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Original Article

IL-6 promoter *-572G* polymorphic allele causes lower level of triglyceridemia

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Abstract: Objectives: Lower blood triglyceridemia (TG) level and TG/HDL-C (high density lipoprotein-cholesterol) ratio are healthy indicators in clinical diagnosis. *IL-6* has been reported to inhibit lipoprotein lipase activity and stimulate lipolysis, subsequently lead to increased concentrations of serum triglycerides. In this study, we examined whether the polymorphism of the *-572C/G* locus in the *IL-6* promoter was linked to hypertriglyceridemia (HTG). Methods: Blood DNA samples from 100 patients with HTG and 162 healthy control subjects were collected and used for screening the *IL-6* promoter polymorphism. TC, TG, and HDL-C were determined by enzymatic method while LDL-C was measured by Immunoturbidimetry. Blood glucose was determined through hexokinase method. Routine PCR and Sanger DNA sequencing were performed to screen and determine the site polymorphisms. All the data were statistically analyzed by SPSS 17.0 software. Results: PCR and Sanger-based DNA sequencing demonstrated that subjects carrying the *CC* genotype of the *-572C/G* locus in the *IL-6* promoter had normal or slightly higher level of blood TG, whereas the carriers of the *CG* or *GG* genotype presented lower levels of blood TG and TG/HDL-C ($P<0.5$). These results imply that the *-572G* allele, not the *-572C* allele, leads to lower level of TG. Conclusion: The data suggests that the *-572G* allele of the *IL-6-572C/G* site might play a role in maintaining low level of blood TG by up-regulating or down-regulating the IL-6 expression and promoting the TG metabolism. This finding might shed new light on the diagnosis of HTG.

Keywords: *Interleukin-6* gene, polymorphism, *-572C/G*, *-597G/A*, hypertriglyceridemia

Introduction

Hyperlipidemia is a common systemic disease resulting from a combination of genetic and environmental factors [1]. According to elevated types of lipids, hyperlipidemias are usually classified into hypercholesterolemia (HTC), hypertriglyceridemia (HTG), or both in combined hyperlipidemia, and low high-density lipoprotein hyperlipidemia. Elevated levels of triglycerides (TG) tend to cause metabolic changes of blood lipid, and subsequently lead to cardiovascular disease, peripheral vascular disease, and cerebrovascular disease [2]. In addition, high levels of blood triglycerides could increase the risk of acute pancreatitis [1].

Hyperlipidemias might be familial [2, 3], or acquired or even idiopathic [4]. Previous reports have demonstrated that gene alterations could cause hyperlipidemias [5-9]. Alterations in a few lipid metabolism-related genes including apolipoprotein A5 (*Apo A5*) [10] and low-density lipoprotein receptor gene (*LDL-R*) are important risk factors for hyperlipidemias. Additionally, interleukin-6 gene (*IL-6*), a multi-effect cytokine and another lipid metabolism-related gene, has been reported to inhibit lipoprotein lipase activity and stimulate lipolysis, and thus lead to increased concentrations of serum triglycerides [11]. Moreover, other studies have demonstrated that IL-6 is correlated to increased levels of serum triglycerides [7, 12-14]. The promoter region *of IL-6* has several polymorphisms including *-174G/C*, *-572C/G*, *-597G/A*, and *-634C/G*, and is implicated with several diseases such as hypertension, coronary heart

Table 1. Subjects collected for study

Group	Number	Male	Female	Age (year)
HTG	100	52	48	44.3 ± 12.85
Healthy	162	83	79	47.01 ± 13.28

disease, and diabetes [15-19]. The *-572C/G* site polymorphism of the *IL-6* promoter has been reported to be linked to acne vulgaris in Pakistan population [20], Alzheimer's disease [21], and hand-foot-and-mouth disease (HFMD) [22]. The *-597G/A* site polymorphism is associated with degeneration of intervertebral discs [23] and type 2 diabetes [24]. In addition, a previous study demonstrated a correlation of *IL-6* gene *-572C>G* polymorphism to dietary intake of n-3 fatty acids and plasma HDL-C level in a sex-specific manner [25]. However, the correlation between these *IL-6* polymorphisms and hyperlipidemia remains unclear, and the *-572C/G* or *-597G/*A sites have not been investigated in the Chinese sub-population in Zunyi. In this study, we chose to explore the association of *-572C/G* or *-597G/A* polymorphism of *IL-6* with hypertriglyceridemia in the Zunyi-population of China.

Materials and methods

Patients

Blood samples from a cohort of 100 HTG patients and 162 unrelated healthy subjects were collected for this study (**Table 1**). HTG was determined based on the Chinese guidelines on prevention and treatment of dyslipidemia in adults (2007) [26] These healthy subjects had no history of cardiovascular and cerebrovascular disease, and their levels of blood glucose and lipids displayed as normal. Patients and healthy subjects did not have the following diseases such as nephrotic syndrome, kidney failure, diabetes, primary hypothyroidism, systemic lupus erythematosus (SLE), liver disease, glycogen storage disease (Pompe's syndrome), lipoatrophy, myeloma, acute porphyria, and polycystic ovary syndrome.

All the patients and healthy subjects were excluded for use of beta-blockers, diuretic, glucocorticoid that could induce secondary hyperlipidemia. The participants did not use drugs that could induce other cardiovascular diseases such as coronary heart disease, ischemic/congestive stroke, and arteriosclerosis. This study was approved by the hospital ethics committee, and all the patients and healthy subjects signed the informed consent form for the hyperlipidemias study.

Blood collection and measurement of blood lipids

Approximately 5 ml blood was collected from each patient and healthy subjects, and 2 ml of the blood was used for measurement of blood lipids and glucose. TC, TG, and HDL-C were determined by enzymatic method while LDL-C was measured by Immunoturbidimetry. Blood glucose was determined through hexokinase method. All the measurements were obtained through Abbort automatic chemistry analyzer. Subjects were selected based on the Chinese guidelines on prevention and treatment of dyslipidemia in adults (2007) [26]. The rest of each blood sample (≥2 ml) was kept at -20°C for future use.

PCR amplification and DNA sequencing

Approximately 2 ml blood obtained from each HTG patient or healthy subject was used for DNA extraction by using Blood Genome Extracting Kit (Sangon Biotech, Shanghai). The PCR primers for the *IL-6* promoter polymorphism analysis (Sangon Biotech, Shanghai, China) are as below: forward, *5'-GGA GAC GCC TTG AAG TAA CTG C-3'* (22 bp); reverse, *5'-GAG TTT CCT CTG ACT CCA TCG CAG-3'* (24 bp). Dream Taq Green PCR Master Mix (2×) was purchased from Thermo Fisher (Shanghai, China). PCR was performed to amplify the *-572C/G* and *-597G/A* sites of IL6 promoter. The 163 bp PCR product was detected in 2% agarose gel. Sanger DNA sequencing was used to screen and determine the site polymorphisms by the Thermo Fisher (Shanghai, China).

Statistical analysis

All the data were statistically analyzed by SPSS 17.0 software. Measurements that matched the normal distribution were represented by means ± standard deviation (X ± S). Data that did not meet the normal distribution were expressed by median (upper quartiles ~ lower quartiles) [M (P_{25}~P_{75})]. Group sample representativeness was determined by Hardy-Weinberg balance test. Allelic frequencies, genotypic frequencies, and their intra-group/intergroup differences were examined by χ^2 test. Difference between genotype and blood

Table 2. Difference of clinical data between HTG and healthy group

Group	Healthy Group (n=162)	HTG group (n=100)	*P* value
Age (year)*	47.01 ± 13.28	44.43 ± 12.85	0.124
Sex (Male/female)	83/79	52/48	0.904
TG (mmol/L)**	1.06 (0.88~1.31)	2.21 (1.91~2.93)	<0.001
TC (mmol/L)*	4.20 ± 0.50	4.42 ± 0.52	<0.001
HDL-C (mmol/L)**	1.22 (1.11~1.38)	1.05 (0.97~1.19)	<0.001
LDL-C (mmol/L)**	2.58 (2.20~2.81)	2.79 (2.41~3.02)	<0.001
Fasting glucose (mmol/L)*	4.62 ± 0.44	4.54 ± 0.50	0.175
TG/HDL-C**	0.86 (0.65~1.07)	2.08 (1.74~2.66)	<0.001
TC/HDL-C*	3.38 ± 0.67	4.12 ± 0.63	<0.001
LDL-C/HDL-C*	2.02 ± 0.56	2.52 ± 0.53	<0.001

Note: *, $\bar{x}$ ± S; **, M (P_{25}~P_{75}). TG/HDL-C: Ratio of serum triglycerides/high density lipoprotein cholesterol; TC/HDL-C: Ratio of serum total cholesterol/high density lipoprotein cholesterol; LDL-C/HDL-C: Ratio of low density lipoprotein cholesterol/high density lipoprotein cholesterol.

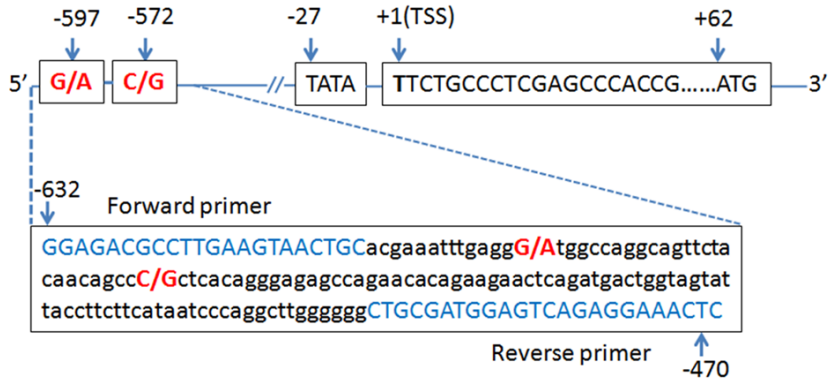

Figure 1. Schematic representation of promoter region of IL-6 gene from -632 to +3 (Gene bank accession number: NG_011640). PCR Nucleotide sequence (163 bp) shown in text box, the 5' and 3' primers for PCR amplification are shown in blue while those for -572C/G and -597A/G SNP are shown in red. TSS, transcription start site.

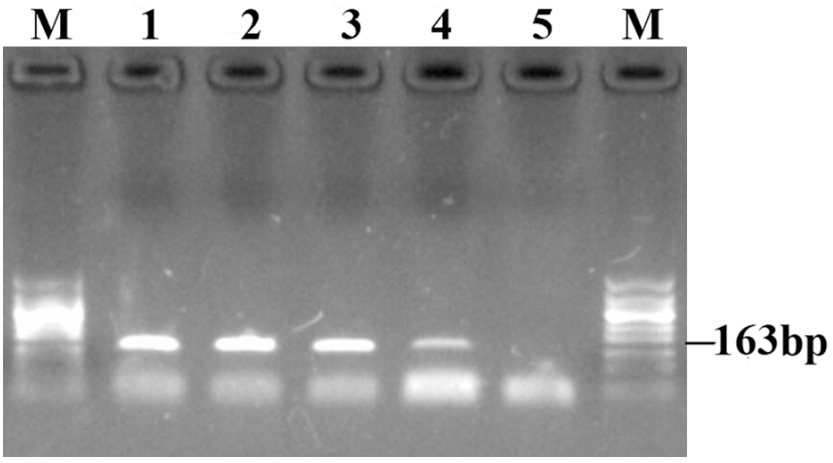

Figure 2. Electrophoretic results of PCR product about promoter region in *IL-6* gene. M: DNA Marker (50 bp); 1, 2, 3, 4: Patients' DNA sample; 5: Negative control.

lipids was determined by Wilcoxon rank-sum test. The correlation between various genotypes and blood lipids was determined by Logistic regression judgment, and $P<0.05$ means the difference is statistically significant.

Results

Clinical data between HTG patients and healthy subjects

No difference was identified between the HTG group and the healthy individual group on age, sex, and glucose level ($P>0.05$). The blood lipid index (TG, TC, LDL-C, TC/HDL-C, LDL-C/HDL-C) between the HTG group and the healthy group is statistically significant ($P<0.05$, **Table 2**).

DNA sequencing revealed IL-6 polymorphism sites -572C/G and -597G/A

The polymorphism of the -572C/G site: The 163 bp PCR products were used for screening polymorphisms at *-572C/G* and *-597G/A* sites through the Sanger DNA sequencing by using the reverse PCR primer (**Figures 1-3**). At the *-572C/G* site, while 51.2% (83 in 162) of the healthy subjects and 55.0% (55 in 100) of the HTG patients carried *CC* genotype, only 6.2% (10 in 162) of the healthy subjects and 7.0% (7 in 100) of

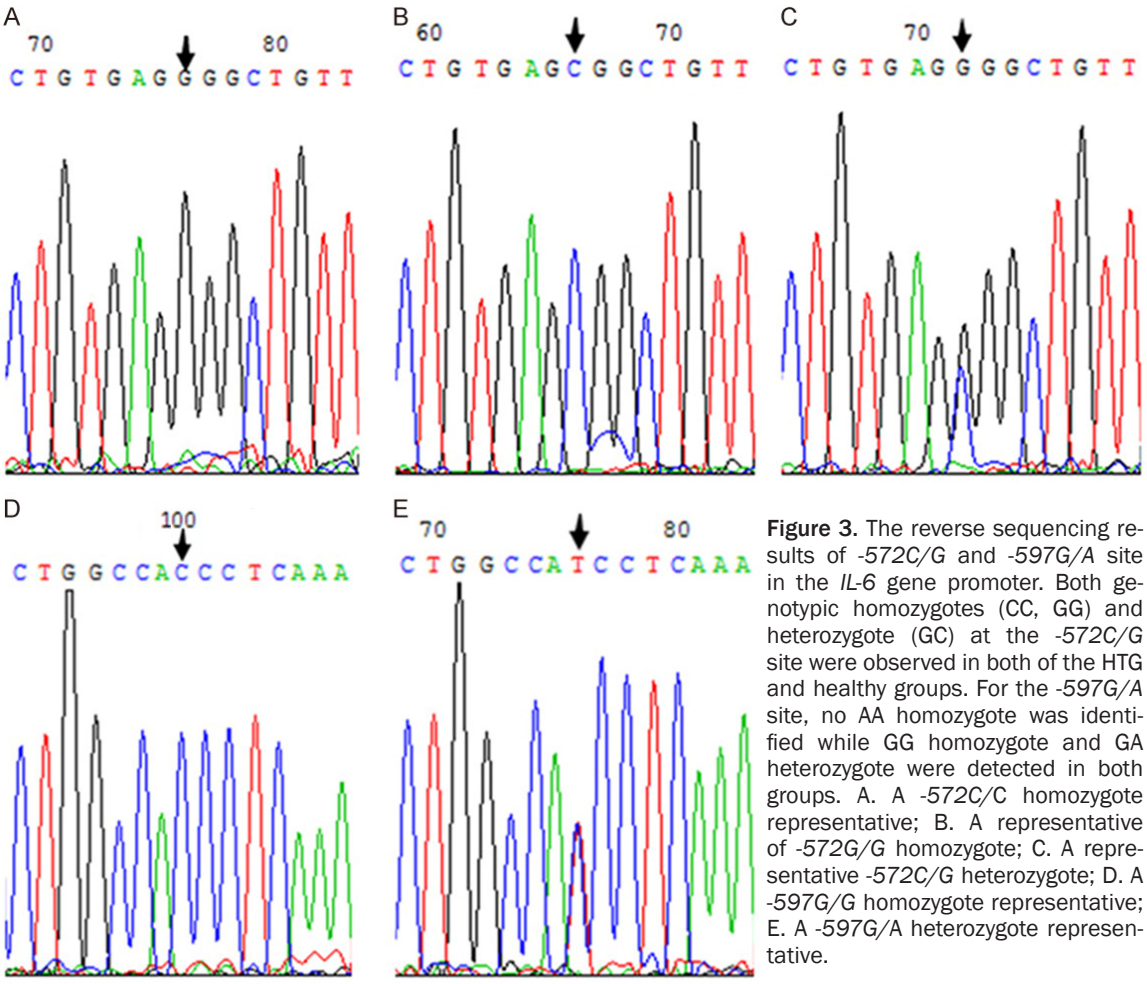

Figure 3. The reverse sequencing results of *-572C/G* and *-597G/A* site in the *IL-6* gene promoter. Both genotypic homozygotes (CC, GG) and heterozygote (GC) at the *-572C/G* site were observed in both of the HTG and healthy groups. For the *-597G/A* site, no AA homozygote was identified while GG homozygote and GA heterozygote were detected in both groups. A. A *-572C/C* homozygote representative; B. A representative of *-572G/G* homozygote; C. A representative *-572C/G* heterozygote; D. A *-597G/G* homozygote representative; E. A *-597G/A* heterozygote representative.

the HTG individuals were *GG* homozygous. The *GC* heterozygotes accounted for 42.6% (69 in 162) and 38.0% (38 in 100) in healthy and HTG group, respectively (**Figure 3A-C**).

The polymorphism of the -597G/A site was extremely low in this sub-population: The polymorphism of the *-597G/A* site was extremely low. While we did find one *GA* heterozygote in the healthy group, no *AA* genotype was identified in both groups (**Figure 3D**, **3E**). Of the 262 samples, 261 were *GG* carriers, and only one *-597G/A* heterozygote was identified in the healthy group. Thus, the *-597G/A site* does not present polymorphism in this sub-population.

The distribution of the genotype and allelic frequency of the -572C/G and -597G/A sites in the HTG and the healthy control group

Both the HTG group and healthy group were from genetic balance population: The *-572C/G* was subjected to Hardy-Weinberg balance test, and the χ^2 value was 0 (P=1) for the distribution of genotype and 0.325 (P=0.850) for the allelic distribution between the HTG group and the healthy group. Both of them matched the Hardy-Weinberg principle of genetic balance (*P*>0.05), indicating that both groups were from genetically balanced populations, and were qualified for representing the local population distribution.

The majority of the population was carriers of the CC and CG genotype at the -572C/G locus: The genotypic frequency and allelic frequency distribution for *-572C/G* was listed in **Table 3**. For the *-572C/G* site, the majority of the population was *CC* and *CG* genotypic carriers, accounting for 93.5% (245 in 262). The *GG* homozygote presented only 6.5% in this population. The genotype and allele distributions of the *-572C/G* site in the HTG group are similar to that in the healthy group. For the genotypic and allelic frequency of *-572C/G* site, no significant differences were detected between the HTG

Table 3. Polymorphism for *-572C/G* in *IL-6* in HTG and healthy group

Group	Cases	Genotype frequency Distribution (%)			Allelic frequency distribution (%)	
		CC	CG	GG	C	G
Healthy	162	83 (51.2)	69 (42.6)	10 (6.2)	235 (72.5)	89 (27.5)
HTG	100	55 (55.0)	38 (38.0)	7 (7.0)	148 (74.0)	52 (26.0)
χ^2			0.551		0.136	
P-value			0.759		0.713	

Table 4. Blood lipid level of different genotype for *-572C/G* in HTG group and normal group

Blood lipid index	Healthy (n=162)		*P*	HTG (n=100)		*P*
	CC	CG+GG		CC	CG+GG	
TG	1.02 ± 0.27	1.13 ± 0.29	0.012	2.51 (2.01~3.30)	2.02 (1.85~2.64)	0.022
TC	4.11 ± 0.52	4.29 ± 0.46	0.021	4.44 ± 0.51	4.39 ± 0.53	0.623
LDL-C	2.42 ± 0.51	2.51 ± 0.49	0.219	2.74 ± 0.51	2.67 ± 0.45	0.518
HDL-C	1.31 ± 0.39	1.28 ± 0.29	0.598	1.09 ± 0.14	1.09 ± 0.15	0.851
TG/HDL-C	0.82 ± 0.28	0.92 ± 0.30	0.026	2.36 (1.92~2.75)	1.91 (1.69~2.37)	0.021
TC/HDL-C	3.30 ± 0.68	3.46 ± 0.65	0.120	4.14 ± 0.65	4.07 ± 0.62	0.564
LDL-C/HDL-C	1.98 ± 0.57	2.05 ± 0.54	0.387	2.55 ± 0.55	2.48 ± 0.50	0.514

Note: TG, TG/HDL index: M (P_{25}~P_{75}) in HTG group; other index: X ± S; lipid concentration: mmol/L.

group and the healthy group (*P*=0.759*, P*= 0.713) (**Table 3**). Statistical analysis of the polymorphism was not carried out for the *-597G/A* site due to its scarcity of variants (only one *GA* heterozygote was found) in this sub-population.

The difference of TG level between the CC carriers and the CG+GG subjects was statistically significant

We further examined whether any specific *-572C/G* genotypes or alleles are linked to the blood lipid levels in the two groups (**Table 4**). The difference of TG blood level between *CC* and *CG+GG* carriers was statistically significant in the healthy group (*P*<0.05), and similar results were obtained for TG/HDL-C and TC. In contrast, no statistically significant difference was observed for other types of blood lipids in this group (*P*>0.05). Similarly, the difference of TG or TG/HDL-C between the *CC* carriers and the *CG+GG* subjects in the HTG group was statistically significant (*P*<0.05), while no statistically significant difference was observed for the other blood lipids in the group (*P*>0.05). In the HTG group, TG level in *CG+GG* genotypic subjects was significantly lower than that in the *CC* genotypic subjects, whereas the findings are opposite in the healthy group. In addition, no significant TC level difference was detected between the *CC* and the *CG+GG* carriers in the HTG group. Since the polymorphism of the *-597G/A* site was low, no statistically allelic or genotypic comparison was performed for the site.

Discussion

Of the blood lipids, TC, TG, HDL-C, and LDL-C are the main parameters for assessing cardiovascular diseases. Many genetic loci have been linked to elevated levels of blood lipids. In this study, we investigated the correlation of the *IL-6* promoter polymorphism with HTG by exploring the genotype and allelic frequency distributions of the *-572C/G* and the *-597G/A* sites in a cohort of 100 HTG patients and 162 healthy subjects. Of the two sites, the polymorphism of the *-597G/A* site was very low in Zunyi sub-population, with only one GA heterozygotic subject and zero genotypic subjects in all 262 subjects examined. Thus, *-597G/A* was not considered as a polymorphic site in this sub-population, and no further analysis was performed for this site. For the *-572C/G* site, although no significant association of *-572C/G* polymorphism with TG level was observed between the HTG and healthy group, we did identify that intra-group *CG+GG* genotype combination was associated with TG level in both groups. Lower blood TG level and TG/HDL-C ratio are healthy indicators in clinical diagnosis. The TG level in *CG+GG* individuals was significantly different from that

in *CC* genotypic subjects in both groups. In the HTG group, *CG+GG* genotype carriers presented significantly lower level of TG and TG/HDL-C ratio compared to *CC* genotypic subjects. In the healthy control group, although the TG level in the *CG+GG* carriers appeared higher than in the *CC* subjects, the TG level was still within the normal range. This finding suggested that the *G* allele of the *-572C/G* site might play a role in maintaining the normal level of TG and TG/HDL-C. In support of our finding, the previous study [25] had revealed that men with *G* allele had significantly higher blood HDL-C concentrations than did CC genotype ($P<0.05$), which implied that *G* allele might be related to lower TG/HDL-C ratio. Taken together, *G* allele of the *-572C/G* site in *IL-6* promoter might play a role in maintaining lower level of blood TG by modulating the *IL-6* expression than in combination with other metabolism-related genes, promoting the TG metabolism. Even so, the exact mechanism merits further investigation.

In conclusion, the findings in this study suggest that *-572G* allele carriers (*CG+GG*) tend to have low level of TG and TG/HDL-C, and the *CG+GG* genotype may play a role in maintaining normal blood TG level. This finding might shed new light on the detection and prediction of HTG in Zunyi sub-population.

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Ethical permission for genetic analysis and collection of test data in the present study was granted by the Research Ethics Committee at Zunyi Medical University (Zunyi, China). Written informed consent was obtained from all participants in the present study. A copy of the consent form is available.

Disclosure of conflict of interest

None.

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