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Association of the Lipoprotein Lipase Gene T+495G Polymorphism With Central Obesity and Serum Lipids in a Twin Study

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PURPOSE: The lipoprotein lipase (LPL) gene polymorphism is possibly involved in the pathophysiology of central obesity and dyslipidemia. The aim of this study was to investigate the association of LPL gene T+495G polymorphism with central obesity and serum lipids.
METHODS: A total of 961 adult twin pairs were enrolled from the program of Chinese Twin Registry, between 2001 and 2002. We used 90 cm of waist circumference in male and 80 cm in female as cut-off values of central obesity. The LPL gene T+495G polymorphism was analyzed with the use of genomic polymerase chain reaction and *Hind*III-restriction fragment length polymorphism. Two statistical methods were performed to test the effect of T+495G polymorphism of LPL gene on the relation between central obesity and lipid levels: one was the generalized estimating equation model for all twin pairs and the other was co-twin matched case-control analysis in 82 central obesity discordant monozygotic twin pairs.
RESULTS: In male twins, central obesity was significantly associated with serum lipids except for high-density lipoprotein (HDL). In female twins, obesity twins had significantly higher levels of triglyceride (TG) and TG/HDL than nonobesity twins. There was no significant association between T+495G polymorphism and lipid levels for all twins, although +495G allele carrier was related with 6.7% decrease of TG was observed only in female twins. The interactions of T+495G polymorphism and central obesity were not found for TG, HDL, and TG/HDL. In central obesity discordant monozygotic twin pairs, central obesity was significantly related with 24.2%, 26.1%, and 4.1% increase of TG ,TG/HDL, and TC, respectively, in +495T/T genotype.
CONCLUSIONS: These results suggest no association and interaction of T+495G polymorphism with central obesity and serum lipids for all twin pairs. Meanwhile, a modest genetic-environmental effect of T+495G polymorphism and central obesity was found in discordant monozygotic twin pairs. Therefore, the +495T/T genotype may be an independent risk factor associated with central obesity and lipids level. However, the role of LPL gene T+ 195 G polymorphism in central obesity and dyslipidemia is complex and remains controversial. This hypothesis needs further investigation.
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KEY WORDS: Lipoprotein Lipase, Genetic Polymorphism, Obesity, Lipids Level, Twin study.

INTRODUCTION

The prevalence of obesity has increased dramatically in industrialized and developed countries, such that the World Health Organization reported overweight and obesity to be a worldwide epidemic. It has been suggested that the pattern of body fat distribution is more important determinant of disease risk, and individuals with a high proportion of abdominal fat have greater risks for developing diabetes (1–3). Dyslipidemia is characterized by high plasma triglyceride (TG) and decreased high-density lipoprotein (HDL) cholesterol levels, as well as by the predominance of small, dense low-density lipoprotein (LDL) particles, and belongs to the modifiable risk factors for cardiovascular diseases and diabetes mellitus (4). Although there has been a substantial research effort focused on the relationship between obesity and dyslipidemia (5), the fact that they do not always coexist suggests that genetic factors might modulate the relationship between them (6). Up to now, apolipoprotein (Apo)E and ApoB-100 gene *Eco*RI polymorphism have been reported their possible influence on the relations between obesity and lipid levels (7, 8). A meta-analysis of 21 studies indicates that the Asn291Ser variant in the lipoprotein lipase (LPL) gene is a risk factor for dyslipidemia, characterized by hypertriglyceridemia and low HDL-C levels (9). Our previous research suggest that lipoprotein lipase gene S447X polymorphism modifies the relationship between central obesity and serum lipids (10); however, research about the association of the lipoprotein lipase gene *Hind*III

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Selected Abbreviations and Acronyms

TG = triglyceride
HDL = high-density lipoprotein
LDL = low-density lipoprotein
Apo = apolipoprotein
LPL = lipoprotein lipase
VLDL = low-density lipoproteins
WC = waist circumference
TC = total cholesterol
GEE = generalized estimating equation
PCR = polymerase chain reaction
MZ = monozygotic
95% CI = 95% confidence interval

polymorphism with central obesity and dyslipidemia are sparse.

The LPL gene is located on the short arm of chromosome 8, spanning about 35 kb and containing 10 exons (11). The *LPL* T+495G polymorphism is most widely studied polymorphism (12). This polymorphism arises as the result of a replacement of a thymine (T) with a guanine (G) base at position +495 in intron 8 and abolishes a *Hin*dIII restriction enzyme recognition site. It has been associated with increased triglyceride levels and low HDL-cholesterol levels (13). LPL is the primary enzyme responsible for the catabolism of TG-rich lipoprotein particles and hydrolyses triglycerides in chylomicrons and very low-density lipoproteins (VLDLs). LPL therefore is the rate-limiting enzyme in lipoprotein and energy metabolism and plays a major role in the determination of the plasma-lipid and lipoprotein profiles (14). Accordingly, LPL is a factor that contributes to the development of the obesity (15). Kobayashi et al. (16) reported that preheparin LPL mass correlated inversely against body mass index and intraabdominal visceral fat area evaluated by computed tomography. Some researchers also postulated that changes in the tissue-specific expression pattern of LPL are expected to affect the initiation and development of obesity (17).

Because both central obesity and serum lipids are related with LPL activity, it is reasonable to think that LPL gene polymorphisms might be involved in modulating the relationship between central obesity and serum lipids. On the basis of this hypothesis, the aim of this study was to investigate the influence of T+495G polymorphism of LPL gene on the relationship between central obesity and serum lipids in a large population of adult twins recruited in the program of Chinese twin registry system (18).

METHODS

Study Site and Population

All twins in this study were recruited from two cities of Chinese twin registry system, Qingdao city in Shandong province (north China) and Lishui city in Zhejiang province (south China), from 2001 to 2002.. Twin Registry twins were initially recruited through local disease control networks and the mass media. From the initial recruitment, medical examination (including blood samples) and questionnaire data were collected from more than 6500 individual female and male twins ages 15 years or order. Questionnaire assessment included a standard battery of twin similarity questions, demographic information, measures of personality, and cigarette smoking and alcohol use (19). Anthropometrical measurements, including height, weight, and waist circumference (WC), were obtained by standard protocols. WC was taken by a soft tape measure in centimeters, at the level of mid-distance between the bottom of rib cage and the top of iliac crest. By the end of 2002, a total of 510 twin pairs from Qingdao city and 500 twin pairs from Lishui city were enrolled for the detailed phenotype studies. Among these 1010 twin pairs, 961 pairs were included in this study based on the following criteria: (1) age 25 years or older; (2) signed informed consent; and (3) both members of the twin pair were healthy. We excluded those twin pairs who refused to participate or had only one member available or were not Han ethnicity. Study protocols were approved by the Ethics Committee for Human Subject Studies of the Peking University Health Science Center.

Blood Sample and DNA Extraction

Venous blood samples were drawn for the measurements of glucose and lipid profile after an overnight fast. Glucose was measured after an 8-h fast using a Hitachi 747 automated spectrometer (Boehringer; Indianapolis, IN). Concentrations of HDL, TG, and total cholesterol (TC) were measured in fresh plasma samples using standard enzymatic procedures. LDL was calculated by Freidewald formula. In addition, TG to HDL ratio (TG/HDL) was also calculated as a powerful predictor of both insulin resistance and cardiovascular disease risk. Genomic DNA was extracted from peripheral blood adjusted to 25 mM ethylene diamine tetraacetic acid by phenol-chloroform extraction using standard procedures (20).

Zygosity Determination

The gender and ABO blood type were used for the initial screen of zygosity. For same-sex twin pairs, determination of zygosity was made by polymerase chain reaction (PCR)-amplified short tandem repeat analysis with a commercially available panel, comprising 10 autosomal, codominant, unlinked loci (including D3S1358, vWA, D16S539, D2S1338, D8S1179, D21S11, D18S51, D19S433, and TH01, FGA), and the gender-determining marker, amelogenin. Monozygotic (MZ) twins were determined when all these unlinked loci and the gender-determining marker were identical.