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Variants in the insulin-degrading enzyme gene are associated with metabolic syndrome in Chinese elders

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Abstract

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities sharing potential common underlying mechanisms. Insulin-degrading enzyme (IDE) plays a primary role in insulin degradation and cellular insulin processing and therefore affects glucose and lipid metabolism. Genetic association studies have been focused on the relationship between the *IDE* gene and the development of MetS. To identify specific genetic risks for MetS associated with *IDE* gene, a case-control association study was performed on 563 Chinese elders in Shanghai, China. Cases were those with MetS (n = 241), and controls were those without MetS (n = 219). Five unrelated genetic markers (single nucleotide polymorphisms) at the *IDE* gene were used for association analyses. The single-locus association analysis revealed that the A/T allele of rs11187033 was associated with MetS (odds ratio = 0.698; 95% confidence interval, 0.526-0.928; $P = .013$). Patients with MetS had more haplotype G-T-Ts than controls ($P = .008$). None of the other 4 single nucleotide polymorphisms was significantly associated with MetS. This result suggests that the rs11187033 at *IDE* gene might contribute to MetS susceptibility in Chinese elders.
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1. Introduction

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities that increases susceptibility to atherosclerosis and therefore cardiovascular and cerebrovascular events. The incidence of MetS is high; and studies have suggested that risk is age related, which has been confirmed using various criteria in many countries [1,2]. Insulin resistance is regarded as the core causative mechanism associated with MetS. Insulin resistance is the inability of cells to respond to insulin, including glucose uptake; subsequently, high plasma glucose and insulin levels are seen. Insulin metabolism is one of the biological pathways that have dominated MetS research in recent years. Insulin-degrading enzyme (IDE), located at the distal end of the chromosome 10 linkage region (120 cM), is a zinc metalloproteinase that degrades intracellular insulin and terminates its action. Appropriate IDE function is important for the preservation of insulin sensitivity.

Genomewide association studies have been widely applied to analyze the correlation between variants of genes and the components of MetS in recent years [3-7]. Based on the "thrifty phenotype" hypothesis proposed earlier [8,9], it is suggested that variants of the genes that regulate physiologic responses in the liver and adipose tissues may affect the metabolism of glucose and lipoprotein. Previous studies involving numerous single nucleotide polymorphisms (SNPs) in the *IDE* gene have yielded promising results that variants in *IDE* were associated with glucose and lipid metabolism [10-13], which are components of MetS. It is unclear whether polymorphisms of the *IDE* gene may increase the susceptibility to MetS. To assess the association between SNPs in the *IDE* gene and MetS, we performed an exploratory case-control association study of MetS using 5 individual genetic markers at the *IDE* gene and their constituent haplotypes covering the introns of *IDE* gene in elder residents of Shanghai, China.

2. Research design and methods

2.1. Subject characteristics

The study consisted of 2017 unrelated Chinese individuals who underwent an annual physical examination in the

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Geriatric Department of Huashan Hospital affiliated with Fudan University, China, from August 2007 to October 2007. All subjects recruited were Han Chinese in origin and older than 60 years. They had resided in Jinan and Xuhui Districts for 20 years or more. Two hundred seventy-three subjects who met the diagnosis of MetS were included at first evaluation, but 32 subjects refused to participate in this study. Finally, a total of 241 MetS subjects were recruited (median age = 72 years), 42 subjects being female and 199 male. The control group consisted of 219 subjects who had none of the 5 criteria of MetS described above and no history of obesity, hyperlipidemia, dyslipidemia, hypertension, and diabetes mellitus. The control group (median age = 71 years) had 35 women and 184 men.

All participants signed the informed consent to the protocol that was reviewed and approved by the Ethical Committee of the National Human Genome Center in China.

2.2. The diagnosis of MetS

Metabolic syndrome was defined according to the criteria of the modified Adult Treatment Panel III of the National Cholesterol Education Program in 2001, which meant at least 3 of the following 5 components: (1) body mass index (BMI) greater than 25 kg/m^2, (2) serum triglycerides of at least 1.7 mmol/L, (3) serum high-density lipoprotein cholesterol (HDL-C) less than 0.9/1.1 mmol/L (male/female), (4) systolic blood pressure (BP) of at least 130 mm Hg or diastolic BP of at least 85 mm Hg or drug treatment of hypertension, and (5) fasting plasma glucose level greater than 5.6 mmol/L or drug treatment of raised glucose [14].

2.3. Exclusion criteria

To reduce any possible drug interference, we chose subjects who had not changed MetS drug treatments within 6 months.

2.4. Anthropometric measurement and blood chemistry

Weight, height, and systolic and diastolic BP were measured. Blood pressure was measured by using a mercury BP device after the subjects had rested for more than 10 minutes. For cases with a systolic BP greater than 140 mm Hg and a diastolic BP greater than 90 mm Hg, the BP was measured 2 more times after rest; and the average value was used. Height and weight were measured by an automatic scale, and BMI was obtained using the standard calculation (BMI = weight [in kilograms]/height [in square meters]). Venous blood was collected after a minimum of 10 hours of absolute diet; fasting plasma glucose, postprandial 2-hour plasma glucose, plasma total cholesterol, serum triglyceride, HDL-C, and low-density lipoprotein were tested using an auto biochemistry instrument. Plasma fasting insulin level was tested by radioimmunoassay (IMK-414; Atom High-tech, Beijing, China). As a marker of insulin resistance, homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as follows: HOMA-IR = [fasting insulin (in micro–international units per milliliter) × fasting glycemia (in millimoles per liter)]/22.5.

2.5. Selection and genotyping of polymorphisms

The *IDE* gene contains 25 exons and spans 112 kilobases in the human chromosome10. Polymorphisms shown to be most related to phenotypes and to be located in the introns, which therefore might be expected to result in changes in the function or expression of the encoded proteins, were chosen. Insulin resistance is common in MetS, and the association between *IDE* gene and type 2 diabetes mellitus (T2DM) had been widely reported. We selected candidate SNPs from T2DM gene databases including dbSNP (http://www.ncbi.nlm.nih.gov/SNP/) and MDBS (http://www.mdbase.org). Five SNPs (rs2275221, rs11187033, rs2209972, rs3781239, and rs7091270) (Table 1) with minor allele frequency of more than 5% in Chinese Han population (www.hapmap.org) were chosen for this test.

Genomic DNA was extracted from peripheral blood leukocytes using a modified phenol/chloroform method. Genotyping was conducted using a 25-μL sample for polymerase chain reaction with a 57°C annealing temperature. The primers were designed by Primerselect (DNAStar, Inc., Madison, WI) and are shown in Table 2. The average success rate of genotyping for each polymorphism was greater than 99%.

2.6. Statistical analysis

Handy-Weinberg equilibrium tests were performed for each polymorphism on an online calculator (http://www.

Table 1
Position for SNPs and primers

NCBI dbSNP	Functional class	Primers	
		Forward	Reserve
rs2275221	Intron 22	5′-tgaataatccagccatcaagaga-3′	5′-tgttactgtaaagaatggcaatgaa-3′
rs11187033	Intron 11	5′-ccttttccattcagtgaacaaca-3′	5′-tcttgcttatctttggttaaactcat-3′
rs2209972	Intron 2	5′-acccctcacagtgtgctctgaa-3′	5′-tccaccaaaagtgtctgctatgc-3′
rs3781239	Intron 10	5′-gtttgggaaagactattcgcatt-3′	5′-aaggaagccctgttgatgttg-3′
rs7091270	Intron 15	5′-tcccagagtccacagaagtttga-3′	5′-cacgcaaagcagtaggggata-3 ′

NCBI indicates National Center for Biotechnology Information.

Table 2
Baseline characteristics of the study population

Characteristics	MetS	Controls	*P*
Subjects (n)	241	219	
Sex (M/F)	199/42	184/35	.78
Age (y)	75.0 ± 8.4	79 ± 6.4	.82
BMI (kg/m^2)	27.0 ± 2.7	22.3 ± 4.7	.74
Serum triglycerides (mmol/L)	1.97 ± 0.92	1.16 ± 0.50	.04
Serum HDL-C (mmol/L)	1.08 ± 0.31	1.20 ± 0.39	.83
HOMA-IR	2.19 ± 0.32	1.67 ± 0.14	.03
Fasting plasma glucose (mmol/L)	5.9 ± 1.1	5.5 ± 0.7	.48
2-h plasma glucose (mmol/L)	7.1 ± 1.6	8.4 ± 2.2	.63
Plasma insulin (mmol/L)	8.7 ± 6.4	7.2 ± 5.6	.061

kursus.kvl.dk/shares/vetgen/_Popgen/genetik/applets/kitest.htm). CLUMP (version 2.3) was used to compare the discrepancies of allele, genotype, and haplotype frequencies between groups [15]. Pairwise linkage disequilibrium (LD) of all possible pairs of the 5 polymorphisms was estimated using 2LD software [16]. The haplotype frequencies were estimated using EHPLUS software [17,18]. After the estimated frequencies of each haplotype were calculated, we used CLUMP again to compare the difference in haplotypes between groups. Those haplotypes with a frequency less than 5% were excluded from the analysis. Power calculations were computed by G*Power program (version 3.0) [19], indicating that our sample size was sufficient to achieve 80% power. *P* values were 2 tailed, and significance was accepted when $P < .05$. Odds ratios with 95% confidence intervals (CIs) were estimated for the effects of high-risk haplotypes and calculated using an Internet-based facility (http://www.pedro.fhs.usyd.edu.au/Utilities/Cicalculator.xls). Quantitative data were compared among groups using the 1-way analysis of variance test by Stats 8.0 (Computer Resource Center, Chicago, IL). Nonparametric data were compared by χ test using Stats 8.0. The logistic regression was analyzed for the relative risk of age, phenotypes, sexes, lifestyles, cholesterol, triglycerides, and insulin resistance.

Table 4
Pairwise LD

SNP 1	SNP 2	Distance (kb)	*D′*
rs3781239	rs7091270	19.628	0.998
rs3781239	rs11187033	44.562	0.847
rs7091270	rs11187033	24.934	0.929

3. Results

3.1. Baseline characteristics

The HOMA-IR and serum triglycerides were higher in the MetS group than in the controls (HOMA-IR, $P = .03$; triglycerides, $P = .04$). There was no significant difference in sex distribution, age, serum total cholesterol, serum HDL-C, fasting plasma glucose, postprandial 2-hour plasma glucose, and plasma insulin levels between the 2 groups (Table 2).

3.2. SNPs allele frequencies and association analysis

The genotype and allele frequencies of the 5 SNPs in the *IDE* gene are listed in Table 3. The MetS patients had less A allele in rs11187033 than the controls (odds ratio, 0.698; 95% CI, 0.526-0.928; $P = .013$). In the MetS group, heterozygous carriers were dominant ($P = .04$). No significant difference in genotype frequency was found between the 2 groups in the 4 other SNP locations. Genotype distributions in the controls showed no deviation from Hardy-Weinberg equilibrium (Table 3).

Table 4 showed results from pairwise LD. It was found that 3 SNPs (rs3781239, rs7091270, and rs11987033) were

Table 3
Genotype and allele frequencies and single-locus association analysis

SNPs	Allele (%)		*P* (*df* = 1)	Odds ratio (95%CI)	Genotype (%)			*P* (*df* = 2)
rs3781239	C	G			C/C	C/G	G/G	
MetS	50 (10.4)	430 (89.6)	.981	1.005 (0.657~1.538)	1 (0.4)	48 (20)	191 (79.6)	.771
Controls	45 (10.4)	389 (89.6)			2 (0.9)	41 (18.9)	174 (80.2)	
rs7091270	G	T			G/G	G/T	T/T	
MetS	107 (22.2)	375 (77.8)	.529	1.108 (0.805~1.526)	11 (4.6)	85 (35.3)	145 (60.2)	.457
Controls	86 (20.5)	334 (79.5)			5 (2.4)	76 (36.2)	129 (61.4)	
rs2275221	C	T			C/C	C/T	T/T	
MetS	443 (95.1)	23 (4.9)	.779	1.088 (0.601~1.970)	211 (90.6)	21 (9.0)	1 (0.4)	.961
Controls	407 (94.7)	23 (5.3)			193 (89.8)	21 (9.8)	1 (0.5)	
rs11187033	A	T			A/A	A/T	T/T	
MetS	302 (62.7)	180 (37.3)	.013	0.698 (0.526~0.928)	93 (38.6)	116 (48.1)	32 (13.3)	.04
Controls	281 (70.6)	117 (29.4)			100 (50.3)	81 (40.7)	18 (9.0)	
rs2209972	C	T			C/C	C/T	T/T	
MetS	109 (22.9)	367 (77.1)	.816	0.964 (0.706~1.316)	18 (7.6)	73 (30.7)	147 (61.8)	.967
Controls	98 (23.6)	318 (76.4)			16 (7.7)	66 (31.7)	126 (60.6)	

Odds ratio (95% CI).

Table 5
Haplotype (rs3781239, rs7091270, and rs11187033) analysis

Haplotype	MetS vs controls			
	MetS	Controls	*P* value	Odds ratio (95%CI)
C-T-A	10.4	10.9	.810	0.948 (0.613~1.465)
G-G-T	20.8	19.5	.621	1.088 (0.778~1.523)
G-T-A	51.1	58.3	.036	0.747 (0.569~0.982)
G-T-T	16.5	10.3	.008	1.733 (1.151~2.610)
Global			.040	

in LD ($D' > 0.5$); and therefore, a haplotype analysis was performed between these 3 SNPs. Haplotypes with probabilities greater than 5% accounted for the most haplotype diversity. More haplotype G-T-Ts were found in the MetS group than in the controls ($P = .008$). In contrast, the controls had more haplotype G-T-As ($P = .036$) (Table 5).

4. Discussion

Insulin-degrading enzyme has been postulated to be a possible contributor to insulin resistance in humans because of its role in intracellular insulin degradation. The *IDE* gene located on chromosome 10q23-25 is near a region involved in the etiology of diabetes mellitus, as suggested by a linkage study [20,21]. Naturally occurring *IDE* missense mutations in the T2DM rat model resulted in decreased catalytic efficiency and a significant 15% to 30% deficit in the degradation of insulin [22]. Human genetic studies show a link of genetic polymorphisms in the *IDE* gene and the increased risk for insulin resistance [23]. Another study, analyzing 14 SNPs in the *IDE* gene, provides compelling evidence that fasting insulin levels, 2-hour insulin levels, BMI, and HOMA-IR are related with multiple interacting trait-modifying sequences in the region of *IDE* genetically [10]. Based on the common disease/common variant hypothesis [24,25], we searched for potential risk genes for the MetS. Five SNPs of *IDE* gene were analyzed, and only allele (A/T) at rs11187033 was found to be different between the MetS group and the controls ($P = .04$). Haplotype analysis revealed that haplotypes G-T-T and G-T-A were correlated with the risk of MetS.

Rs11187033 has been considered to be one candidate locus for T2DM (www.wipo.int/pctdb). In this study, rs11187033 was found to increase the risk of MetS, but not T2DM (data not shown). Several known factors can influence the functions of IDE, one of which may be related with rs11187033: (1) IDE activity is inhibited noncompetitively by select free fatty acids and their coenzyme A thioesters [26]. (2) There are 3 cysteine residues (C178, C812, and C819) of IDE responsible for its sensitivity [27]. These cysteines residues may be susceptible to nitrosylation, which has negative effects on insulin sensitivity and can be affected by hydrogen peroxide [28]. (3) Adenosine triphosphate can induce a conformational change in IDE and may have effects on insulin metabolism [29]. Other factors may also be involved.

No significant difference in genotype frequencies or allele at the other 4 SNPs was found between the MetS group and the controls. A modest association between rs2209972 and T2DM has been reported, but others found no relationship between T2DM and rs2209972 [11,30]. We could not find an association of rs2209972 with T2DM in these Chinese elders [31]. On the other hand, considering that MetS is the result of interaction between multiple metabolic elements, we suggested that polymorphisms at the SNP might exert a magnified effect on the metabolic course in vivo.

The subjects in this study had been living in the same urban area for relatively long periods of time and did not show significant differences in smoking and physical exercise. We hypothesized that common genetic variations in the *IDE* gene may influence MetS susceptibility. Moreover, it has been shown that age was an independent risk factor of MetS [32]; and elderly people are more likely to develop MetS than younger populations in other studies.

5. Conclusions

The underlying causes of MetS are extremely heterogeneous. Using a case-control study, we investigated the *IDE* gene locus on the molecular level and found that persons with A/T allele variant at SNP 11187033 were more likely to develop MetS. Haplotype distribution differences (G-T-T or G-T-A) suggested an association with the risk or no risk of MetS. The haplotype of SNPs in this report may be useful for further study in MetS.

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