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Common Variations in Perilipin Gene, Central Obesity, and Risk of Type 2 diabetes in US Women

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Abstract

Objective—The variations in perilipin gene (*PLIN*) were previously associated with obesity and insulin sensitivity. We examined whether *PLIN* variability was associated with diabetes risk and whether obesity status modified such associations.

Research Methods and Procedures—We conducted a nested case-control study of 431 incident cases of type 2 diabetes and 791 healthy control women from the Nurses' Health Study. Obesity was defined by body mass index or waist circumference (central obesity).

Results—In the sample of all participants, *PLIN* variations were not significantly associated with the incidence of diabetes. The central obesity status (By NCEP ATP III definition of waist circumference greater than 35 inches) significantly interacted with *PLIN* polymorphisms in relation to diabetes risk (P for interaction=0.027, 0.009, and 0.02 for rs2289487, rs8179043, and rs894160 respectively). In non-obese (central) women, carriers of rs2289487, rs8179043 and rs894160 had significantly greater risk of type 2 diabetes, adjusting for diabetes risk factors (OR=1.52, 1.03–2.25; 1.54, 1.07–2.23, and 1.57, 1.09–2.27 respectively). Haplotypes possessing the three polymorphisms were also significantly associated with diabetes risk (global test, P=0.01). As compared with the most common haplotype 111, haplotype 222 and 211 (1 codes the common and 2 codes the minor alleles) were associated with 44% (OR=1.44, 95% CI 1.09–1.91), P=0.01) and 70% (OR=1.70, 95% CI 1.04–2.77; P=0.03) greater risk respectively. The *PLIN* variations were not significantly associated with the disease risk among women with central obesity.

Discussion—Our data indicate that central obesity may modify the associations between *PLIN* variations and diabetes risk in women.

INTRODUCTION

Adipose tissue is now recognized as an important endocrine organ that plays pivotal roles in regulating energy balance, glucose and lipid metabolisms, and insulin sensitivity (1; 2). The

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alteration of the metabolic and endocrine functions of adipose tissue is frequently associated with insulin resistance and type 2 diabetes (3; 4). Moreover, the variability in the genes regulating adipose metabolism has been found to predispose to both obesity and type 2 diabetes (5–9).

White adipose tissue stores most of the body's fat reservoir in lipid droplets, which are earning recognition as active organelles regulating energy homeostasis and adipose metabolism (10). Perilipin covers the lipid droplet surface and modulates the turnover of the stored fat (11–13). Ablation of perilipin results in a lean phenotype with high level of adipocyte lipolysis, enhanced leptin production, and peripheral insulin resistance in animals (11; 13; 14). In earlier analyses, we have identified several sequence variations in perilipin gene (*PLIN*) that were associated with diabetes risk factors including central obesity, fasting glucose levels, and insulin sensitivity especially in women (15–18). However, little is known whether *PLIN* variations affect diabetes risk.

In this study, we examined the associations between common polymorphisms in *PLIN* gene and the risk of type 2 diabetes in a prospective, nested case-control study from the Nurses' Health Study. Given the tight relation between *PLIN* and adiposity, especially central fatness, we particularly assessed the modification effects of obesity on the associations between *PLIN* variations and diabetes risk.

SUBJECTS and METHODS

Study population

The Nurses' Health Study cohort was established in 1976 when 121,700 female registered nurses aged 30–55 years and residing in 11 large US states completed a mailed questionnaire on their medical history and lifestyle (19). The lifestyle factors, including smoking, menopausal status and postmenopausal hormone therapy, and body weight, have been updated by validated questionnaires every 2 years. Samples for the present study were selected from a subcohort of 32,826 women who provided a blood sample between 1989 and 1990 and were free from diabetes, cardiovascular disease, stroke, or cancer at the time of blood collection. Incident cases were defined as self-reported diabetes confirmed by a validated supplementary questionnaire and diagnosed at least 1 year after blood collection through 2000. The supplementary questionnaire obtained information on symptoms, diagnostic tests, and hypoglycemic therapy used to define type 2 diabetes cases. Medical record review confirmed the diagnosis of type 2 diabetes using this questionnaire for 98% of cases using the National Diabetes Data Group criteria (20). We used the American Diabetes Association diagnostic criteria for diagnosis of diabetes cases during the 1998 and 2000 cycles (21). The present study included 431 diabetes cases and 791 control subjects who were successfully measured on waist circumference and body mass index.

Definition of obesity

In 1986, participants were instructed to measure their waist circumference at the level of the umbilicus and their hips at the largest circumference with a tape measure while standing relaxed and to report values to the nearest quarter inch. In 1987, the validity of self reported waist and hip measures was assessed in a random sample of 140 participants living in the greater Boston, Massachusetts area (22). The average of two technician measurements spaced six months apart was compared with the self-reported current weight and waist and hip circumference values on the most recent questionnaire. After adjustment for age and within-person variability, the Pearson correlation coefficients between the self-reported measures and the average of the two technician assessments were 0.95 for waist circumference and 0.88 for hip circumference. Body mass index was calculated as weight in

kilograms divided by the square of height in meters. We defined obesity as those with BMI more than 30 kg/m^2. Both waist circumference and waist-to-hip ratio have been used as measures of central obesity in epidemiological studies (23). We used waist circumference as the primary measure for central fatness because of its better correlation with the technician-measurements in the validation study than waist-to-hip ratio. Central obesity was defined by waist circumference greater than 35 inches according to National Cholesterol Education Program-Adult Treatment Panel III (ATP III) definition (24).

SNP selection and genotype Determination

DNA was extracted from the buffy coat fraction of centrifuged blood using the QIAmp Blood Kit (Qiagen, Chatsworth, CA). We included four previously reported SNPs at *PLIN* locus, rs2289487, rs894160, rs2304795, and rs1052700 (also known as *PLIN1* 6209T>C, *PLIN4* 11482G>A, *PLIN5* 13041A>G and *PLIN6* 14995A>T respectively) (16). We also selected SNPs from HapMap database (HapMap data Release 20/phase II). Two SNPs (from five available SNPs) that are commonly distributed (CEU, minor allele frequency ≥ 5%) were included in the present study. The SNPs were genotyped using Taqman SNP allelic discrimination by means of an ABI 7900HT (Applied Biosystems, Foster City, CA). Replicate quality control samples were included and genotyped with >99% concordance.

Statistical analyses

A chi-square test was used to assess whether the genotypes were in Hardy-Weinberg equilibrium (HWE) and to compare the genotype and allele frequencies between case and control subjects. Odds ratios (ORs) were calculated using unconditional logistic regression adjusting for type 2 diabetes risk factors, including age, physical activity (<1.5, 1.5–5.9, 6.0–11.9, 12–20.9, and ≥21.0 metabolic equivalent hours/week), smoking (never, past, and current), alcohol intake (nondrinker and drinker [0.1–4.9, 5–10, or >10 g/day]), family history of diabetes, menopausal status (pre- or postmenopausal [never, past, or current hormone use]), and BMI. The interactions between obesity and *PLIN* genotypes were assessed using a likelihood ratio test. We created two interaction terms for the heterozygotes and the minor allele homozygotes and used a 2 degree of freedom test. The SAS statistical package was used for the analyses (SAS, Version 8.2 for UNIX). Haplotype analysis was conducted using THESIAS program that is based on the Stochastic-EM algorithm (SEM) (25). All *P*-values are two-sided.

RESULTS

The allele frequency of the *PLIN* polymorphisms ranged from 0.09 to 0.38 in the healthy women and the genotype distribution did not significantly deviate from HWE (P>0.05). Polymorphisms rs2289487 (intron 2), rs8179043 (intron 6) and rs894160 (intron 6) were in strong pair-wise LD (D'>0.99; and r^2 ranges from 0.64 to 0.93) (Figure 1). Table 1 presents the baseline characteristics of diabetes cases and control subjects by central obesity, which defined by waist circumference greater than 35 inches (by NCEP ATP III definition) (24). In women without central obesity, the cases had significantly higher BMI than the controls. Such a difference was not observed in women with central obesity.

We first examined the associations between *PLIN* genotypes and diabetes risk in all study samples including obese and non-obese women. Overall, there was not significant difference in the distribution of *PLIN* genotypes between diabetes patients and healthy controls (data not shown). We then assessed the potential interactions between obesity and *PLIN* genotypes in relation to diabetes risk. To evaluate the effects of body fat distribution, we used waist circumference to define central obesity and use BMI to represent the overall obesity. Significant interactions were found between polymorphisms rs2289487, rs8179043,

and rs894160 (P for interaction=0.027, 0.009, and 0.02 respectively) and central obesity in relation to diabetes risk. Polymorphisms rs2289487, rs8179043, and rs894160 were associated with significantly increased risk of type 2 diabetes in non-obese women, adjusting for conventional diabetes risk factors including age, BMI, smoking, alcohol consumption, physical activity, family history of diabetes, and menopausal status (Table 2). The genetic effects fit dominant inheritance models (OR=1.52, 95%CI 1.03–2.25; OR=1.54, 95%CI 1.07–2.23; and OR=1.57, 95CI 1.09–2.27; Figure 2). In women with central obesity, no polymorphism was significantly associated with diabetes risk. There was not significant interaction between obesity defined by BMI and *PLIN* variations in relation to diabetes risk.

We further analyzed the haplotype associations in women with and without central obesity. Because rs2289487, rs8179043, and rs894160 were in a LD block (Figure 1), we inferred the haplotypes from these three polymorphisms. In line with the analyses for individual polymorphisms, the three-SNP haplotypes were significantly associated with diabetes risk in women without central obesity (global test, P=0.01). Haplotypes 222 and 211 were associated with 44% and 70% increased risk of type 2 diabetes compared with the most common haplotype 111 (1 codes the common and 2 codes the minor allele, Table 3). *PLIN* haplotypes were not associated with diabetes risk in women with central obesity.

DISCUSSION

Unequivocal evidence from experimental, epidemiological and clinical studies during the past decades causally links dysfunction of adipose tissue with the development of type 2 diabetes (26; 27). Also, variations in genes regulating adipose metabolisms have been associated with diabetes risk (5–9). Perilipin is a key regulatory protein for adipose metabolism. The function of perilipins is to prevent lipolysis in basal condition, favoring the fat deposition. Animals lacking perilipin were lean, resistant to diet-induced or genetic obesity, and had peripheral insulin resistance (11; 13; 14). In human studies, the common variations in *PLIN* gene have been associated with several risk factors for diabetes, including obesity, weight gain, insulin resistance, and hypertension (16; 28–30).

Little is known about the relation between *PLIN* variations and diabetes risk. Polymorphism rs894160 (also known as 11482G>A) in intron 6 of *PLIN* gene was previously associated with lower perilipin contents and increased lipolysis in women (31). As such, elevated lipolysis may lead to augmentation in fatty acid release from adipose tissue. It is well established that fatty acids from adipose tissue are closely related to the metabolism of glucose and adversely affect peripheral insulin sensitivity (32–34). This may partly account for the elevated diabetes risk associated with rs894160 and other polymorphisms in LD with it. In addition, adipose tissue is increasingly recognized as a key endocrine organ synthesizing and secreting a wide range of hormonal products (namely adipokines) that are involved in the pathogenesis of diabetes (35). Adipose lipolysis may reprogram adipokine expression (36). It is possible the metabolic changes related to *PLIN* polymorphisms may affect the endocrine function of adipose tissue that in turn leads to the development of diabetes. Nevertheless, data linking *PLIN* and the endocrine function of adipocytes are sparse. Further studies are needed to test these hypotheses. The polymorphisms associated with diabetes risk in non-obese women were in strong LD. We assume that the genetic effects are likely attributed to the same causal variant.

The data from the present study indicate that the genetic effects of *PLIN* may be dependent on obesity status, especially the centric distribution pattern of body fat. The accumulation of abdominal fat has strong associations with many factors that are constituents of type 2 diabetes (34). Compelling evidence has shown that abdominal fat is more pathogenic for the metabolic disorders than the other fat depots (34; 37; 38). We used waist circumference as a

convenient surrogate for abdominal adiposity (39). It has been documented that the transcription of perilipin may differ in central adipose tissue from adipose tissue in other deports and central obesity may substantially affect the expression of perilipin (40–42). Our findings support a potential modulation effect of abdominal fat on the genetic effects of *PLIN*. The genetic associations were observed in non-obese (central) women only. We assume this maybe partly because the obese individuals, who in general had high levels of many metabolic risk factors, were less sensitive to the gene-associated changes.

Our study was conducted in a prospective setting. Such a study design has an advantage of avoiding the potential influence of several sources of bias inherent in the studies enrolling prevalent patients, e.g. selection bias and survival bias. Also, having comprehensively measured lifestyle components, we were able to adjust for the potential confounding effects of the non-genetic factors. As a limitation, population stratification may bias the associations. However, the majority of the participants are white (~96%). Further adjustment for ethnicity or removing the minorities from the analyses did not appreciably change the results. In addition, our findings are restricted to women and may not be generalizable to men.

In summary, our data for the first time indicate that central obesity may significantly modify the associations between the genetic variations in *PLIN* and the risk of type 2 diabetes in women. Further studies are warranted to replicate our findings and to delve into the underlying mechanisms.

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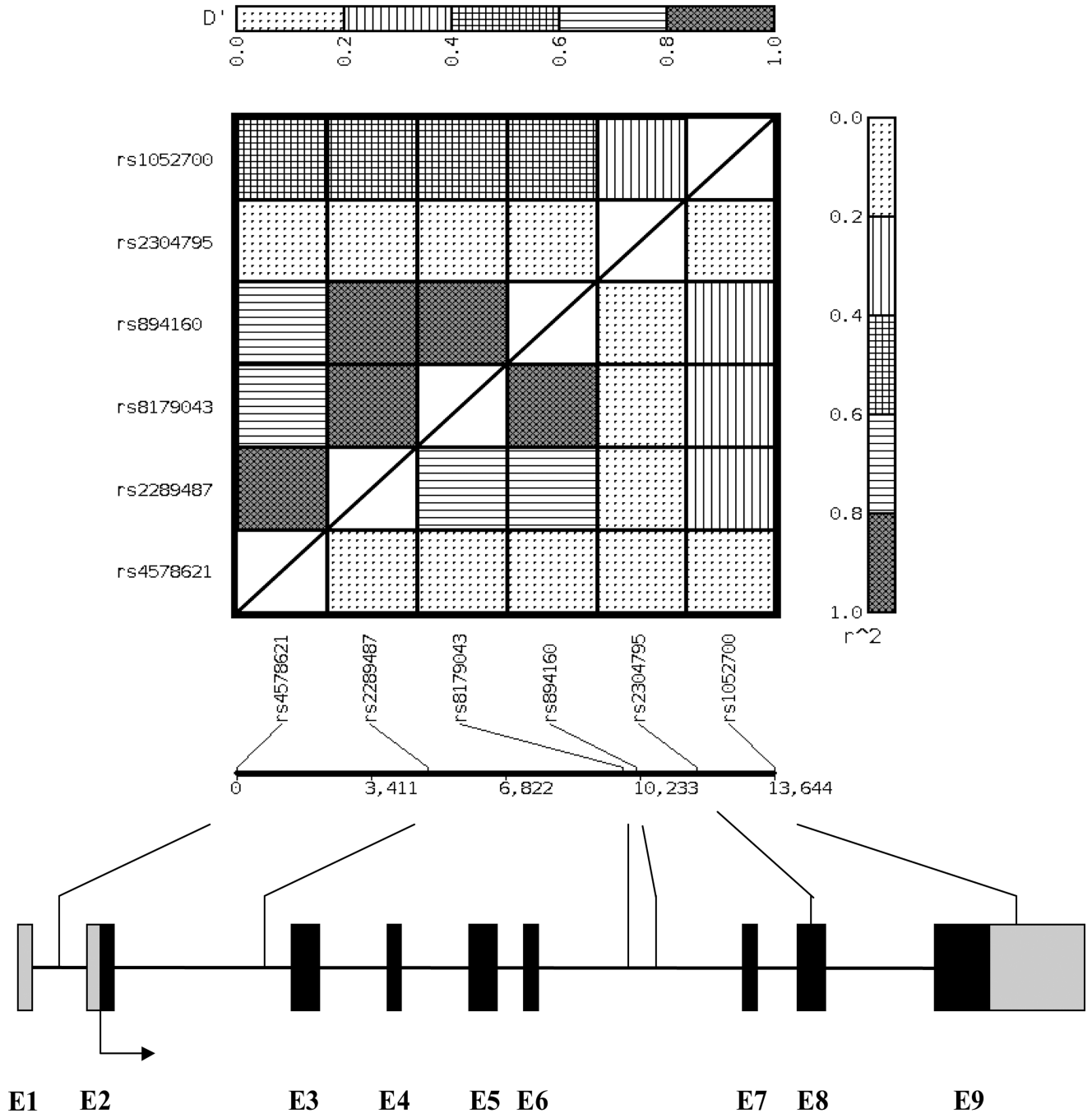

FIGURE 1.

The location of *PLIN* polymorphisms (not drawn to scale) and pairwise linkage disequilibrium matrix (D' is presented above the diagonal and r^2 is presented below the diagonal). The exons of *PLIN* gene are depicted by black boxes and the promoter and 3' UTR are denoted by smaller gray boxes. The direction of transcription is labeled with arrows. The position and identity of polymorphisms are indicated with lines.

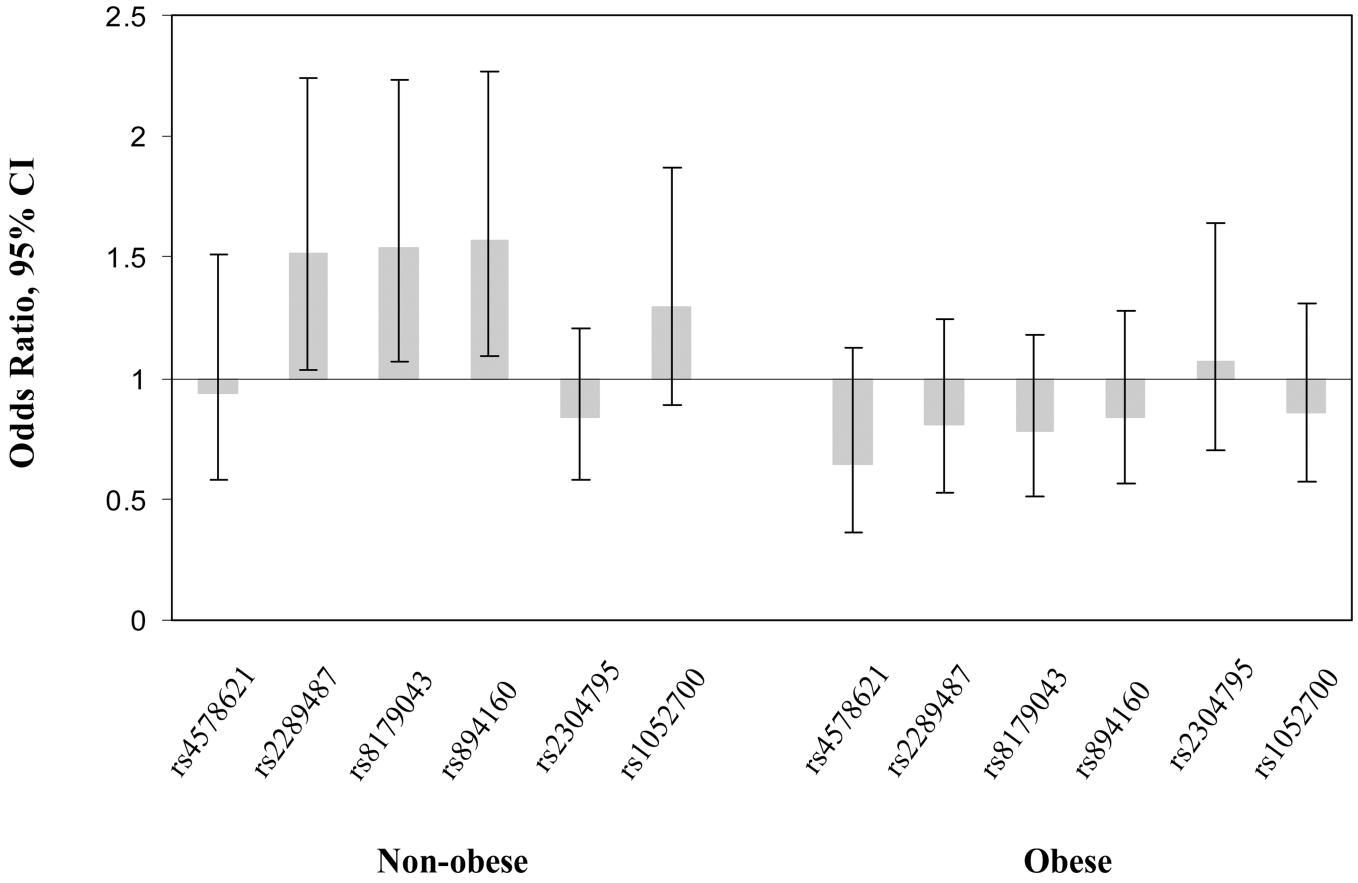

FIGURE 2.

The adjusted associations of *PLIN* variations (carriers v.s non-carriers) with the risk of type 2 diabetes by central obesity. The Odds ratio and 95% confidence intervals (CI) are presented. Analyses were adjusted for age, BMI, smoking, alcohol consumption, physical activity, family history of diabetes, and menopausal status.

Table 1

Baseline characteristics of diabetes patients and controls by central obesity

	Non-obese			Obese		
	Diabetes	**Controls**	**P**	**Diabetes**	**Controls**	**P**
n of participants	201	575		230	216	
Age, years	57±7	57±7	0.51	57±9	57±9	0.80
Body mass index, kg/m^2	26.6±3.7	24.4±3.8	<0.001	32.5±4.9	32.4±5.3	0.89
Physical activity, MET hours/week	13.2±14.6	17.0±20.0	0.01	11.4±14.6	11.8±15.2	0.76
Alcohol consumption, g/day	3.2±7.7	5.6±9.1	<0.001	2.5±6.3	4.5±10.8	0.02
Current smoker, %	12.9	9.9	0.33	12.6	7.4	0.12
Postmenopausal status, %	81.1	81.0	0.98	85.6	82.4	0.35
Family history of diabetes, %	47.3	19.8	<0.001	50.0	26.8	<0.001

Central obesity was defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) definition, as waist circumference greater than 35 inches; the data are presented as mean ± SD (continuous) and percentage (categorical).

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Table 2

Associations between PLIN polymorphisms and the risk of type 2 diabetes by central obesity

		No. (%)		Odds Ratio
		Cases	Controls	(95% CI)
Non-obese				
rs2289487	TT	62 (32.6)	210 (38.5)	1
	TC	91 (47.9)	262 (48.0)	1.35 (0.89–2.04)
	CC	37 (19.5)	74 (13.5)	2.18 (1.26–3.78)
	TC+CC			1.52 (1.03–2.25)
rs8179043	CC	82 (42.0)	279 (50.1)	1
	CT	91 (46.7)	225 (40.4)	1.51 (1.03–2.23)
	TT	22 (11.3)	53 (9.5)	1.67 (0.91–3.08)
	CT+TT			1.54 (1.07–2.23)
rs894160	GG	86 (44.3)	285 (51.8)	1
	GA	90 (46.4)	218 (39.6)	1.55 (1.05–2.28)
	AA	18 (9.3)	47 (8.6)	1.67 (0.87–2.21)
	GA+AA			1.57 (1.09–2.27)
Obese				
rs2289487	TT	98 (44.9)	81 (38.4)	1
	TC	94 (43.2)	95 (45.0)	0.89 (0.57–1.41)
	CC	26 (11.9)	35 (16.6)	0.60 (0.31–1.13)
	TC+CC			0.81 (0.53–1.24)
rs8179043	CC	118 (53.7)	97 (45.8)	1
	CT	83 (37.7)	95 (44.8)	0.79 (0.51–1.23)
	TT	19 (8.6)	20 (9.4)	0.70 (0.33–1.47)
	CT+TT			0.78 (0.51–1.18)
rs894160	GG	116 (53.7)	100 (47.6)	1
	GA	81 (37.5)	92 (43.8)	0.82 (0.53–1.28)
	AA	19 (8.8)	18 (8.6)	0.80 (0.38–1.70)
	GA+AA			0.82 (0.54–1.24)

Adjusted for age and BMI, cigarette smoking, alcohol consumption, physical activity, and menopausal status.

Table 3

PLIN haplotypes and the risk of type 2 diabetes according to central obesity

	Polymorphisms			Frequency		Odds Ratios	P	Global, P
	rs2289487	rs8179043	rs894160	Cases	Controls	(95% CI)		
Non-obese								
H1	1	1	1	55.9	62.5	1.0	-	0.01
H2	2	2	2	32.7	28.5	1.44, 1.09–1.91	0.01	
H3	2	1	1	9.4	7.3	1.70, 1.04–2.77	0.03	
Obese								
H1	1	1	1	66.2	60.9	1.0	-	0.32
H2	2	2	2	27.2	30.0	0.86, 0.62–1.19	0.37	
H3	2	1	1	5.2	7.1	0.66, 0.36–1.21	0.18	

H1-H3, haplotype 1-haplotype 3. ‘1’ codes the common and ‘2’ codes the minor alleles; analyses were adjusted for age, body mass index, alcohol consumption, physical activity, family history of diabetes, and menopausal status.