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Original Article

Interleukin-6 genotypes and serum levels in Chinese Hui population

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Abstract: Interleukin-6 (IL-6) is a key pro-inflammatory cytokine involved in different physiologic and pathophysiologic processes, and circulating levels of IL-6 differ greatly between individuals. The Chinese Hui is one of the largest ethnic minorities, little is known about the distribution of IL-6 genetic variations and their effects on serum levels in Hui population. The aim of the present study is to determine the prevalence of -174G/C (rs1800795), -597G/A (rs1800797), and -634C/G (rs1800796) polymorphisms in the IL-6 gene promoter region and their association with IL-6 serum levels in the Ningxia Hui population. A total of 96 Hui subjects, (57 men and 39 women; mean age 49.65 ± 19.73 years) unrelated nationality residents in Ningxia Hui Autonomous Region were enrolled. Genotyping of the three polymorphisms were performed by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) combined with gel electrophoresis and then confirmed by direct sequencing. The -174G/C (97.92% GG, 2.08% GC, and 0% CC) and -597G/A (98.96% GG, 1.04% GA, and 0% AA) polymorphisms were rare. The frequencies of -634C/G genotypes CC, CG, and GG were found to be 54.17%, 40.62%, and 5.21%, respectively in total studied subjects, the derived allele frequencies for the C and G alleles were 74.48% and 25.52%. Increased IL-6 levels were correlated with the IL-6 -634G allele carriers (CG+GG genotypes). The results suggest that IL-6 -174G/C and -597G/A are rare but -634C/G is common in the Ningxia Hui population, and the -634G allele is associated with circulating levels of IL-6.

Keywords: Interleukin-6, genetic polymorphism, Hui nationality, Chinese

Introduction

Interleukin-6 (IL-6) is a key pro-inflammatory cytokine which plays a central role in host defense mechanisms [1, 2]. Produced in response to diverse stimuli, including infection, IL-1, interferon, and tumor necrosis factor [3-5], IL-6 is one of the most important mediators of the acute-phase response and a primary determinant of hepatic production of C-reactive protein [1, 6, 7]. IL-6 has been found to be the predominant cytokine detected at elevated levels in a variety of disease states, such as Alzheimer's disease, cancer, atherosclerosis, cardiovascular disease, type 2 diabetes mellitus, drug addiction, periodontitis, osteoporosis, sepsis, and systemic-onset juvenile chronic arthritis [8-15].

Polymorphisms in the promoter region of the IL-6 gene may result in inter-individual variation in transcription and expression [13]. Genetic variants could therefore influence an individual's susceptibility to a diverse range of diseases [16, 17]. The human IL-6 gene is located at chromosome 7p21 and contains 5 exons, with only a few very rare polymorphisms in its coding sequence [12]. This fact might support the hypothesis that the observed differences in IL-6 concentration among individuals are influenced by mutation in the IL-6 gene promoter region [18]. It has been shown that a G to C polymorphism at the -174 position of the IL-6 promoter region appears to affect IL-6 transcription, and the presence of the C allele may be associated with systemic onset juvenile chronic arthritis [19].

There are 56 ethnic groups in China. Han is the largest population, accounting for approximately 91% of the country's total population. The Chinese Hui is one of the largest ethnic minorities, with a population of over 12 million. The majority of the Chinese Hui live in the Ningxia

Table 1. IL-6 genotypes and alleles frequencies

Polymorphisms	Genotypes frequencies (n, %)			Allele frequencies (%)	
	11	12	22	1	2
-174G/C	94 (97.92)	2 (2.08)	0 (0)	190 (98.96)	2 (1.04)
-597G/A	95 (98.96)	1 (1.04)	0 (0)	191 (99.48)	1 (0.52)
-634C/G	52 (54.17)	39 (40.62)	5 (5.21)	143 (74.48)	49 (25.52)

Hui Autonomous Region. The Chinese Hui descended from Central Asian, Arabs, and Persian merchants who came to China during the 7th century [20]. To retain religious purity and group identity, the Hui have always isolated themselves socially from other people, in enclaves. Hui marriage practices tend toward endogamy in all respects, especially in the rural part of Ningxia Hui Autonomous Region. The Hui population is culturally and religiously conservative [21].

Ethnic differences were highly noted for IL-6 polymorphisms. For example, the CC homozygote at the -174 position of the IL-6 promoter region was found to be completely absent in the Korean [22], Japanese [23], Afro-Caribbeans [19], and Han Chinese [15], while significantly increased in the Finnish Caucasian [24]. However, little is known about the distribution of IL-6 genetic variations and their effects on serum levels in Hui population. The aim of the present study is to determine the prevalence of -174G/C (rs1800795), -597G/A (rs1800797), and -634C/G (rs1800796) polymorphisms in the IL-6 gene promoter region and their association with IL-6 serum levels in the Ningxia Hui population.

Material and methods

Subjects

A total of 96 Hui subjects, (57 men and 39 women; mean age 49.65 ± 19.73 years) unrelated nationality residents in Ningxia Hui Autonomous Region were enrolled. All the subjects were healthy and had no cardiovascular and cerebrovascular disease. Diabetes, cancer, hepatic disease, and other diseases which can affect serum IL-6 levels were also excluded. There was also no history of cigarette smoking among these subjects. Individuals were selected after careful physical examination, chest X-radiograph, ECG, urine and blood tests. The study has been approved by the Medical Ethics Committee of Ningxia People's Hospital, and written informed consent was obtained from all participants.

Determination of genotype

Determination of IL-6 -174G/C, -597G/A, and -634C/G genotypes was performed by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) as described previously [12, 14, 15]. In brief, the primers were 5'- AGTGGGCTGAAGCAGGTGA -3' (sense) and 5'- CTTTGTTGGAGGGTGAGGG -3' (antisense). This set encompasses the region of interest in the IL-6 promoter and should generate a 617-bp product. Amplification products were then digested with restriction endonuclease of NlaIII, FokI, and BsrBI to detect -174G/C, -597G/A, and -634C/G genotypes, respectively. The size of the digestion products were determined by electrophoresis on 2% agarose gel stained with ethidium bromide. 30 amplification products were sent to direct DNA sequencing.

Biochemical analysis

Venous blood samples were obtained after at least a 10-hour overnight fast and then centrifuged at 2500 rpm for 30 minutes at 4°C and immediately stored at -80°C until analysis. Serum levels of IL-6, total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), and triglycerides (TG) were measured as described previously [15, 25].

Statistical analysis

Genotypes and alleles frequencies were obtained by direct count. Differences in the distribution of alleles and genotypes between the groups and deviation from Hardy-Weinberg equilibrium were assessed by χ^2 test. Continuous variables were expressed as mean and standard deviation (SD). Student's t-test was used to compare continuous variables from two groups. All significant tests were two-tailed and were considered statistically significant at $P < 0.05$. SAS software (Version 8, SAS Institute, Cary, NC) was used in all statistical analysis.

Table 2. Clinical characters according to IL-6 -634C/G genotypes

Parameters	IL-6 -634C/G genotypes		P
	CC (n = 52)	CG+GG (n = 44)	
Age (years)	51.26 ± 11.27	51.50 ± 11.45	0.9180
Gender (male/female)	32/20	25/19	0.6389
BMI (kg/m^2)	23.25 ± 1.38	23.14 ± 1.26	0.6865
TC (mmol/L)	4.96 ± 0.65	5.03 ± 0.74	0.6229
TG (mmol/L)	1.74 ± 0.62	1.81 ± 0.70	0.6046
HDL-C (mmol/L)	1.54 ± 0.59	1.51 ± 0.47	0.7862
LDL-C (mmol/L)	2.68 ± 0.64	2.71 ± 0.69	0.8257
IL-6 (pg/ml)	2.51 ± 0.73	2.98 ± 0.88	0.0052

Results

Table 1 summarizes the distributions of genotypes and alleles frequencies of three IL-6 promoter polymorphisms. The genotypes distributions among the subjects were all in agreement with the predicted Hardy-Weinberg equilibrium values (-174G/C, χ^2 = 0.0106, P = 0.9179; -597G/A, χ^2 = 0.0026, P = 0.9591; -634C/G, χ^2 = 0.4524, P = 0.5012). Among the 96 individuals studied, 94 carried the GG wild type of -174G/C, only 2 carried the GC genotype, and the CC genotype was not detected at all. For -597G/A polymorphism, 95 carried the GG, only 1 carried the GA, and the AA genotype was not detected. The frequencies of -634C/G genotypes CC, CG, and GG were found to be 54.17%, 40.62%, and 5.21%, respectively in total studied subjects, the derived allele frequencies for the C and G alleles were 74.48% and 25.52%. 30 samples sent to direct DNA sequencing were consistent with the results by PCR-RFLP.

The effects of the different IL-6 -634C/G genotypes on clinical parameters are shown in **Table 2**. Because the numbers of individuals with GG genotype were small, the carriers of the G allele (CG+GG) were pooled into one group. There were no significant differences in age, gender or BMI between the two groups. Also no statistical differences were found on TC, TG, HDL-C, and LDL-C between the two genotypes. However, individuals with CC genotype showed lower level of IL-6 than that with CG+GG genotype.

Discussion

We assessed the three IL-6 promoter polymorphisms in the Ningxia Hui population, and the quite different prevalence of the three polymorphisms was found. The -174G/C (97.92% GG, 2.08% GC, and 0% CC) and -597G/A (98.96% GG, 1.04% GA, and 0% AA) polymorphisms are extremely rare, while -634C/G (54.17% CC, 40.62% CG, and 5.21% CG) is common in Hui population. The results are consistent with a recent study in Chinese Han population, which found IL-6 -174G/C and -597G/A were rare but -634C/G was common in 232 healthy Han individuals [15]. The Hui Chinese have diverse origins [20], and many are direct descendants of Silk Road travelers. Their ancestors include Central Asian, Arabs, and Persian who married Han Chinese. In the subsequent centuries, they gradually mixed with Han and Mongols Chinese. There were extensive genetic admixtures in the formation of Hui population. Evidence from other genetic studies also supported the genetic admixture hypothesis [20, 26].

By further literature review of allele frequencies of three IL-6 promoter polymorphisms in the world, we found the prevalence of the alleles varied substantially between continental populations. The IL-6 -174C allele frequencies reported in Caucasians (40.34%-56.60%) [19, 27, 28] were much higher than those found in Koreans (0.24%) [22], Japanese (0%) [23], Han Chinese (0.32%) [15], and Hui Chinese (1.04%) (**Table 3**). Similarity, Caucasians had higher A allele frequencies (37.01%-60.28%) [27-29] of IL-6 -597G/A than in Koreans (0.24%) [22], Japanese (0%) [30], Han Chinese (0%) [15], and Hui Chinese (0.52%) (**Table 4**). In contrast, the frequencies of the IL-6 -634C allele in Caucasians (3.51%-9.81%) [27, 28, 31] were much lower than those in Korean (75.00%) [22], Japanese (84.51%) [32], Han Chinese (78.02%) [15], and Hui Chinese (74.48%) (**Table 5**). High frequencies of population-specific alleles are useful particularly for mapping genes responsible for disease susceptibility and other traits in a population [33]. Therefore, the IL-6 -634C/G polymorphism might be a more useful marker for an association study in eastern Asians including Hui Chinese than in Caucasians.

It is of note, in African-American, the -174C allele frequency (7.68%) [34] and the -597G A allele frequency (6.65%) [35] were similar, apart from a slight variation, to those in eastern Asian

Table 3. Frequencies of the various IL-6 -174G/C genotypes reported among different populations

Populations	Numbers investigated	Genotypes frequencies (%)			Allele frequencies (%)	
		GG	GC	CC	G	C
Finnish* [28]	485	19.18	48.45	32.37	43.40	56.60
Czech* [27]	107	34.58	49.53	15.89	59.35	40.65
British* [19]	383	37.60	44.12	18.28	59.66	40.34
Asian Indian* [37]	40	75.00	17.50	7.50	83.75	16.25
Afro-Caribbeans* [19]	101	91.09	8.91	0	95.54	4.46
Afro-American* [34]	43	84.65	15.35	0	92.33	7.68
Korean† [22]	1037	99.52	0.48	0	99.76	0.24
Japanese† [23]	311	100	0	0	100	0
Han Chinese† [15]	232	99.57	0.43	0	99.78	0.32
Hui Chinese	96	97.92	2.08	0	98.96	1.04

*P < 0.05 in comparison with Hui Chinese. †P > 0.05 in comparison with Hui Chinese.

Table 4. Frequencies of the various IL-6 -597G/A genotypes reported among different populations

Populations	Numbers investigated	Genotypes frequencies (%)			Allele frequencies (%)	
		GG	GA	AA	G	A
Czech* [27]	107	15.89	47.66	36.45	39.72	60.28
Finnish* [28]	483	21.33	46.79	31.88	44.72	55.28
British* [29]	127	36.22	53.54	10.24	62.99	37.01
Asian Indian* [37]	40	72.50	20.00	7.50	82.50	17.50
Afro-American* [35]	579	87.57	11.57	0.86	93.35	6.65
Korean† [22]	1024	99.51	0.49	0	99.76	0.24
Japanese† [30]	189	100	0	0	100	0
Han Chinese† [15]	232	100	0	0	100	0
Hui Chinese	96	98.96	1.04	0	99.48	0.52

*P < 0.05 in comparison with Hui Chinese. †P > 0.05 in comparison with Hui Chinese.

Table 5. Frequencies of the various IL-6 -634C/G genotypes reported among different populations

Population	Numbers Investigated	Genotypes Frequency (%)			Alleles Frequency (%)	
		CC	CG	GG	C	G
Finnish* [28]	485	0	7.01	92.99	3.51	96.49
British* [31]	2600	0.35	9.38	90.27	5.04	94.96
Czech* [27]	107	0	19.63	80.37	9.81	90.19
Asian Indian* [37]	40	27.50	57.50	15.00	56.25	43.75
Afro-American* [36]	63	3.18	12.70	84.12	9.52	90.48
Korean† [22]	990	56.26	37.48	6.26	75.00	25.00
Japanese† [32]	142	71.83	25.35	2.82	84.51	15.49
Han Chinese† [15]	232	59.48	37.07	3.45	78.02	21.98
Hui Chinese	96	54.17	40.62	5.21	74.48	25.52

*P < 0.05 in comparison with Hui Chinese. †P > 0.05 in comparison with Hui Chinese.

populations, whereas, the -634C allele frequency (9.52%) [36] was similar to those in Caucasians. Asian Indian had these allele frequencies [37] that were intermediate to those of the Caucasian and eastern Asian populations. Data confirm previous reports about evolutionary trees suggested that European and southwest Asian (Indian) populations diverged from the Chinese population, with an estimated genetic distance of at least 20,000 years [38].

Circulating levels of IL-6 differ greatly between individuals [18], and genetic factors are thought to play a major role, along with environmental factors, particularly inflammation [15]. In the present study, increased IL-6 levels were correlated with the IL-6 -634G allele carriers (CG+GG genotypes). However, the effects of the different IL-6 -634C/G genotypes on serum IL-6 levels yielded conflicting results. Our results were consistent with previous studies conducted in Japanese and Koreans [10, 32]. In Japanese type 2 diabetic subjects, the presence of the -634G allele was associated with an elevated production and secretion of IL-6 protein by peripheral blood mononuclear cells in vivo after given various inflammatory stimuli compared with the -634C allele [32]. On the other hand, in Caucasian population, IL-6 -634C allele was associated with the increased IL-6 levels [29]. Besides, in Caucasian male patients with myocardial infarction and in dyslipidemia, no relationship was detected between IL-6 -634C/G polymorphism and circulating IL-6 levels [39]. This discrepancy between genotype and phenotype among different populations was also reported by other reports [25, 40, 41]. In addition, the -634C allele was common in eastern Asian populations, whereas in Caucasians the -634C allele was rare, in particular, CC homozygote was not found in some studies of the Caucasian population [27, 28]. Thus, further research is necessary in order to clarify the functional impact of the polymorphisms within the IL-6 promotor region in Hui Chinese.

In conclusion, the results in this study suggest that IL-6 -174G/C and -597G/A are rare but -634C/G is common in the Ningxia Hui population, and the -634G allele is associated with circulating levels of IL-6. Functional genomic studies are needed to verify the relevance of the IL-6 promotor polymorphisms to IL-6 level in Hui Chinese in the future.

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Disclosure of conflict of interest

None.

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