878320	TT	48 (0.240)	31 (0.155)	2.23	0.328
			TC	105 (0.525)	89 (0.445)		
	IL-6	rs1474347	CC	46 (0.230)	33 (0.165)	3.34	0.188
			CA	102 (0.510)	138 (0.690)		
		rs2069831	CC	50 (0.250)	51 (0.255)	2.28	0.320
			CT	110 (0.550)	123 (0.615)		
Homozygous model	IL-1	rs1516792	GG	35 (0.175)	41 (0.205)	1.25	0.535
			AA	55 (0.275)	76 (0.380)		
		rs1878320	TT	48 (0.240)	31 (0.155)	2.42	0.298
			CC	47 (0.235)	80 (0.400)		
	IL-6	rs1474347	CC	46 (0.230)	33 (0.165)	3.67	0.160
			AA	52 (0.260)	29 (0.145)		
		rs2069831	CC	50 (0.250)	51 (0.255)	4.73	0.094
			TT	40 (0.200)	26 (0.130)		

Table 4. Haplotype analysis of IL-1 rs1516792 and rs1878320 and IL-6 rs1474347 and rs2069831.

Gene	Haplotype	Control group	Disease group	OR	95% CI	χ^2	*p*
IL-1	AC	113.35 (0.283)	174.76 (0.437)	1.962	1.463-2.632	20.454	0.000
	AT	106.65 (0.267)	60.24 (0.151)	0.488	0.343-0.694	16.305	0.000
	GC	85.65 (0.214)	74.24 (0.186)	0.836	0.591-1.184	1.017	0.313
	GT	94.35 (0.236)	90.76 (0.227)	0.951	0.684-1.321	0.091	0.763
IL-6	AC	110.37 (0.276)	106.13 (0.265)	0.948	0.694-1.295	0.114	0.736
	AT	95.63 (0.239)	89.87 (0.225)	0.922	0.664-1.281	0.233	0.629
	CC	99.63 (0.249)	118.87 (0.297)	1.275	0.933-1.741	2.331	0.127
	CT	94.37 (0.236)	85.13 (0.213)	0.876	0.628-1.221	0.613	0.434

rs1878320 and IL-6 rs1474347 and rs2069831 with echocardiographic indexes (Table 5) uncovered that there was an obvious association between polymorphism of rs1878320 locus in IL-1 gene and IVS (P=0.047), between polymorphism of rs1516792 locus in IL-1 gene and LVOT (P=0.041) and between the IL-6 rs2069831 polymorphism and LVEF (P=0.035). The IVS was reduced in the patients with TC genotype, the LVOT was lowered in the patients with GG genotype, and the LVEF declined in the patients with TT genotype.

4. Discussion

As one of the leading causes of sudden cardiac death in people aged 25-40 years old, HCM poses a great threat to young people around the world [11,12]. HCM is caused by cardiomyocyte hypertrophy-induced thickened ventricular wall, decreased heart compliance and insufficient ejection of the heart. The root cause is the changes in genetic substances of the family factor [13]. The disease is often accompanied by changes in the immune system during the pathogenesis, including increased secretion of

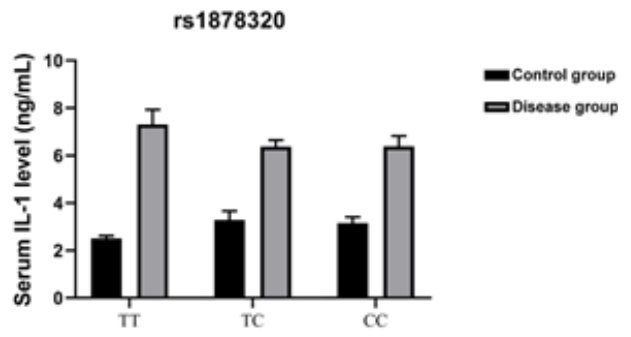

Fig. 2. Correlation between IL-1 rs1878320 genotype and serum IL-1 level.

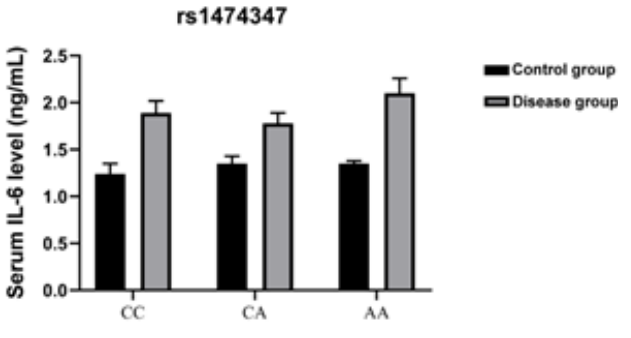

Fig. 3. Association between IL-6 rs1474347 genotype and serum IL-6 level.

pro-inflammatory mediators leading to increased inflammatory response, and increased proliferation and differentiation of immune cells resulting in increased secretion of various cytokines, making cardiomyocytes more vulnerable, aggravating the condition, and greatly increasing the incidence rate of sudden death [14]. Given this, studying the effects of various cytokines in the immune system on HCM and the specific mechanisms is conducive to clarifying the specific pathogenesis of the disease and provides new ideas for the treatment of HCM.

IL-1 and IL-6, important cytokines in the body, participate in modulating various physiological processes and life activities, including promoting cell differentiation and enhancing immune cell viability [15]. Moreover, both IL-1 and IL-6 are related to the development of many diseases such as recurrent aphthous stomatitis [16]. Gene polymorphism is one of the important factors affecting disease susceptibility, which has been regarded as a vital tool for the prediction of disease development. The IL-1 gene polymorphism is proven to have an association with the progression of such diseases as Alzheimer's disease [17] and vasculitis [18]. Furthermore, the IL-6 gene polymorphism is also correlated with the progression of diseases like periodontitis [19] and thrombosis disorder [20]. In this study, it was found that the allele distribution of IL-1 rs1878320 showed an obvious difference between disease group and control group (P=0.000): the frequency of T allele was lower in disease group than that in control group. There was a difference in the genotype distribution of IL-1 rs1878320 (P=0.001) and IL-6 rs1474347 (P=0.000) between disease group and control group: the frequency of TC genotype of IL-1 rs1878320 was lower in disease group than that in control group, and that of CA genotype of IL-6 rs1474347 was higher in disease group than that in control group. The above results suggest that IL-1 and IL-6 gene polymorphisms have certain influences on the susceptibility to HCM.

Meanwhile, a difference was detected in the distribution of the dominant model of IL-6 rs1474347 between disease group and control group (P=0.021): the frequency of CC +

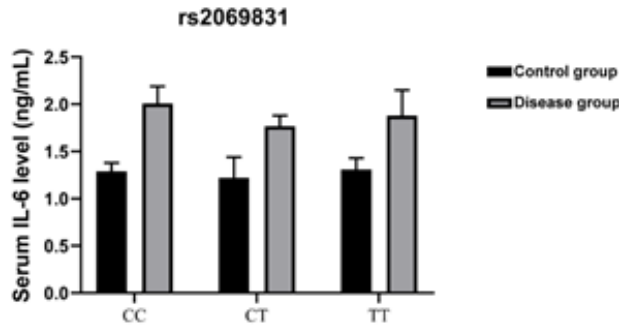

Fig. 4. Relation between IL-6 rs2069831 genotype and serum IL-6 level.

Table 5. Correlations of genotypes of IL-1 rs1516792 and rs1878320 and IL-6 rs1474347 and rs2069831 with echocardiographic indexes

Gene	Locus	Genotype	IVS (mm)			LVOT (mm)			LVEF (E/A)		
			Control group	Disease group	*p*	Control group	Disease group	*p*	Control group	Disease group	*p*
IL-1	rs1516792	GG	10	19	0.741	27	15	0.041	1.4	0.7	0.414
		GA	11	18		31	18		1.5	0.8	
		AA	11	18		33	19		1.4	0.8	
	rs1878320	TT	10	19	0.047	31	17	0.374	1.3	0.7	0.274
		TC	9	15		33	17		1.4	0.9	
		CC	12	19		32	18		1.4	0.8	
IL-6	rs1474347	CC	11	17	0.264	29	16	0.271	1.5	0.7	0.136
		CA	10	18		33	16		1.3	0.8	
		AA	12	18		35	18		1.6	0.7	
	rs2069831	CC	11	17	0.264	32	20	0.462	1.4	0.9	0.035
		CT	10	19		31	19		1.3	0.7	
		TT	10	20		30	18		1.1	0.6	

CA in the dominant model was 171 (0.855). The frequency of AC haplotype of IL-1 gene was overtly higher in disease group than that in control group (P=0.000), while the frequency of AT haplotype was lower in disease group than that in control group (P=0.000). These results indicate that gene polymorphisms affect HCM by jointly influencing the susceptibility to the disease *via* the combination of multiple genotypes of the same locus (IL-6 rs1474347), or the combination of different loci in the same gene (IL-1 rs1516792 and rs1878320).

Besides, it was discovered in this study that the polymorphism of IL-1 rs1516792 was associated with serum IL-1 level (P<0.05). The IL-1 level was higher in disease group than that in control group, implying that IL-1 acts as a crucial pro-inflammatory factor in HCM, which is in line with the findings of other studies. At the same time, the IL-1 level was notably increased in HCM patients carrying AA genotype, suggesting that the level of inflammation is high in the body of such patients, the disease may progress more rapidly and severely, and the prognosis is poor. Blocking antibodies or neutralizing drugs against IL-1 are able to reduce the IL-1 level in HCM patients and may inhibit the progression of the disease.

Finally, combined with the results of cardiac color Doppler ultrasound examination, it was detected that there was an obvious association between IL-1 rs1878320 polymorphism and IVS (P=0.047), between IL-1 rs1516792 polymorphism and LVOT (P=0.041) and between IL-6 rs2069831 polymorphism and LVEF (P=0.035), and the IVS was reduced in the patients with TC genotype, the LVOT was lowered in the patients with GG genotype, and the LVEF declined in the patients with TT genotype, indicating that IL-1 and IL-6 gene polymorphisms authentically affect the clinical indicators of HCM, and that the condition of HCM patients can be assessed by combining IL-1 and IL-6 gene polymorphisms with echocardiographic results in clinical practice.

5. Conclusions

The IL-1 and IL-6 gene polymorphisms are obviously correlated with the susceptibility and progression of HCM.

Conflict of Interests

The author has no conflicts with any step of the article preparation.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Hainan West Central Hospital.

Informed Consent

Signed written informed consents were obtained from all participants before the study.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

NL and CL designed the study and performed the experiments, CL and YW collected the data, YW and HL analyzed the data, NL prepared the manuscript. All authors read and approved the final manuscript.

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Non.

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