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Full Length Research Paper

The association between C-572G polymorphism of the Interleukin 6 gene promoter and type 2 diabetes mellitus in a Chinese Han population

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As an important inflammatory marker, plasma interleukin-6(IL-6) is associated with type 2 diabetes. However, the distribution of C-572G polymorphism of the IL-6 and its association with type 2 diabetes in Han population are still unclear. The objective of this study was to explore the distribution of C-572G polymorphism in healthy Han subjects and to evaluate the association between the human interleukin-6 C-572G polymorphism and type 2 diabetes in Han population. In cohort one, 326 nondiabetic subjects were analyzed and found there were no differences about clinical and chemistry characteristics including SBP, DBP, BMI, FBG, Fins, TC, LDL, TG, HDL, WHR, even in age and gender in the -572G/G, -572C/G and -572C/C genotype. In cohort two, 358 Han subjects with type 2 diabetes mellitus, significant difference were observed among the -572G/G, -572C/G and -572C/C genotype especially in TG, FBS, FINS and HOMA-IR. The concentration of plasma IL-6 in cohort two was measured and found that there was a significant association between genotypes and plasma IL-6 concentration (G/G vs G/C vs C/C: 8.29±2.77pg/ml vs 6.08±1.62 pg/ml vs 6.46±1.48 pg/ml; P=0.013, for C/C vs G/G; P=0.040, for C/G vs G/G). It may be concluded that there is a significant association between C-572G and T2DM in Liaoning Han population.

Key words: Interleukin 6, C-572G polymorphism, type 2 diabetes, Liaoning Han population.

INTRODUCTION

Diabetes mellitus (DM) is currently estimated to affect more than 90 million Chinese, and dramatically increasing 1 million each year, in which type 2 diabetes mellitus accounts for 90 to 95% (Yang et al., 2010), and predicted to double by 2030 (Wild et al., 2004). The development of type 2 diabetes mellitus is a complicated multi-step and multi-factor process. The pathogenesis of type 2 diabetes mellitus have not clearly elucidated so far. In recent decades, there is growing evidence which proved that elevated circulating inflammatory plasma interleukin-6(IL-6) is involved in type 2 diabetes mellitus (Pradhan et al., 2001; Pickup, 2004). Several studies have shown that interleukin-6(IL-6) could be used to predict the development of type 2 diabetes and as a potential molecular marker for type 2 diabetes (Pradhan et al., 2001; Huth et al., 2006).

Interleukin-6(IL-6) is a central mediator of the acute-phase response and a primary determinant of hepatic production of C-reactive protein (Heinrich et al., 1990). As a pleiotropic cytokine, IL-6 is secreted by a variety of tissues including activated leukocytes, endothelial cells and adipocytes (Pradhan et al., 2001). Furthermore, IL-6 plays an important roles in the regulation of the immune response, inflammation and haematopoiesis (Nishimoto and Kishimoto, 2006). Consistent with other genes, the promoter of IL-6 might control, at least in part, the expression level of IL-6. Therefore, the IL-6 gene promoter polymorphism is very important for IL-6 expression level. Three main polymorphisms have been reported so far in the promoter region of the IL-6 gene such as G -174C, G-572C and G-597A (Brull et al., 2001; Cardellini et al., 2005; Koh et al., 2009). Both G-174C and G -572C are related to type 2 diabetes, respectively

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in Italy and Korean, but it is not clear in Liaoning Han population (Cardellini et al., 2005; Koh et al., 2009).

In the present study, we investigated the distribution of three genotypes G-572G, C-572G and C-572C in Liaoning Han population. The result showed that the genotypes were consistent with Hardy-Weinberg equilibrium proportions. Furthermore, we analysed the association between the human interleukin-6 C-572G gene variants and type 2 diabetes in Liaoning Han population. As about type 2 diabetes cohorts, our results showed that there was a significant association between genotypes and plasma IL-6(G/G vs G/C vs C/C: 8.29 ± 2.77pg/ml vs 6.08 ± 1.62 pg/ml vs 6.46 ± 1.48 pg/ml; P = 0.013, for C/C vs G/G; P = 0.040; for C/G vs G/G). These results indicated that the Interleukin 6 G-572G gene variant was a potential genetic risk factor for type 2 diabetes.

MATERIALS AND METHODS

Ethical approval was granted by the institutional ethical committees and all subjects were gave written informed consent before recruitment.

Subjects

In order to study the distribution of C-572G polymorphism of the interleukin-6 gene promoter in healthy Han population, we studied a total sample of 366 subjects (202 males and 164 females) aged 19-75 in a healthy Chinese Han population from Liaoning district. In cohort 1, 325 unrelated nondiabetic Liaoning Han subjects were studied and recruited at the Fourth Affiliated Hospital of China Medical University. In cohort 2, 358 Liaoning Han subjects with Type 2 diabetes mellitus were recruited at the Fourth Affiliated Hospital of China Medical University. In order to study the correlation between T2DM and C-572G polymorphism of the interleukin-6 gene, the study population consisted of two groups(i)A control group of 326 individuals with normal glucose tolerance(NGT) who were selected from 366 individuals (172 males and 154 females, aged 40 ~ 65 years, average aged 52.8 ± 9.2 years), NGT (a fasting plasma glucose concentration of <0.1mmol/L and a 2h plasma glucose concentration of <7.8 mmol/L, were defined according to the 1999 WHO criteria; We excluded subjects who have serious heart, brain and kidney diseases and have diabetes family history. (ii) a group of 358 Liaoning Han individuals with T2DM (of whom 194 males and 164 females, aged 40~65 years, average aged 54.4 ± 8.3 years) were recruited from the Fourth Affiliated Hospital of China Medical University, NGT (a fasting plasma glucose concentration of ≥7.0 mmol/L and a 2 h plasma glucose concentration of ≥11.1 mmol/L, were defined according to the 1999 WHO criteria. Subjects were excluded from the study if they displayed 1 diabetes and secondary diabetes, autoimmune disorder, infection as determined by medical questionnaire, insulin treatment and oral hypoglycaemic drugs.

DNA isolation and genetyping

Genomic DNA was isolated from peripheral blood according to standard procedures. For The C-572G specific PCR, a 163bp fragment was amplified, the forword primer 5'-GGAGACGCC TTGAAGTAACTGC-3', Reverse primer 5'-GAGTTTCCTCTGACTCCATCGCAG-3'; The C-572G polymorphisms in the promoter of human IL-6 gene was determined by Mbil enzyme digestion. The PCR product was digested by Mbil enzyme. G-572G was digested into two fragments as 101bp and 62bp; G-572G was digested into three fragments as 163, 101 and 62 bp; G-572G can not be digested by Mbil enzyme.

Statistical analysis

Statistical analyses were performed with SPSS version 17.0. Hardy–Weinberg Equilibrium was determined by Haploview version 3.32. Differences in clinical and metabolic variables between the control group and the T2DM group were tested by Student's t-test and a general linear model for adjustment of covariates. The association between T2DM and genotype was calculated as the odds ratio (OR) [95% confidence intervals (CIs)] using a logistic regression analysis. A chi-square test was used to test whether there was a difference among the genotype groups and between control subjects and T2DM patients. Each variable was examined for normal distribution patterns. Significantly, skewed variables were log-transformed. For descriptive purposes, mean values were presented using untransformed and unadjusted values. Results were expressed as mean ± SE, and a two-tailed value of P < 0.05 was considered statistically significant.

RESULTS

The distribution of C-572G polymorphism of the Interleukin 6 gene promoter in Healthy Liaoning Han population

In Liaoning district, there are three genotypes in Han population about C-572G polymorphism of the Interleukin 6 gene such as GG, CG and CC genotype. Observed genotype frequency is consistent with expected frequency (χ^2 = 2.481, P = 0.289) by the Hardy-Weinberg law test, which show that genetic balance of gene frequency has already reached and the sample is group representative. The further analysis of C-572G polymorphism of the Interleukin 6 gene promoter was performed for gender distribution, which have no significant difference between visible genotype and allele frequency (P > 0.05, Table 1).

The distribution of C-572G polymorphism of the Interleukin 6 gene promoter in different races

Compared with the frequency of C-572G polymorphism of the Interleukin 6 gene promoter from other countries people, such as Britain, France, Korea, America, Italy, Japan and so on, we found that there is no significant difference between Han and Japanese and Korean (P > 0.05). However, there is a significant difference between Han and Britain, France, America, Italy and so on (Hrnciar et al., 1999; Pradhan et al., 2001; Bastard et al., 2002; Festa et al., 2002; Pickup, 2004; Wellen and Hotamisligil, 2005; Nieto-Vazquez et al., 2008).

From Table 2, the most genotype is CC in Liaoning Han,

Table 1. The distribution of C-572G polymorphism of the Interleukin 6 gene promoter in Healthy Liaoning Han population.

	N	Genotype (n, %)						Allele (n, %)			
		CC		CG		GG		C		G	
Male	202	124	61.39	73	36.14	5	2.47	321	79.46	83	20.54
Female	164	110	67.07	52	31.71	2	1.22	272	82.93	56	17.07
Total	366	234	63.93	125	34.15	7	1.92	593	81.01	139	18.99
		χ^2 = 1.725 P = 0.422						χ^2 = 1.418 P = 0.234			

Table 2. The distribution of C-572G polymorphism of the Interleukin 6 gene promoter in different races.

	N	Genotype (n, %)						Allele (n, %)			
		GG		GC		CC		G		C	
Britain *!	2458	2224	90.5	225	9.1	9	0.4	4673	95.1	243	4.9
America *!	111	90	81.0	21	19.0	0	0.0	201	90.5	21	9.5
Japan	470	21	4.5	133	28.3	316	67.2	175	18.6	765	81.4
Korea	1477	68	4.6	547	37.0	862	58.4	683	23.1	1409	76.9
France *!	495	435	87.9	57	11.5	3	0.6	927	93.6	63	6.4
Italy *!	156	131	84.0	23	14.7	2	1.30	285	99.9	27	0.1
Spain*!	296	246	83.1	49	16.6	1	0.3	541	91.4	50	8.4
Denmark*!	4382	4037	92.1	325	7.4	20	0.5	8399	95.8	365	4.2
China(Han)	366	7	1.9	125	34.2	234	63.9	139	19.0	593	81.0

Notes: Comparison of genotype or allele between other countries and Liaoning Han, ! refers to the Caucasian.

Table 3. The comparison of clinical and biochemistry characters in 366 -572C/G different genotype subjects.

Clinical data	CC genotype (n = 234)	CG genotype (n = 125)	GG genotype (n = 7)	F value (*P* value)
Men/female)	124/110	72/53	4/3	0.356 (0.701)
Age (years)	44.0 ± 11.4	42.3 ± 10.8	43.9 ± 10.4	0.950 (0.388)
BMI (kg/m^2)	24.16 ± 2.1	24.0 ± 2.2	23.9 ± 1.37	0.229 (0.795)
WHR	0.85 ± 0.08	0.84 ± 0.08	0.86 ± 0.09	0.330 (0.719)
SBP (mmHg)	122.8 ± 11.1	123.3 ± 13.0	118.6 ± 8.6	0.593 (0.553)
DBP(mmHg)	79.7 ± 8.7	78.7 ± 8.0	78.6 ± 5.2	0.597 (0.551)
FBG (mmol/L)	5.0 ± 0.4	5.0 ± 0.4	5.2 ± 0.2	0.984 (0.375)
Fins (uu/mL)	6.33 ± 1.6	6.22 ± 1.49	6.29 ± 1.4	0.16 (0.853)
TC (mmol/L)	4.37 ± 0.81	4.34 ± 0.72	4.38 ± 1.03	0.031(0.969)
LDL (mmol/L)	2.70 ± 0.91	2.90 ± 1.29	2.91 ± 0.89	1.606 (0.202)
TG (mmol/L)	1.69 ± 0.92	1.84 ± 1.03	2.16 ± 1.19	1.649 (0.194)
HDL (mmol/L)	1.32 ± 0.27	1.36 ± 0.31	1.31 ± 0.33	0.757 (0.470)

Japanese and Korean, which frequency is 63.9, 67.2, 58.4%, respectively. The middle genotype is CG and the least is GG. However, the CC genotype is the least in the Caucasian from Britain, France, America, Italy, Spain and Denmark, the genotype frequency is 0.4, 0.6, 0, 1.3, 0.3 and 0.5%, respectively. The middle genotype is CG and the most is GG. The allele C is the most common genotype in Liaoning Han, Korean and Japanese, in which the frequency is 81.0, 76.9, 81.4%, respectively and the allele G is rare. Whereas allele C is rare in the Caucasian from Britain, France, America, Italy, Spain and Denmark, in which the frequency is 4.9, 6.4, 9.5, 0.1, 8.4 and 4.2%, respectively.

The relation between clinical and biochemistry character and C-572G polymorphism of the Interleukin 6 gene

The distribution of CC, CG and GG genotype is 234, 125 and 7, respectively from 366 subjects. Table 3 shows the comparison of three genotypes in clinical and

Table 4. The comparison of clinical data between blood sugar normal control group and type 2 diabetes mellitus group.

Clinical data	T2DM	NGT	*P* value
N (M/F)	358(194/164)	326(172/154)	0.708
Age (years)	49.37 ± 6.02	49.1 ± 6.08	0.483
BMI(kg/m^2)	25.00 ± 2.09**	23.90 ± 1.91	0.000
WHR	0.86 ± 0.09*	0.84 ± 0.08	0.003
SBP(mmHg)	130.4 ± 14.9**	122.1 ± 11.2	0.000
DBP (mmHg)	82.2 ± 8.1**	79.0 ± 8.0	0.000
FBG (mmol/L)	8.84 ± 4.0**	5.0 ± 0.39	0.000
FINS (uU/ML)	8.84 ± 4.0**	6.4 ± 1.7	0.000
TC (mmol/L)	5.17 ± 0.86*	5.03 ± 0.61	0.014
TG (mmol/L)	1.99 ± 0.85**	1.61 ± 0.28	0.000
LDL(mmol/L)	2.88 ± 0.93	2.74 ± 1.06	0.065
HDL (mmol/L)	1.17 ± 0.20**	1.29 ± 0.22	0.000
HOMA-IR	3..67 ± 1.49**	1.43 ± 0.39	0.000

Notes: T2DM group compared with NGT group, * significant difference; **extremely significant difference; HOMA-IR refers to non-normal distribution, t-test was performed after natural logarithm processing.

biochemistry characters including gender, age, SBP, DBP, BMI, FBG, Fins, TC, LDL, TG, HDL, WHR.

The comparision of clinical character between blood sugar normal control group and type 2 diabetes mellitus group

There is no obvious difference between control and type 2 diabetes mellitus group in age, gender, LDL and HDL. However, there is a significant difference between control and type 2 diabetes mellitus group in BMI, WHR, SBP, DBP, FBG and TC. The type 2 diabetes mellitus group is higher than control (Table 4).

The distribution of C-572G polymorphism of the Interleukin 6 gene promoter in T2DM group and control

There are three genotypes on IL-6 gene -572 site in two research groups (T2DM group and control) including CC, CG and GG genotype. The genotype frequency decreased according to the sequence of CC, CG and GG. As about CC, there is not obvious difference between T2DM group and control ($\chi^2 = 5.012$, P = 0.082). There is significant difference between the merge of CC and CG genotype and GG genotype ($\chi^2 = 4.44$, P = 0.035) (Table 5). The GG genotype frequency of T2DM group is higher than control, on the contrary, CC is lower in T2DM group than control.

GG genotype is significant difference compared with CC genotype ($\chi^2 = 4.797$, P = 0.029) (Table 6). CC genotype as the control, OR value of GG genotype is 2.78 ($P < 0.05$). There are no significant difference between allele GG and CC. These results show that individuals with GG genotype have a higher risk of developing into T2DM.

The revelance between clinical and biochemistry characters of T2DM and C-572G polymorphism of the Interleukin 6 gene promoter

There are obvious differences about three different genotypes distribution in T2DM groups. CC genotype is the most, the CG genotype is middle and the GG is least. T2DM groups with three different genotype respectively have no significant difference in age, gender, BMI, WHR, SBP, DBP, TC, LDL and HDL ($P > 0.05$) (Table 7). In order to elucidate the relationship between T2DM and C-572G polymorphism of the Interleukin 6 gene promoter, we tested clinical and biochemistry characters the subjects with T2DM. There are statistic significant difference between CC genotype and GG genotype in the subjects with T2DM, the same as previous results and it also show that there is statistic significant difference between CG genotype and GG genotype especially in TG, FBP, FINS and HOMA-IR.

The association between C-572G polymorphism of the Interleukin 6 gene promoter and type 2 diabetes mellitus

In order to understand whether the patients with type 2 diabetes associated with C-572G polymorphism of the Interleukin 6 gene promoter, we tested the plasma concentration of Interleukin 6. There was no obvious difference between CC genotype and CG genotype (CC:

Table 5. The distribution of C-572G polymorphism of the Interleukin 6 gene promoter in T2DM group and control.

IL-6-572C/G	T2DM	(N=358)	NGT	(N = 326)	χ² (*P*▪)
	N	%	N	%	
CC	212	59.2	208	64.0	5.01(0.08)▵
CG	129	36	112	34.4	0.57(0.45)▲
GG	17	4.7	6	1.84	4.79(0.03)▲
C	553	77.2	528	81.0	
G	149	22.8	124	19.0	1.023(0.312)
CC+CG	341	95.3	320	98.1	4.44(0.035) *
CG+GG	146	40.8	118	36.2	1.514(0.22)

Notes: ▵, The results is from three genotypes comparison.; ▲, shows the results compared with CC genotype; * refers to the results from comparison between GG genotype and the merge of CC and CG genotype.

Table 6. The risk comparison of T2DM between -572C/G genotype and allele.

IL-6-572C/G	χ²	*P*	OR	95%CI
CG/CC*	0.571	0.45	1.13	0.82 ~ 1.55
GG/CC	4.497	0.029	2.78	1.08 ~ 7.19
CC+CG/GG	4.441	0.035	0.376	0.15 ~ 0.97
CG+GG/CC	1.514	0.219	1.214	0.89 ~ 1.65
G/C	1.023	0.312	1.147	0.88 ~ 1.50

Notes: * Indicate results of comparison between CG genotype and CC genotype.

Table 7. Clinical characteristics of patients with T2DM among genotypes of C-572G polymorphism of the Interleukin 6 gene promoter.

Genotype	CC	CG	GG	F value	P value
N (M/F)	212 (111/101)	129(73/56)	17(10/7)	0.733	0.693
Age (years)	49.20 ± 6.0	49.78 ± 6.0	48.41 ± 6.8	0.599	0.550
BMI (kg/m²)	24.97 ± 2.2	24.92 ± 2.0	26.10 ± 1.7	2.439	0.089
WHR	0.84 ± 0.08	0.85 ± 0.07	0.85 ± 0.10	0.365	0.695
SBP (mmHg)	131.4 ± 14.1	129.5 ± 16.1	125.8 ± 14.8	1.525	0.219
DBP (mmHg)	81.98 ± 7.95	82.36 ± 8.63	83.29 ± 5.87	0.257	0.773
FBG (mmol/L)	8.47 ± 1.2**	8.78 ± 1.39**	9.71 ± 1.68	8.313	0.000
FINS(uU/ML)	8.10 ± 2.58**	10.48 ± 3.4**	13.9 ± 6.39	43.123	0.000
TC (mmol/L)	5.17 ± 0.89	5.17 ± 0.84	5.19 ± 0.77	0.006	0.994
TG (mmol/L)	1.98 ± 0.84*	2.01 ± 0.82*	2.52 ± 1.20	3.092	0.047
LDL (mmol/L)	2.90 ± 0.93	2.85 ± 0.97	2.90 ± 0.70	0.153	0.859
HDL (mmol/L)	1.17 ± 0.21	1.17 ± 0.18	1.12 ± 0.19	0.480	0.619
HOMA-IR	3.34 ± 1.17 *	3.2 ± 1.42**	6.22 ± 2.70	44.31	0.000

Notes: * compared to GG genotype, P < 0.05; ** compared to GG genotype, P < 0.01.

6.08 ± 1.62 pg/ml vs CG:6.458 ± 1.48 pg/ml, p > 0.05). In contrast, there was significant difference between CC genotype or CG and GG genotype (CC: 6.08 ± 1.62 pg/ml vs GG: 8.29 ± 2.77 pg/ml, p = 0.013; CG: 6.08 ± 1.62 pg/ml vs GG:8.29 ± 2.77 pg/ml; p = 0.040) (Figure 1).

Analysis of logistic regression models for potential T2DM risk factors

In order to screen the main risk factors in patients with T2DM, we performed the single variable factor analysis of Logistic regression models. Then, we used the method of

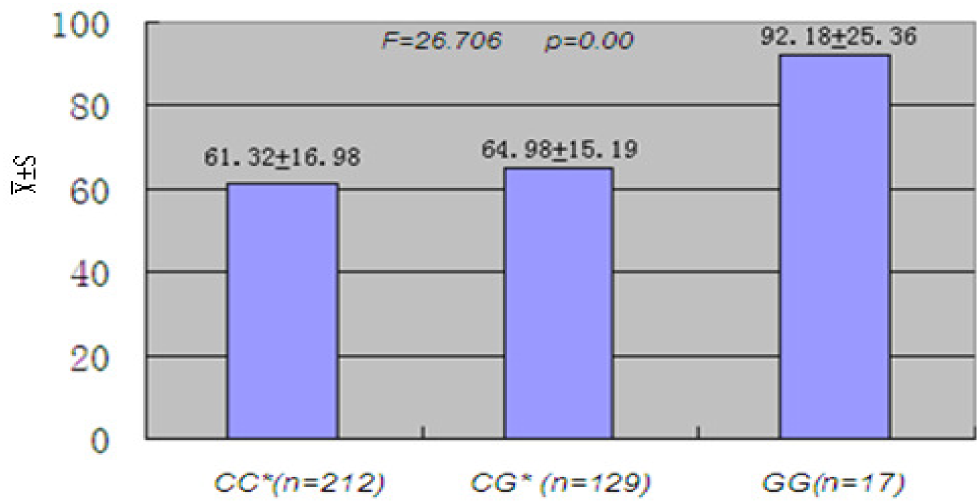

Figure 1. The comparison of the concentration of IL-6 in different genotype patients with T2DM
Notes: * compared to GG genotype, P = 0.000.

Table 8. The analytical results of multivariate logistic for patients with T2DM.

Risk factor	B	S.E.	Wald	Sig.	OR	95% CI
BMI	0.078	0.038	4.2	0.04	1.081	0.98 ~ 2.35
FBG	5.25	1.192	19.40	0.000	190.52	4.68 ~ 242.65
Fins	1.018	0.512	3.948	0.047	2.767	1.962 ~ 9.67
TG	5.129	1.627	9.935	0.002	168.83	13.12 ~ 321.57
572GG	1.027	0.485	4.490	0.034	2.793	2.04 ~ 9.85

step by step regression to screen independent risk factor by introducing candidate variables into multivariate logistic regression models. Strikingly, several risk factors were identified including BMI, FBG, Fins in patients with T2DM (Table 8).

DISCUSSION

The pathogenesis and mechanism of type 2 diabetes mellitus have not yet been clarified. Family studies, twin studies and ethnic studies explained genetic factors which play an important role type 2 diabetes mellitus. Most scholars believe that most type 2 diabetes mellitus is a non-Mendelian genetics, multi-factor gene or genetic disease. In addition to genetic susceptibility of type 2 diabetes mellitus, environmental factors have more important influence than others. At the same time, different ethnic groups and geographic areas at both the genetic and phenotypic existed heterogeneity.

Epidemiological survey shows that, the ratio of patients with type 2 diabetes mellitus increased with increasing age. Type 2 diabetes mellitus in China occurred in people over 40 years old and the elderly. Therefore, this study selected over 40 years old Liaoning Han population as research object which excluded a family history of type 2 diabetes mellitus in the control group in order to increase the homogeneity of the two groups. *Insulin resistance and hyposecretion of insulin* are two major features in the pathogenesis of type 2 diabetes (Alberti and Zimmet, 1998). It is an important way for exploring the genetic factors in type 2 diabetes mellitus to investigate two aspects which lead to abnormal expression of candidate genes. More and more studies suggested that chronic low immune system activation may be the pathogenesis of insulin resistance and type 2 diabetes mellitus determinants.

Recent studies show that insulin resistance was related with circulating immune markers change, chronic inflammation and so on. IL-6 is the most closely with the endocrine of inflammatory cytokines (Papanicolaou and Vgontzas, 2000). The expression of IL-6 was related with indicators of obesity in many reactions, such as BMI, waist-hip-ratio (WHR), the percentage of body fat. The expression of IL-6 increased under insulin resistance in T2DM (Vozarova et al., 2001). Therefore, IL-6 is considered as an independent risk factor for diabetes, which can reduce cell surface GLUT (glucose transporter)-4 expression, thereby decreasing the transportation of insulin-mediated glucose and fat in fat cells to promote diabetes. IL-6 can reduce the insulin receptor substrate-1 (insulinreceptorsubstrate1, IRS-1) tyrosine phosphorylation and downstream phosphatidylinositol-3 - kinase (phosphatidylinositol3-kinase, PI3K) activity, resulting in insulin resistance (Senn et al., 2002). The concentration of plasma IL-6 can predict the risk which the future health of people suffering from type 2 diabetes, but elevated plasma interleukin-6 weather is the etiology of T2DM or results is not clear. Insulin can promote elevated plasma IL-6 through various mechanisms (LaPensee et al., 2008). Krogh-Madsen found that IL-6 expression had been significantly increased under high insulin in type 2 diabetes mellitus patients (Krogh-Madsen et al., 2004). Both IL-6 and hyperinsulinemia promote each other, creating a vicious cycle, increased diabetes symptoms. On the other hand, IL-6 can be used as the origin of acute response factors to affect the incidence of diabetes. In the early stage of diabetes, IL-6 increases insulin secretion, resulting in hyperinsulinemia. When IL-6 increases to a certain extent, the inhibition of insulin secretion harms the B cells to aggravate the development of diabetes.

The study of correlation between type 2 diabetes mellitus and a functional IL-6 gene polymorphism was designed to find out the cause of type 2 diabetes mellitus. It is helpful to explain the reasons for some individuals susceptible to type 2 diabetes mellitus.

Our results showed that there are significant difference C-572G polymorphism of the Interleukin 6 gene promoter in type 2 diabetes mellitus group and control group. 572GG genotype was 2.78 times as much as the CC genotype on the risk of type 2 diabetes mellitus (90% CI: 1.08 ~ 7.19, P = 0.029). Whereas the CG genotype compared with CC genotype, the risk of diabetes was no significant increase. The risk of type 2 diabetes mellitus was no significant difference between CC allele GG allele. These results suggested that type 2 diabetes mellitus had associated with -572C/G polymorphism of IL-6 gene promoter. 572GG genotype was genetic risk factors and susceptibility genes of type 2 diabetes mellitus. These results were consistent with previous study results that the GG genotype of the cells had secreted high levels of IL-6. The results of this study was the same as Nieto, suggesting that IL-6 gene polymorphism was genetic risk factors of type 2 diabetes mellitus (Chang et al., 2004; Herbert et al., 2006; Stephens et al., 2007; Nieto-Vazquez et al., 2008; Huth et al., 2009). The number of scholars studies showed that the incidence of type 2 diabetes had associated with IL-6 gene 174C/G polymorphism. These studies may help explain the reasons why a number of healthy people susceptibility to develop into type 2 diabetes, and inflammation at gene level was confirmed participation in the incidence of type 2 diabetes, which emphasized the role of inflammation in type 2 diabetes pathogenesis, these these will provides a theoretical basis on anti-inflammatory treatment of type 2 diabetes.

Obesity is an independent risk factor of type 2 diabetes, epidemiological investigations revealed that obesity itself can cause insulin resistance (Riserus et al., 2009). Insulin receptor of obese people in peripheral target tissues decreased. Accordingly, the inhibition of hepatic glucose production will be weakened by insulin. Meanwhile, increased free fatty acids can affect glucose utilization and need to secrete more insulin, adding especially genetic background, finally leading to B cell dysfunction. Our study also confirmed this conclusion: patients with type 2 diabetes, BMI and WHR levels were higher than control, and the difference was significant. Our study found that BMI was higher in patients carrying GG genotype than CC or CG genotype. There was statistically significant difference between GG genotype and the CG or CC genotypes including fasting blood glucose level, fasting insulin, triglyceride levels and insulin resistance index. Possible reasons were that, the carrying GG genotype secreted more IL-6, accordingly, stimulating insulin secretion, resulting in hyperinsulinemia. Therefore, both insulin resistance and fasting blood sugar increasing. However, insulin resistance led to dyslipidemia. Our study suggests that IL-6 gene -572C→G mutation may be one of the reason to develop into hyperinsulinemia, insulin resistance and dyslipidemia

Our study found that there were different concentration of plasma IL-6 in patients with type 2 diabetes among different IL-6 gene -572C / G genotypes such as GG, CC and CG genotypes (respectively 8.29 ± 2.77, 6.08 ± 1.62 and 6.46 ± 1.48, unit: pg / ml). Especially, there was significant difference between GG and CC or CG genotype (P = 0.013, P = 0.040). This was consistent with the results from mononuclear cells. Accordingly, there was no significant difference about the concentration of plasma IL-6 in non-diabetic population. These results further provided a strong evidence that C-572G polymorphism of the Interleukin 6 gene promoter was potential reason why people with GG genotype easily to develop into 2 type diabetes. So in type 2 diabetes early, GG genotype have a higher level of IL-6, which could be used to predict the risk of diabetes by detecting the levels of IL-6.

In recent years, type 2 diabetes etiology and pathogenesis have made some progress, but the mechanism of type 2 diabetes have not completely revealed yet. Whereas, it is effective way to clone the type 2 diabetes genes and make the genetic map. This study was a preliminary study of the association between C-572G polymorphism of the Interleukin 6 gene promoter and type 2 diabetes, the results shown that IL-6 -572G allele could be type 2 diabetes susceptibility gene, also suggested that inflammation in type 2 diabetes could play a role in the pathogenesis. Increasing of the expression of IL-6 in type 2 diabetes may be one of the causes.

These will provide a new rationale for future prevention, diagnosis and treatment.

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