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Associations between genetic variants and the severity of metabolic syndrome in subjects with type 2 diabetes

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ABSTRACT. Metabolic syndrome (MetS) includes obesity, dyslipidemia, elevated blood pressure, and dysglycemia. Subjects with type 2 diabetes (T2D) exhibit features of MetS. The etiology of MetS is complex, involving both environmental and genetic factors. In this study, we examined the

role of specific candidate genetic variants on the severity of MetS in T2D subjects. A total of 240 T2D subjects aged 35-64 years were recruited. Waist circumstance, plasma triglycerides, high-density lipoprotein cholesterol, fasting plasma glucose, and blood pressure were measured to define MetS. Subjects were divided into 4 groups according to MetS components. Target genes involved in fibrotic and inflammatory processes, insulin and diabetes, cell growth and proliferation, and hypertension were genotyped. A total of 13 genes and 103 single-nucleotide polymorphisms (SNPs) were analyzed to evaluate their genetic association with MetS severity in T2D subjects. Univariate ordinal logistic regression using a dominant model (homozygous for the major allele *vs* carriers of the minor allele) revealed 6 SNP markers within 4 genes with genotypes associated with MetS risk. For the SNP genotypes of rs362551 (*SNAP25*), rs3818569 (*RXRG*), rs1479355, rs1570070 (*IGF2R*), and rs916829 (*ABCC8*), heterozygotes showed a lower risk of MetS compared with the reference group. In addition, the CC genotype was comparable to the TT genotype for rs3777411. There was no gender-specific effect. In conclusion, our results suggest that among the Han Chinese population, several SNPs increase the risk of severe MetS in T2D subjects. Further study in a large population should be conducted.

Key words: Chinese; Metabolic syndrome; Obesity; Polymorphism; Type 2 diabetes

INTRODUCTION

The combination of central obesity, elevated blood pressure, dysglycemia, elevated serum triglyceride (TG), and decreased serum high-density lipoprotein-cholesterol (HDL-C) levels has been defined as metabolic syndrome (MetS) (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). MetS carries a 2- and 4-fold increased risk of developing further cardiovascular disorders and type 2 diabetes (T2D) compared to subjects without MetS (Eckel et al., 2005). This has become a public health problem and an important issue for clinicians to detect the early stage of MetS. The key risk factors and pathogenesis of MetS are obesity and/or insulin resistance, which both are also closely associated with other risk factors of MetS. However, MetS has a complex etiology determined by the interplay between genetic and environmental factors through mechanisms involving obesity-related proinflammatory and prothromobotic processes (Eckel et al., 2005; Opie, 2007). Associations between genetic variants and complex diseases are not well understood. Over the last decade, the genetic susceptibility of MetS has been explored, but the results are inconsistent (Pollex and Hegele, 2006). T2D subjects exhibit most of the characteristics of MetS; therefore, more than 70% of T2D subjects fulfill the MetS criteria (Xiang et al., 2012). Furthermore, the more features of MetS in patients, the greater their risk of their developing T2D. Therefore, the impact of genetic variation on the severity of T2D in subjects with MetS with various components should be examined.

Genetic make-up may influence the development of MetS in different ways (Hegele and Pollex, 2005). The most common putative hypothesis is that each component of MetS has

a genetic basis; therefore, genetic variants associated with individual components of the MetS phenotype may facilitate MetS development. Second, some metabolic traits may share common pathways with MetS development, which involve specific candidate genes. Finally, several genome-wide linkage scans have been attempted to detect chromosomal segments that are linked with complex and/or quantitative traits in MetS. Several studies have explored the link between MetS and different chromosome loci with varying relevant traits **(**Kissebah et al., 2000; Arya et al., 2002; Loos et al., 2003**)**. However, no specific gene or mutation has been identified.

Although a genetic component may underlie MetS, the identification of associated genes has been challenging. According to a recent review article regarding genetic analysis and MetS, several genetic association studies of MetS showed positive associations (Pollex and Hegele, 2006). Only 1 study was conducted in a Chinese population. Furthermore, limited data were available to explore the role of genetics on the severity of MetS and/or the combination with T2D. Therefore, we explored the potential genetic association with various severities of MetS in T2D subjects among candidate genes in the Chinese population.

MATERIAL AND METHODS

Study population

The study was extended from our previous genetic study evaluating the association between diabetic subjects and nephropathy. The detailed results have been published elsewhere (Hsieh et al., 2006, 2011). Briefly, case and control groups of 264 patients with T2D, all ethnically Han Chinese, were recruited from the Tri-Service General Hospital in Taipei, Taiwan. The control group included 120 T2D patients without nephropathy; the case group included 144 diabetic patients with nephropathy. All recruited patients were aged 30-75 years and had been diagnosed with diabetes for more than 5 years.

Measurements of anthropometric and biochemical variables and general data

Plasma glucose was measured using the glucose oxidase method (YSI 203 glucose analyzer; Yellow Spring Instrument Company, Inc., Yellow Spring, OH, USA). Serum total cholesterol, TG, and low-density lipoprotein-cholesterol (LDL-C) were measured using the dry, multilayer analytical slide method with a Fuji Dri-Chem 3000 analyzer (Fuji, Tokyo, Japan). Serum level HDL-C was determined using an enzymatic cholesterol assay method after dextran sulfate precipitation. Waist circumference was measured horizontally at the level of the natural waist, which was identified as the level at the hollow molding of the trunk when the trunk was laterally concave. Body mass index was calculated as the subject's body weight (kg) divided by the squared height of the subject (m^2). The nursing staff measured both the systolic blood pressure and diastolic blood pressure using standard mercury sphygmomanometers fitted on the right arm of each subject when seated.

Definition of MetS and grouping

The most widely used criteria for defining MetS were proposed by the US National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). MetS com-

ponents were characterized by obesity (waist ≥90 and ≥80 cm among male and female subjects, respectively, according to Asian criteria), hypertension (blood pressure ≥130/80 mmHg), hypertriglyceridemia (TG ≥ 150 mg/dL), low serum HDL-C (<40 mg/dL in males and <50 mg/dL in females), and impaired fasting glucose (≥100 mg/dL). The pre-treatment levels of TG and/or HDL-C were used to evaluate the criteria. The patients fulfilled 2 components of MetS criteria if they had received lipid-lowering therapy. Subjects who were taking anti-hypertensive agents fulfilled the hypertension criteria. The definite diagnosis of MetS required at least 3 of 5 criteria. All of our subjects had T2D and carried at least 1 component of MetS. Those who did not meet any other criteria or met 1 other component of MetS were classified in group 1, while those who met 3 to 5 criteria of MetS were classified in group 2 to 4 respectively.

Approval was obtained from the Internal Review Board of the Tri-Service General Hospital before conducting the study, and an approved Informed Consent form was signed from each subject before entering this study.

Gene selection, DNA extraction, and genotyping

Several candidate genes were evaluated in our study because of their putative roles in the pathogenesis or development of MetS, including: i) fibrotic and inflammatory genes (*ABCC8*, *LPL*, *AHSG*); ii) insulin and diabetes-related genes (*IGF2R*, *PCSK2*, *SNAP25*); iii) genes involved in cell growth and proliferation (*EGFR*, *RXRG*); and iv) the renin-angiotensin system (*ACE*, *AGT*, *AGTR1*, *LRP3*, *KCNS3*). The 13 genes and selected single-nucleotide polymorphism (SNP) numbers are listed in Table 1. DNA was isolated from blood samples using the QIAamp DNA blood kit following manufacturer instructions (Qiagen; Hilden, Germany). The quality of isolated genomic DNAs was evaluated using agarose gel electrophoresis and the quantities were determined using spectrophotometry. Genotyping was performed using the commercial TaqManw Genotyping assays of Applied Biosystems Inc. (Foster City, CA, USA). TaqManw polymerase chain reaction (PCR) was performed according to the manufacturer standard protocol as follows: 5 ng genomic DNA was mixed with 2X TaqMan Universal PCR Master Mix and 20X TaqMan Assay Mix to a final volume of 5 mL, which was then dispensed into a 384-well plate. Each sample was subjected to 40 amplification cycles on the GeneAmpw PCR System 9700 instrument (Applied Biosystems). Fluorescent signals of the 2 probes, corresponding to 2 different alleles, were analyzed using PRISMw 7900HT Sequence Detection System (Applied Biosystems). Genotypes were determined automatically using the sequence detection software provided with the detection system. SNP IDs referred to the dbSNP database of the National Center for Biotechnology Information, as well as Applied Biosystem assay IDs.

Statistical analysis

The mean values of the demographic parameters are reported as means ± standard deviation and compared by the Student *t*-test. Both allele and genotype frequencies of SNP markers were tested between genders, as well as the severity of MetS. In addition, univariate ordinal logistic regression was performed to evaluate the relative risk severity of MetS for the SNP genotypes. The reference group in the regression model was arbitrarily assigned. All analyses were performed using SAS 9.1 (Cary, NC, USA). A P-value less than 0.05 was considered to be statistically significant. All results are shown with SNP genotypes with a significant risk for MetS based on the results of ordinal logistic regression.

Table 1. Thirteen genes (103 SNPs) analyzed in the study.

Gene symbol	Numbers of SNP	Gene name
ABCC8	14	ATP-binding cassette, sub-family C, member 8
ACE	5	Angiotensin I converting enzyme
AHSG	5	Alpha-2-HS-glycoprotein
AGT	1	Angiotensinogen
AGTR1	1	Angiotensin II receptor, type 1
EGFR	6	Epidermal growth factor receptor
IGF2R	10	Insulin-like growth factor 2 receptor
KCNS3	1	Potassium voltage-gated channel, delayed-rectifier, subfamily S, member 3
LPL	5	Lipid protein lipase
LRP3	3	Low density lipoprotein receptor-related protein 3
PCSK2	33	Proprotein convertase subtilisin/kexin type 2
RXRG	9	Retinoid X receptor, gamma
SNAP25	10	Synaptosomal-associated protein
Total	103	

RESULTS

The demographic characteristics of the 4 groups are summarized in Table 2. The numbers of subjects were 65, 78, 48, and 49 from groups 1-4, respectively. There was no difference in gender, diabetic duration, or age among groups. Except for fasting plasma glucose levels, all other MetS components, including body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, TG, and HDL-C levels differed significantly according to the arbitrary grouping. Table 3 shows the relative risk of MetS for the genotypes of selected SNP markers using univariate ordinal logistic regression with significant differences in MetS severity. For the SNP genotypes of rs362551 (*SNAP25*), rs3818569 (*RXRG*), rs1479355, rs1570070 (*IGF2R*), and rs916829 (*ABCC8*), heterozygotes showed a lower risk of developing MetS compared with the reference group, with odds ratios of 0.57, 0.53, 0.56, 0.59, and 0.54, respectively (with 95% confidence interval of 0.35-0.94, 0.32-0.88, 0.32-0.98, 0.36,0.95, and 0.30-0.97 respectively). In addition, the CC genotype was compared to the TT genotype for rs3777411 (*IGF2R*), and CC carriers showed a lower risk of developing MetS with an odds ratio of 0.36 (95% confidence interval of 0.15-0.86). Six selected SNP markers showed a significant association with MetS; no differences in allele and genotype frequencies were observed for both gender and severity of MetS (Tables 4 and 5).

Table 2. Demographic data of the study population.

Patients	Group 1	Group 2	Group 3	Group 4	P
Number (male/female)	49 (26/23)	48 (21/27)	78 (38/40)	64 (24/40)	0.251
Age (years)	59.8 ± 1.2	59.2 ± 1.2	61.0 ± 1.0	61.2 ± 1.1	0.658
Diabetic duration (years)	15.1 ± 0.9	13.9 ± 1.1	14.0 ± 1.0	14.7 ± 1.0	0.485
BMI (kg/m^2)	22.4 ± 0.7	24.9 ± 0.5	25.9 ± 0.3	27.7 ± 0.5	<0.01
Waist (cm)	78.0 ± 1.1	87.7 ± 1.3	90.1 ± 0.9	95.6 ± 1.2	<0.01
SBP (mmHg)	125.8 ± 3.0	133.0 ± 2.5	130.3 ± 1.8	138.1 ± 1.9	<0.01
DBP (mmHg)	71.4 ± 1.4	78.9 ± 1.7	75.0 ± 1.4	78.8 ± 1.3	<0.01
FPG (mg/dL)	175.2 ± 8.1	175.8 ± 8.58	171.1 ± 6.32	172.4 ± 7.61	0.856
TG (mg/dL)	99.6 ± 4.0	135.7 ± 10.4	182.8 ± 16.7	313.0 ± 24.2	<0.01
HDL-C (mg/dL)	53.9 ± 2.9	46.1 ± 4.6[3,4]	38.0 ± 1.0	33.5 ± 0.8	<0.01

Data are reported as means ± SD; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; FPG = fasting plasma glucose; TG = triglyceride; HDL-C = high-density lipoprotein-cholesterol.

Table 3. Relative risk of metabolic syndrome for genotypes of single-nucleotide polymorphism markers using univariate ordinal logistic regression.

Gene name	Genotype	OR†	95%CI‡
ABCC8	rs916829		
	GG	1	-
	AG*	0.54	0.30-0.97
IGFR2	rs1570070		
	GG	1	-
	AA	0.92	0.33-2.58
	AG*	0.59	0.36-0.95
IGFR2	rs3777411		
	TT	1	-
	CC*	0.36	0.15-0.86
	CT	0.42	0.18-1.00
IGFR2	rs1479355		
	TT	1	-
	CC	0.87	0.45-1.66
	CT*	0.56	0.32-0.98
RXRG	rs3818569		
	GG	1	-
	AA	1.11	0.18-6.67
	AG*	0.53	0.32-0.88
SNAP25	rs362551		
	CC	1	-
	AA	1.74	0.67-4.51
	AC*	0.57	0.35-0.94

†OR = odds ratio; ‡95%CI = 95% confidence interval; *statistically significant. ABCC 8: ATP-binding cassette, sub-family C, member 8; IGFR2 = insulin-like growth factor 2 receptor; RXRG: retinoid X receptor, gamma; SNAP25 = synaptosomal-associated protein.

Table 4. Allele and genotype frequencies of selected single-nucleotide polymorphism markers by gender.

SNP	Males		Females		Total		P value
	N	%	N	%	N	%	
rs916829							
A	20	9.09	26	10.08	46	9.62	0.72
G	200	90.91	232	89.92	432	90.38	
AG	20	18.18	26	20.16	46	19.25	0.7
GG	91	81.82	103	79.84	193	80.75	
rs1570070							
A	51	23.83	72	27.91	123	26.06	0.32
G	163	76.17	186	72.09	349	73.94	
AA	2	1.87	11	8.53	13	5.51	0.08
AG	47	43.93	50	38.76	97	41.1	
GG	58	54.21	68	52.71	126	53.39	
rs3777411							
C	145	65.91	160	64	305	64.89	0.67
T	75	34.09	90	36	165	35.11	
CC	43	39.09	48	38.4	91	38.72	0.7
CT	59	53.64	64	51.2	123	52.34	
TT	8	7.27	13	10.4	21	8.94	
rs1479355							
C	101	47.64	123	48.43	224	48.07	0.87
T	111	52.36	131	51.57	242	51.93	
CC	22	20.75	33	25.98	55	23.61	0.39
CT	57	53.77	57	44.88	114	48.93	
TT	27	25.47	37	29.13	64	27.47	
rs3818569							
A	39	18.06	38	14.73	77	16.24	0.33
G	177	81.94	220	85.27	397	83.76	
AA	2	1.85	2	1.55	4	1.69	0.57
AG	35	32.41	34	26.36	69	29.11	
GG	71	65.74	93	72.09	164	69.2	
rs362551							
A	54	25	62	24.03	116	24.47	0.81
C	162	75	196	75.97	358	75.53	
AA	6	5.56	10	73.75	16	6.75	0.53
AC	42	38.89	42	32.56	84	35.44	
CC	60	55.56	77	59.69	137	57.81	

Table 5. Allele and genotype frequencies of selected single-nucleotide polymorphism markers by severity of metabolic syndrome.

	Group 1		Group 2		Group 3		Group 4		P value
SNP	N	%	N	%	N	%	N	%	
rs916829									
A	11	11.22	14	14.89	14	8.97	7	5.38	0.11
G	87	88.78	80	85.11	142	91.03	123	94.62	
AG	11	22.45	14	29.79	14	17.95	7	10.77	0.08
GG	38	77.55	33	70.21	64	82.05	58	89.23	
rs1570070									
A	31	31.63	27	28.72	35	23.03	30	23.44	0.38
G	67	68.37	67	71.28	117	76.97	98	76.56	
AA	4	8.16	1	2.13	3	3.95	5	7.81	0.2
AG	23	46.94	25	53.19	29	38.16	20	31.25	
GG	22	44.9	21	44.68	44	57.89	39	60.94	
rs3777411									
C	70	71.43	61	66.3	98	64.47	76	59.38	0.3
T	28	28.57	31	33.7	54	35.53	52	40.63	
CC	22	44.9	18	39.13	30	39.47	21	32.81	0.4
CT	26	53.06	25	54.35	38	50	34	53.13	
TT	1	2.04	3	6.52	8	10.53	9	14.06	
rs1479355									
C	44	44.9	50	54.35	76	49.35	54	44.26	0.45
T	54	55.1	42	45.65	78	50.65	68	55.74	
CC	8	16.33	11	23.91	22	28.57	14	22.95	0.17
CT	28	57.14	28	60.87	32	41.56	26	42.62	
TT	13	26.53	7	15.22	23	29.87	21	34.43	
rs3818569									
A	24	24.49	15	16.3	19	12.34	19	14.62	0.08
G	74	75.51	77	83.7	135	87.66	111	85.38	
AA	1	2.04	1	2.17	0	0	2	3.08	0.12
AG	22	44.9	13	28.26	19	24.68	15	23.08	
GG	26	53.06	32	69.57	58	75.32	48	73.85	
rs362551									
A	27	27.55	23	25	35	22.73	31	23.85	0.85
C	71	72.45	69	75	119	77.27	99	76.15	
AA	2	4.08	2	4.35	5	6.49	7	10.77	0.26
AC	23	46.94	19	41.3	25	32.47	17	26.15	
CC	24	48.98	25	54.35	47	61.04	41	63.08	

DISCUSSION

In this study, we found several SNP markers that were associated with MetS severity in subjects with T2D. Subjects with T2D had dyslipidemia (including low HDL-C and high TG concentration) and a higher frequency of hypertension and obesity. Interestingly, some T2D subjects did not show other cardiovascular disorder risk factors. Our data indicate a possible genetic role for this discrepancy to explain the high prevalence of MetS in T2D.

There were no differences in the frequencies of the alleles and genotypes among subjects with different severities of MetS. However, there were 6 selective SNP markers showing a significant association with MetS. *ABCC8*, which encodes sulfonylurea receptor 1, is located beside KIR6.2, a part of a pancreatic beta-cell potassium channel (Inagaki et al., 1995) thought to be involved in T2DM (Barroso et al., 2003; Klupa et al., 2009). Previous studies reported that genetic variants of *ABCC8* were associated with high TG concentration (Nikolac et al., 2012) and obesity (Hani et al., 1997) in T2D patients. Our results suggest that rs916829 with the AG genotype had a protective effect on MetS development compared to the GG genotype.

This SNP had been examined for its role in the development of diabetes-related traits primarily associated with fasting plasma insulin (Meigs et al., 2007). Retinoid X receptor, gamma (RXRG) is a member of the RXR family of steroid hormone nuclear receptors. The *RXRG* gene is located near the chromosome 1q21-q23 region and functions in lipid homeostasis. RXR forms heterodimers in combination with peroxisome proliferator-activated receptors and is involved in maintaining homeostasis in glucose and lipid metabolism (Shulman and Mangelsdorf, 2005). This implies that RXR plays a role in the pathogenesis of T2D-related traits. This was also demonstrated in a previous study, in which an RXR agonist inhibited hepatic glucose production and increased peripheral glucose disposal (Davies et al., 2001). A recent study suggested that the *RXRG* gene contributes to genetic dyslipidemia in familial combined hyperlipidemia subjects (Sentinelli et al., 2013). Another study revealed the genetic role of *RXRG* in the development of dyslipidemia of T2D patients (Wang et al., 2002). Our study presented 1 SNP (rs3818569, which was merged with rs1128977) in the *RXRG* gene, displaying a positive correlation with the development and severity of MetS with the GG genotype. Interestingly, this SNP is also involved in the development of diabetic nephropathy and retinopathy (Hsieh et al., 2011), indicating an important role in the development of diabetes-related traits sharing similar pathophysiological processes.

Insulin-like growth factor (IGF), a growth factor with insulin-like characteristics, has been implicated in the development of diabetic microvascular complications. The binding receptors to epidermal growth factor, including IGFR2, were shown to play a role in the development of microvascular complications in T2D (Jialal et al., 1985). This gene encodes a receptor for both IGF2 and mannose 6-phosphate, which function mainly in immune- or cancer-related disorders. The genetic role of *IGFR2* on MetS was not examined in previous studies. We found that the 3 SNPs were positively associated with the development and severity of MetS. Our results also suggest that these SNP markers carry additional cardiovascular risk factors, thereby increasing the risk of developing further diabetic complications. SNAP25 is a presynaptic plasma membrane protein that functions in synaptic vesicle membrane docking and the fusion pathway, and is well known to be involved in regulating insulin secretion (Takahashi et al., 2004). A recent genome-wide association study suggested an important genetic role of specific polymorphisms in *SNAP25* on the personality trait neuroticism (Terracciano et al., 2010). However, no such correlation was explored in MetS-related trait disorders. Our results imply that this gene/SNP plays a role in MetS development.

This study had several limitations. There were several criteria required to define MetS and we used only 1 for analysis. It is unknown whether the results would be the same using other criteria. Second, the *post-hoc* analysis was performed using data from our previous study that was focused on diabetic nephropathy, which may lessen the power of the trial. Finally, this study used a case-control design and enrolled a relatively small number of patients. A larger, prospective study is needed that includes a functional assay to investigate the exact role of these SNP markers on the severity of MetS among patients with T2D.

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