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Variants -250G/A and -514C/T in the *LIPC* gene are associated with hypertensive disorders of pregnancy in Chinese women

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ABSTRACT. We examined the influence of the promoter polymorphisms -250G/A (rs2070895) and -514C/T (rs1800588) in the human hepatic lipase (*LIPC*) gene on dyslipidemia and hypertensive disorders complicating pregnancy (HDCP) in a Chinese population. Clinically defined HDCP patients (N = 321) and healthy pregnant women (N = 331) were recruited and genotyped using polymerase chain reaction-restriction fragment length polymorphism for the two *LIPC* single nucleotide polymorphisms (SNPs). The results showed significant relationships between HDCP and triglycerides, apolipoprotein A1, and high-density lipoprotein cholesterol ($P < 0.05$), which confirmed that HDCP was accompanied by dyslipidemia. The results also demonstrated that in gestational hypertension (GH) patients, both total cholesterol (TC) and systolic blood pressure (SBP) levels were related to the two SNPs ($P \leq 0.004$), although no significant

association was found between HDCP and *LIPC* genotypes or alleles. Significant linkage disequilibrium of the two SNPs was found in both HDCP patients ($R^2 = 0.867$) and controls ($R^2 = 0.91$). Body mass index (BMI) was associated with -250G/A in women with mild preeclampsia (MPE) (P = 0.01). Carriers of the mutant homozygote -250AA genotype presented higher BMI in the MPE group. In conclusion, the *LIPC* -250G/A and -514C/T variants influenced TC and SBP levels in GH patients and the BMI level in the MPE group, although there was no evidence to validate an association between HDCP and *LIPC* allele, genotype, or haplotype frequencies.

Key words: *LIPC* gene; SNP; Gestational hypertension; Preeclampsia; Lipid metabolism

INTRODUCTION

Hypertensive disorders complicating pregnancy (HDCP) is the most common obstetric complication, and can be classified into gestational hypertension (GH), mild preeclampsia (MPE), severe preeclampsia (SPE), and eclampsia (Gunningham et al., 2001). Ischemia, impaired trophoblast invasion, endothelial dysfunction, genetic susceptibility, abnormal lipid metabolism, and immune factors all contribute to the pathogenesis of HDCP (Williams and Broughton, 2011).

Previous studies confirmed that HDCP results from the combined effects of hereditary and environmental factors (Serrano et al., 2004). To date, however, no gene has been reported to be involved in the pathogenesis of HDCP. Srinivas et al. (2009) found that metabolic syndrome is associated with preeclampsia. An unfavorable lipid profile, which is associated with an increased risk of cardiovascular disease, has also been found in women who suffer from HDCP. Therefore, the potential role of dyslipidemia in the genesis or development of HDCP has attracted increasing attention. Dyslipidemia, which is characterized by increased low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and triglyceride (TG) levels and decreased high-density lipoprotein cholesterol (HDL-C) levels, was found to be associated with increased risk of preeclampsia (PE) (Enquobahrie et al., 2004). Numerous candidate genes that are involved in regulating plasma concentrations and characteristics of lipids and lipoproteins were demonstrated to be responsible for the PE dyslipidemia (Saarela et al., 2006). Enquobahrie et al. (2005) found that the human hepatic lipase (*LIPC*) -514TT genotype and overweight status, when occurring together, were associated with a 3-fold increase in the risk of PE among Peruvian women. However, little attention has been paid to the association between the *LIPC* gene single nucleotide polymorphisms (SNPs) and the risk of HDCP in the Chinese population.

The *LIPC* gene, locating on the chromosome region 15q21-q23 (Sparkes et al., 1987), encodes the hepatic lipase (HL) enzyme, which is known to play a central role in regulating the concentration and structure of plasma lipids (Ameis et al., 1990). Four SNPs (-514C/T, -250G/A, -763A/G, and -710T/C) in the promoter region of the *LIPC* gene were found to be associated with LIPC enzyme activity, dyslipidemia, and insulin resistance

(Tahvanainen, 1998; Pihlajamaki et al., 2000; Andersen et al., 2003). Notably, these characteristics are potential risk determinants of HDCP (Pouta et al., 2004). However, not all studies reached similar conclusions (Hegele et al., 1999; Su et al., 2002). Furthermore, some studies reported that these associations were modified by other factors, including obesity, plasma lipids, physical activity, and diet (Deeb et al., 2003; Riestra et al., 2009; Kashani Farid et al., 2010; Ahmad et al., 2011). Previous research found that the effects of body mass index (BMI) and the -514C/T polymorphism on HL activity appeared to be additive and independent (Nie et al., 1998).

Based on the evidence that LIPC is a crucial regulator of lipid metabolism, we aimed to examine the influence of the *LIPC* gene -250G/A and -514C/T variants on dislipidemia and HDCP in Chinese women using serum lipid parameter analysis and the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method.

MATERIAL AND METHODS

Study population

Clinically defined HDCP patients (the HDCP group, N = 321) and healthy pregnant women (the control group, N = 331) were recruited retrospectively from Fujian Women's and Children's Healthcare Hospital from 2009 to 2011. The protocol was approved by the Institute Ethics Committees of both Fujian Medical University and Fujian Women's and Children's Healthcare Hospital, and each subject provided written informed consent. The HDCP patients included GH (N = 58), SPE (N = 207), and MPE (N = 56). Controls [blood pressure (BP) <140/90 mmHg, no antihypertensive medication, and no diagnosed diseases] were recruited according to geographical distribution. All participants were of Han Chinese ethnicity in a genetically isolated population.

The inclusion criteria for recruitment were primiparous, singleton pregnancies, not receiving any medication known to interfere with lipid metabolism or lipid determination. The exclusion criteria were: a history of hemolysis, liver dysfunction, and low platelets (HELLP) syndrome; chronic renal disease; diabetes mellitus; multiple gestations; preexisting hypertension.

Measurements of lipids and lipoproteins

After an overnight fast, peripheral blood samples were collected. Plasma was separated for lipid and lipoprotein analysis. The clinical investigation of lipid profiles (TC, TG, apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), and HDL-C), blood glucose, and creatinine were performed by using an automated chemistry analyzer (Olympus AU5400, Japan) and an enzymatic kit (Roche Diagnostics GmbH).

Genotyping

Genomic DNA was extracted from the blood samples by using a DNA extraction kit according to manufacturer instructions (TIANGEN, China). The purity of extracted DNA was

measured by UV spectrophotometry (NanoDrop, ND-1000). The two SNPs were genotyped by using the PCR-RFLP method. The primers of the -250G/A and -514C/T polymorphisms were F: 5'-GATACTTTGTTAGGGAAGACTGCC-3', R: 5'-GGATCACCTCTCAATGGGTC-3'; and F: 5'-CGCCTTTTCCCTACCTGATTTTG-3', R: 5'-TTCCACGTGGCTGCCTAAG-3' (Shanghai Generay Biotech Co., Ltd.), respectively. The PCR conditions were: initial denaturation at 94°C for 2 min, followed by 30 cycles of denaturation at 98°C for 30 s, annealing at 64°C for 30 s, and extension at 72°C for 30 s, with a final extension at 72°C for 7 min (GeneAmp 2720 Thermocycler; ABI Corp., USA). PCR products were then digested with 1 μL restriction enzymes *Dra*I and *Nla*III (Fermentas China Co. Ltd., Shenzhen, China) at 36°C, followed by electrophoresis on 2% agarose gel.

To validate the results, genotyping experiments were repeated and direct sequencing was performed in 10% of the samples. The genotypes of these samples were completely consistent.

Haplotype analysis

The SHEsis online software (http://analysis2.bio-x.cn/myAnalysis.php) was applied to estimate Hardy-Weinberg equilibrium, linkage disequilibrium coefficients, allele frequencies, genotype frequencies, and haplotype frequencies. The same program was used to examine correlations between haplotype and HDCP or controls. All statistical tests were two-sided and P values <0.05 were considered to be statistically significant.

Statistical analysis

Statistical analyses were performed with the SPSS for Windows software (version 13.0; Chicago, IL, USA). Differences in clinical characteristics between cases and controls were evaluated using independent Student *t*-tests. Quantitative measurements are reported as means ± SD. The chi-square test was used to compare categorical variables. PE was characterized by hypertension (BP ≥140/90 mmHg on two or more occasions at an interval of more than 6 h) and proteinuria (protein excretion ≥300 mg/dL in a 24-h urine collection) or +1 on a dipstick in women who were normotensive in early pregnancy (less than 20 weeks gestation). SPE was characterized by hypertension (BP ≥160/110 mmHg on two or more occasions at an interval of more than 6 h) and proteinuria (protein excretion ≥500 mg/dL per 24 h) or +3 on a dipstick. Differences in lipid traits based on genotypes were evaluated using analysis of covariance (ANCOVA) and were adjusted by maternal age, gestational age at delivery, and pregnancy BMI. Univariate ANOVA was used to test relationships between genotypes and traits that showed statistically significant differences. The comparisons of associations are reported as odds ratios (OR) with the corresponding 95% confidence interval. P values <0.05 were considered to be statistically significant.

RESULTS

Main characteristics of patients and controls

The main characteristics of the patients and controls are summarized in Table 1.

Maternal age, pregnancy BMI, systolic blood pressure (SBP), diastolic blood pressure, and plasma TG, TC, glucose, blood urea nitrogen, creatinine, and uric acid levels were significantly higher in the HDCP group compared with the controls. There was no significant difference in ApoB and HDL-C levels between the two groups. Our study also showed that premature delivery and lower newborn weight were clearly related to HDCP.

Table 1. Main characteristics of the hypertensive disorders complicating pregnancy (HDCP) and normotensive pregnancies.

Variable	HDCP (N = 321)	Normotensives (N = 331)	P
Maternal age (years)	29.10 ± 5.57	27.89 ± 4.17	0.002*
Gestational age (weeks)	36.00 ± 3.74	38.81 ± 2.47	<0.001*
Pregnancy BMI (kg/m^2)	28.26 ± 5.12	24.92 ± 3.02	<0.001*
Newborn weight (g)	2512.14 ± 904.60	3271.85 ± 449.46	<0.001*
SBP (mmHg)	148.39 ± 20.92	110.66 ± 9.92	<0.001*
DBP (mmHg)	93.90 ± 14.30	68.80 ± 7.79	<0.001*
TG (mM)	3.92 ± 1.87	3.27 ± 1.28	<0.001*
TC (mM)	6.74 ± 1.92	6.34 ± 1.20	<0.001*
ApoA1 (g/L)	1.86 ± 0.47	2.00 ± 0.25	<0.001*
ApoB (g/L)	1.22 ± 0.47	1.22 ± 0.26	0.963
HDL-C (mM)	1.90 ± 0.47	1.85 ± 0.37	0.166
Glu (mM)	5.76 ± 1.74	5.24 ± 1.52	<0.001*
BUN (mM)	4.25 ± 1.67	3.59 ± 0.98	<0.001*
Cr (mM)	64.73 ± 17.09	55.08 ± 10.73	<0.001*
Uric acid (μM)	361.74 ± 97.42	285.50 ± 63.67	<0.001*

Data are reported as means ± SD. BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; TG = triglyceride; TC = total cholesterol; ApoA1 = apolipoprotein A1; ApoB = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; Glu = glucose; BUN = blood urea nitrogen; Cr = creatinine. *P < 0.05.

Allele, genotype, and haplotype frequencies in patients and controls

The genotypic distribution of each polymorphism did not deviate from Hardy-Weinberg equilibrium in either the HDCP or the control group. Based on the chi-square test, -250G/A and -514C/T genotypes and alleles were not associated with HDCP. This suggested that these SNPs did not contribute to the risk of developing HDCP during pregnancy in our population. The ORs of the association between the two SNPs and HDCP were also calculated. The results of the dominant inheritance models suggested that subjects with the allele -250A or -514T would not be at an increased risk of HDCP.

Haplotype analysis based on these two *LIPC* SNPs was performed to evaluate the association between HDCP and the four haplotypes. We found significant linkage disequilibrium between the two SNPs (-250G/A and -514C/T) in HDCP patients (R^2 = 0.867) and controls (R^2 = 0.91). The common haplotypes (frequency >0.03) were -250A/-514T and -250G/-514C. No significant differences for the estimated frequencies of the four haplotypes between patients and controls were detected, and no haplotype showed an increased risk of developing HDCP (Table 2).

Lipid levels of different genotypes in patients

No significant differences were found between different genotypes of the two SNPs (-250G/A and -514C/T) and lipid traits in HDCP patients. One-way ANOVA based on

subgroups showed the following results: BMI levels among different genotypes of the -250G/A polymorphism differed significantly in the MPE group (P = 0.01); TC and SBP levels differed significantly in the GH group among different genotypes of the -250G/A polymorphism (P = 0.004 and P = 0.014, respectively) and the -514C/T polymorphism (P = 0.003 and P = 0.004, respectively), as shown in Table 3. Results of the general linear model showed that mild-type individuals with homozygous -250GG and -514CC genotypes presented lower TC levels in the GH subgroup (P = 0.001 and P = 0.017, respectively), and these genotypes were also associated with lower SBP levels (P = 0.004 and P = 0.001, respectively). Of particular note, BMI in the MPE group was only related to the -250G/A polymorphism. Participants with the -250AA genotype had higher BMI compared to those with GG and GA genotypes (P = 0.003; Table 4).

Table 2. Associations between the -250G/A and -514C/T polymorphisms and the risk of HDCP.

		Cases [N (%)]	Controls [N (%)]	OR (95%CI)	P value
-250G/A genotype	GG	120 (37.4)	119 (36.0)	1 (reference)	0.977
	GA	151 (47.0)	161 (48.6)	1.059 (0.770-1.456)	0.726
	AA	50 (15.6)	51 (15.4)	0.985 (0.734-1.321)	0.917
	GA+AA	201 (62.6)	212 (64.0)	1.029 (0.666-1.590)	0.897
-250G/A allele	G	391 (60.9)	399 (60.3)		0.81
	A	251 (39.1)	263 (39.7)		
-514C/T genotype	CC	127 (39.6)	126 (38.1)	1 (reference)	0.979
	CT	151 (47.0)	160 (48.3)	1.065 (0.777-1.460)	0.695
	TT	43 (13.4)	45 (13.6)	0.977 (0.741-0.341)	0.986
	CT+TT	194 (60.4)	205 (61.9)	1.010 (0.636-1.602)	0.967
-514C/T allele	C	405 (63.1)	412 (62.2)		0.75
	T	237 (36.9)	250 (37.8)		
Haplotypes	-250A/-514C	18.09 (0.028)	14.02 (0.021)	-	-
	-250A/-514T	232.91 (0.363)	248.98 (0.376)	0.962 (0.767-1.207)	0.74
	-250G/-514C	387.91 (0.604)	397.98 (0.601)	1.039 (0.828-1.304)	0.74
	-250G/-514T	3.09 (0.005)	1.02 (0.002)	-	-

Haplotype frequencies <0.03 were ignored.

Table 3. Lipid levels of the -250G/A and -514C/T polymorphisms among the HDCP subgroups.

		-250G/A			P	-514C/T			P
		GG (N = 18)	GA (N = 27)	AA (N = 11)		CC (N = 18)	CT (N = 29)	TT (N = 9)	
MPE	TG	3.17 ± 0.40	4.29 ± 0.37	3.89 ± 0.69	0.138	3.36 ± 0.41	4.13 ± 0.36	3.86 ± 0.83	0.379
	TC	5.87 ± 0.38	6.91 ± 0.36	6.90 ± 0.66	0.115	5.85 ± 0.38	6.93 ± 0.33	6.86 ± 0.77	0.098
	ApoA1	1.88 ± 0.11	1.83 ± 0.11	1.74 ± 0.19	0.811	1.89 ± 0.11	1.82 ± 0.10	1.69 ± 0.23	0.726
	ApoB	1.18 ± 0.10	1.19 ± 0.10	1.22 ± 0.18	0.978	1.15 ± 0.10	1.21 ± 0.09	1.20 ± 0.22	0.916
	HDL-C	1.88 ± 0.12	1.96 ± 0.11	2.22 ± 0.20	0.367	1.89 ± 0.12	2.01 ± 0.10	2.08 ± 0.24	0.644
	BMI	29.26 ± 1.04	27.05 ± 0.94	33.10 ± 1.67	0.010*	29.06 ± 1.09	27.69 ± 0.94	33.15 ± 2.11	0.074
	SBP	140.28 ± 3.55	137.23 ± 3.34	141.55 ± 6.14	0.771	140.66 ± 3.40	135.51 ± 3.00	150.15 ± 6.94	0.156
		GG (N = 23)	GA (N = 28)	AA (N = 7)	P	CC (N = 24)	CT (N = 28)	TT (N = 6)	P
GH	TG	3.65 ± 0.45	3.28 ± 0.41	4.51 ± 0.82	0.391	3.62 ± 0.44	3.30 ± 0.42	4.51 ± 0.82	0.408
	TC	5.53 ± 0.22	6.23 ± 0.20	7.12 ± 0.40	0.004*	5.52 ± 0.21	6.27 ± 0.20	7.12 ± 0.39	0.003*
	ApoA1	1.83 ± 0.12	2.00 ± 0.11	1.89 ± 0.21	0.577	1.85 ± 0.12	1.99 ± 0.11	1.89 ± 0.21	0.681
	ApoB	1.06 ± 0.15	1.15 ± 0.13	1.46 ± 0.27	0.459	1.07 ± 0.15	1.15 ± 0.14	1.46 ± 0.27	0.472
	HDL-C	1.87 ± 0.11	1.93 ± 0.10	2.00 ± 0.19	0.82	1.90 ± 0.10	1.89 ± 0.10	1.99 ± 0.19	0.892
	BMI	30.53 ± 0.93	27.66 ± 0.83	27.52 ± 1.71	0.073	30.56 ± 0.89	27.51 ± 0.84	27.53 ± 1.70	0.05
	SBP	131.06 ± 1.88	139.11 ± 1.66	137.00 ± 3.37	0.014*	130.69 ± 1.80	139.77 ± 1.66	137.04 ± 3.27	0.004*

Data are reported as means ± SD. MPE = mild preeclampsia; GH = gestational hypertension. For other abbreviations and their units, see Table 1. *P < 0.05.

Table 4. Association analysis in the GH and MPE groups.

		Genotype (N)	Means ± SD	P value
GH				
SBP (mmHg)	-250G/A	GG (23)	130.011 ± 5.298	0.004*
		GA+AA (35)	138.054 ± 1.912	
	-514C/T	CC (24)	129.329 ± 2.517	0.001*
		CT+TT (34)	138.408 ± 1.868	
TC (mM)	-250G/A	GG (23)	5.084 ± 0.314	0.001*
		GA+AA (35)	6.677 ± 0.225	
	-514C/T	CC (24)	5.942 ± 0.299	0.017*
		CT+TT (34)	6.697 ± 0.225	
MPE				
BMI (kg/m^2)	-250G/A	AA (7)	34.204 ± 1.791	0.003*
		GG+GA (51)	28.150 ± 0.681	

GH = gestational hypertension; MPE = mild preeclampsia; SBP = systolic blood pressure; TC = total cholesterol; BMI = body mass index. *P < 0.05.

DISCUSSION

Hyperlipidemia is one of the main symptoms of HDCP, and therefore, genes associated with lipid metabolism in pregnancy might represent susceptibility genes of HDCP (Descamps et al., 2005). A recent study using bioinformatic analysis identified altered glycosylation of circulating *ApoE* isoforms in PE (Atkinson et al., 2009). Changes in clinical traits have also been found between case and control groups; however, not all findings were similar. Carriers of the *LIPC* -514TT genotype with pre-pregnancy overweight status experienced a 3-fold increase in the risk of PE compared to carriers of the *LIPC* -514CC/CT genotype with a lean status (pre-pregnancy BMI <25 kg/m^2) in Peruvian women (Enquobahrie et al., 2005). In our study population, the -514C/T polymorphism showed no relationship with BMI; however, -250AA genotype carriers had significantly higher BMIs in the MPE group. Bernard et al. (2007) found that the combined effect of *LIPC*, *LIPE*, and *ApoC*III genetic polymorphisms may increase the likelihood of GH, but seemingly not of PE, suggesting that the pathogenesis of the two disorders may differ.

In our study, the -250G/A and -514C/T polymorphisms did not show different genotypic and allelic frequency distributions between HDCP patients and controls, suggesting that these polymorphic sites do not, respectively, contribute to the etiology of HDCP in Chinese women. The haplotype analysis approach is expected to be more powerful compared to single locus analysis. However, the analysis of haplotypes consisting of two SNP loci (-250G/A and -514C/T) in linkage disequilibrium still showed the absence of significant associations (P > 0.05). In conclusion, we were unable to validate *LIPC* -250G/A and -514C/T as common HDCP susceptibility genes. However, the SBP levels in the GH subgroup appeared to be affected by different genotypes. Mutant genotypes of these two sites were related to higher SBP levels.

A few researchers have reported associations of *LIPC* genetic polymorphisms with lipid and lipoprotein abnormalities, insulin resistance, and HL enzyme activity. A genome-wide association study (GWAS) showed that the *LIPC* -514T allele was strongly associated with HDL-C (P = 2 x 10^{-32}) (Kathiresan et al., 2008). Meng et al. (2010) showed that the HDL-C concentration was higher in individuals with the -250AA and -250GA genotypes than in those with the -250GG genotype. Tahvanainen et al. (1998) showed that patients with

the -514T allele had elevated TG concentrations in HDL, intermediate-density lipoprotein (IDL), and LDL, as well as IDL-C. Further study suggested that carriers of the -514T variation showed increased HDL2 cholesterol concentration, but the variant did not affect HDL3 cholesterol and total HDL-C concentrations (Juo et al., 2001). In the Framingham offspring study, Couture et al. (2000) showed that carriers of the *LIPC* -514T allele had significantly higher HDL-C concentrations due to an increase in the HDL2 cholesterol sub-fraction, especially in women. In our study, no significant differences were found between different genotypes of the two SNPs (-250G/A and -514C/T) and lipid traits in HDCP patients. Analyses based on subgroups found that the TC and SBP levels differed significantly among different genotypes of the -250G/A and -514C/T polymorphisms in the GH group. In particular, mutant genotypes of the -250G/A and -514C/T polymorphisms may play a role in increasing the TC level.

Not all studies support a significant association between *LIPC* promoter -514C/T polymorphisms and lipoprotein metabolism. Studies in Finnish men (Tahvanainen et al., 1998) and a Canadian population (Zambon et al., 2003) showed that the *LIPC* gene promoter -514C/T polymorphisms had no influence on HDL-C or ApoA1 levels. Conclusions of different studies also vary in China. A study from the West China Medical University found that the -514C/T polymorphisms was not associated with HDL-C and ApoA1 concentrations (Fang and Liu, 2002). By contrast, a study in Hong Kong found that the T allele in the healthy control group was associated with a reduction in LIPC activity, and that HDL-C concentrations were significantly higher in carriers of the TT genotype (Tan et al., 2001). These different results may be due to differences in races, sample size, or lifestyles.

In summary, there was no strong evidence to support an association between *LIPC* and HDCP in Han Chinese women. However, *LIPC* variants were associated with BMI, SBP, and lipid profiles in patients.

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Conflicts of interest

The authors declare no conflict of interest.

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