Interleukin-6 Receptor Gene 48892 A/C Polymorphism Is Associated with Metabolic Syndrome in Female Taiwanese Adolescents

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Background: This study was to evaluate the relationship between the interleukin-6 receptor (*IL-6R*) 48892 A/C single-nucleotide polymorphism (SNP) (rs8192284) and the metabolic syndrome (MetS) and its components among young adolescents in Taiwan. **Methods:** We enrolled 925 adolescents (451 boys and 474 girls). Modified National Cholesterol Education Program Adult Treatment Panel-III (NCEP ATP-III) criteria were applied to define MetS (with age- and gender-specific 90th percentile cutoff point of variables). Subjects had three or more of the following cardiometabolic abnormalities that occur in MetS: high blood pressure, high fasting glucose, high triglyceride (TG), low high-density lipoprotein cholesterol (HDL-C), and obesity. The characteristics of the MetS components associated with different alleles and genotypes of the *IL-6R* rs8192284 SNP were compared. **Results:** Frequencies of alleles and genotypes of the *IL-6R* 48892 polymorphism were similar in both sexes. Boys with C-alleles had borderline lower TG levels than A-allele carriers (66.0 ± 30.1 vs. 70.3 ± 34.6 mg/dL, $p=0.07$). However, girls with C-alleles had higher waist circumference (WC) (68.0 ± 7.9 vs. 67.0 ± 7.7 cm) and lower HDL-C levels (50.7 ± 11.1 vs. 52.2 ± 11.7 g/dL) than A-allele carriers ($p=0.05$). The prevalence of MetS and its components, high WC and low HDL-C level, were higher in female C-allele carriers (all $p < 0.05$) but not in boys. The odds ratios for high WC, low HDL-C levels, and MetS for female C-allele carriers were 1.54 (95% confidence interval [CI]: 1.01–2.34), 1.49 (95% CI: 1.01–2.18), and 2.19–2.39 (95% CI: 1.15–4.51), respectively, when compared with A-allele carriers. **Conclusions:** The *IL-6R* 48892 A/C polymorphism is associated with high TG and WC, and low HDL-C levels in adolescents. Additionally, there is a gender difference in the incidence of MetS, indicating a possible gene–gender interaction of the *IL-6R* 48892 A/C polymorphism in MetS among Taiwanese adolescents.

Introduction

OBESITY IS A widespread and growing problem in the world, and it is associated with a simultaneous deterioration in chronic disease risk profiles, even among children (Gidding *et al.*, 1996). Obesity during childhood and adolescence is associated with cardiovascular risk factors, including higher blood pressure (BP), glucose intolerance, and abnormal lipid profiles (Lauer *et al.*, 1988; Falkner, 1993). The clustering of central obesity, hypertension, glucose intolerance, and dyslipidemia has been called metabolic syndrome (MetS) and is associated with an increased risk of type 2 diabetes (T2D) and cardiovascular disease (CVD) (Reaven and Laws, 1994).

Interleukin-6 (IL-6) is a cytokine that is involved in glucose and lipid metabolism (Al-Khalili *et al.*, 2006). Circulating IL-6

levels have been correlated with obesity and insulin sensitivity (Fried *et al.*, 1998; Bastard *et al.*, 2000). IL-6 must bind to the IL-6 receptor (IL-6R) before the IL-6/IL-6R complex can exert its effects. The level of IL-6R was recently shown to be correlated with obesity (Pecoits-Filho *et al.*, 2002). Thus, it is reasonable to hypothesize that genetic variants of the *IL-6R* gene are associated with obesity, T2D, and possibly MetS. The *IL-6R* gene is located on chromosome 1q21 (Kluck *et al.*, 1993), a region known to be associated with T2D (Elbein *et al.*, 1999; Das *et al.*, 2004). In recent years, genetic variants of the *IL-6R* polymorphism have been identified and shown to be associated with T2D, obesity, and features of MetS in different ethnic populations (Wolford *et al.*, 2003; Hamid *et al.*, 2004; Wang *et al.*, 2005; Esteve *et al.*, 2006; Song *et al.*, 2007; Qi *et al.*, 2007; Zhang *et al.*, 2009; Jiang *et al.*, 2010). However, the results did not reach agreement on genetic associations in relation to

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these parameters in different ethnic populations. A D358A genetic variant (rs8192284, merged to rs2228145) of this gene is mostly evaluated in several ethnic populations. However, these results were limited to the adult population, without taking gender into consideration. Therefore, in this study, we explored the association between obesity, MetS, and its components, and the rs8192284 single-nucleotide polymorphism (SNP) of the *IL-6R* gene in Taiwanese adolescents.

Materials and Methods

Study design

The Taipei Children Heart Study-II was an epidemiologic study that evaluated the obesity and CVD risk factors among school children in Taipei during 2003. The detailed demographic characteristics were described in our previous work (Chu *et al.*, 1998). To obtain a representative distribution of demographic and lifestyle characteristics, we conducted a cross-sectional survey among junior high school students in Taipei. After a multistage sampling of 85 junior high schools, we randomly selected 1797 school children for this survey. After excluding missing data, a total of 925 children (451 boys and 474 girls) with the mean age of 13.1 years (ranging from 11 to 15 years) were included in the final analyses.

Data collection

All of the participating children completed a structured questionnaire detailing their gender, age, puberty development, and lifestyle characteristics, including cigarette smoking and alcohol consumption. The Ethical Committee of the Scientific Institute approved this study and informed consent was obtained from the parents and the children. Research technicians measured body weight to an accuracy of 0.1 kg using a standard beam balance scale, with subjects barefoot and wearing light indoor clothing. Body height was recorded to the nearest 0.5 cm using a ruler attached to the scale. Body mass index (BMI) was calculated as body weight (kg) divided by the square of their height (m). Obesity is defined as the 90th percentile BMI or waist circumference (WC), according to age and gender specifications. BP was measured in the right arm, using an appropriate cuff size, after 10 min of rest in a seated position; the first and fifth Korotkoff sounds were recorded as systolic BP (SBP) and diastolic BP (DBP). We measured BP again after a 5-min rest, and the average was used in the analysis.

Biochemical measurements

We collected blood samples after students had fasted for 12 h, after following their usual dietary pattern for the previous 3 days, in order to reduce extraneous variations. Any student who had recently attended a holiday feast or family party was re-contacted several weeks later for blood sampling. Fasting plasma glucose (FPG) concentrations were analyzed immediately after blood sampling; other assays were performed within 2 weeks of the blood samples being stored at -4°C . We measured plasma glucose using a standard method, triglyceride (TG) using an enzymatic procedure, and high-density lipoprotein-cholesterol (HDL-C) by an enzymatic method with magnesium precipitation using the Synchron CX5 analyzer (Beckman Instrument, Palo Alto, CA).

The intra-assay coefficients of variation for biochemical assays were $<10\%$.

Definition of MetS

Subjects having three or more of the following cutoff levels, defined as greater than the 90th percentile in the population, were defined as having MetS: obesity, high TG, FPG, or BP levels, and low HDL-C levels. MetS was divided into two groups according to the criteria used for adiposity (MetS 1–2 with respect to abnormal BMI and WC).

SNP genotyping

The genotype of *IL-6R* rs8192284 SNP was determined by TaqMan[®] assay. Assays-on-Demand TaqMan assays were used for genotyping the SNP. TaqMan probes and Universal PCR Master Mix were obtained from Applied Biosystems (Foster City, CA). Allele-specific fluorescence was measured using the ABI PRISM[®] 7900 HT Sequence Detector System (Applied Biosystems).

Statistical analyses

We used mean and standard deviation to describe the distributions of age, body weight, body height, BMI, WC, SBP, DBP, TG, HDL-C, and FPG levels with gender specification. We further divided the cohort into subgroups based on their *IL-6R* rs8192284 genotype (AA, AC, and CC) or allele (A and C) with gender specification. Because the distributions of TG were skewed, logarithmic transformation was applied to the statistical analyses. We compared the differences in anthropometric and biochemical characteristics across gender or *IL-6R* rs8192284 SNP (genotype or allele) using analysis of variance. We further performed *post hoc* multiple comparison tests using the Scheffe's method to examine all pairwise comparisons. Chi-square tests were used for the comparison of proportions and to examine the association between the *IL-6R* rs8192284 SNP (genotype or allele), MetS, and its components. To determine whether *IL-6R* rs8192284 SNP is a predictor of anthropometric measures, BP, lipid profiles, and glucose levels, we assessed the association with those factors and the *IL-6R* rs8192284 SNP using multivariate regression models. In separate models, we analyzed anthropometric measures and biochemical profiles with the *IL-6R* rs8192284 SNP before and after adjusting for age, cigarette smoking, alcohol drinking, and puberty development. Finally, we used logistic regression analyses to assess the association between the *IL-6R* rs8192284 SNP and MetS and its components before and after adjusting for age, cigarette smoking, alcohol drinking, and puberty development. A two-tailed $p < 0.05$ was considered statistically significant. All statistical analyses were conducted using the statistical package SAS (SAS Institute, Inc., Cary, NC).

Results

The allelic frequencies and genotypes of the *IL-6R* rs8192284 polymorphism were similar in both genders (Table 1). The allele and genotype frequency distributions for rs8192284 were in Hardy-Weinberg equilibrium. The male C-allele carriers had borderline lower TG levels than A-allele carriers (66.0 ± 30.1 vs. 70.3 ± 34.6 mg/dL, $p = 0.07$). However, female C-allele carriers had higher WCs (68.0 ± 7.9 vs.

TABLE 1. INTERLEUKIN-6 RECEPTOR rs8192284 POLYMORPHISM ALLELE AND GENOTYPE FREQUENCIES

	Boys		Girls		Chi-square
	N	%	N	%	p-Value
Genotype	(n=451)		(n=474)		0.25
AA	170	37.7	160	33.8	
AC	221	49.0	235	49.6	
CC	60	13.3	79	16.7	
Allele	(n=902)		(n=948)		0.11
A	561	62.2	555	58.5	
C	341	37.8	393	41.5	

67.0±7.7 cm) and lower HDL-C levels (50.7±11.1 vs. 52.2±11.7 g/dL) than A-allele carriers ($p=0.05$) (Table 2). Boys with the A-carrier genotype had higher TG levels than non-A carriers. However, girls with the C-carrier genotype had higher WCs than non-C carriers ($p<0.05$) (Table 3). Similarly, during multiple regression analysis, male C-allele carriers had nonsignificant lower TG levels than A-allele carriers. Female C-allele carriers had higher WCs and lower HDL-C levels than A-allele carriers, which remained statistically significant after adjusting for the other factors (Table 4). Further, male subjects with the A-carrier genotype had higher TG levels than those with the C genotype ($p<0.05$), and female subjects with the C-carrier genotype had higher WCs than their counterparts with the A genotype ($p<0.05$) and borderline lower HDL-C ($p=0.06$), after adjusting for confounding factors (Supplementary Tables S1 and S2; Supplementary Data are available online at www.liebertpub.com/gtmb). The prevalence of MetS and its components, high WC and low HDL-C level, was higher in female C-allele carriers

TABLE 2. CLINICAL CHARACTERISTICS OF METABOLIC SYNDROME IN TAIWANESE CHILDREN WITH THE A/C ALLELE OF INTERLEUKIN-6 RECEPTOR rs8192284

Variable	A allele Mean ± SD	C allele Mean ± SD	ANOVA p-Value
Boys (n = 451)	(n = 561)	(n = 341)	
BMI (kg/m ²)	20.9 ± 4.0	21.0 ± 4.0	0.76
WC (cm)	71.8 ± 10.3	71.9 ± 10.7	0.89
SBP (mm Hg)	118.3 ± 15.2	117.7 ± 14.7	0.58
DBP (mm Hg)	68.2 ± 11.7	68.2 ± 11.3	0.98
TG (mg/dL)	70.3 ± 34.6	66.0 ± 30.1	0.07
HDL-C (mg/dL)	49.4 ± 11.2	50.3 ± 11.8	0.26
FPG (mg/dL)	88.9 ± 8.1	89.0 ± 7.9	0.99
Girls (n = 474)	(n = 555)	(n = 393)	
BMI (kg/m ²)	20.0 ± 3.3	20.1 ± 3.6	0.73
WC (cm)	67.0 ± 7.7	68.0 ± 7.9	0.05
SBP (mm Hg)	112.7 ± 13.9	112.7 ± 12.5	0.97
DBP (mm Hg)	67.9 ± 11.7	67.8 ± 10.4	0.94
TG (mg/dL)	69.0 ± 28.0	71.8 ± 33.4	0.34
HDL-C (mg/dL)	52.2 ± 11.7	50.7 ± 11.1	0.05
FPG (mg/dL)	88.1 ± 8.2	87.9 ± 7.2	0.75

Data are presented as mean ± SD.

$p<0.05$ is considered to be statistically significant.

BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; SD, standard deviation; ANOVA, analysis of variance.

(all $p<0.05$) but not in male carriers. In summary, the prevalence of MetS was highest among subjects with the CC genotype, intermediate with AC, and lowest with the AA genotype ($p<0.05$; Supplementary Tables S3 and S4). Finally, by logistic regression analysis, boys did not show any difference between the A/C allele and MetS or risk characteristics. However, the odds ratios of a high WC, low HDL-C levels, and MetS for female C-allele carriers were 1.54 (95% confidence interval [CI]: 1.01–2.34), 1.49 (95% CI: 1.01–2.18), and 2.19–2.39 (95% CI: 1.15–4.51) (by different adiposity criteria), respectively, when compared with A-allele carriers. The odds ratio remained higher for C-allele carriers after adjusting for confounding factors (Table 5). Additionally, the CC genotype was an independent predictor of higher WC, low HDL-C, and higher prevalence rate of MetS compared with the AA genotype in girls but not in boys (Supplementary Tables S5 and S6).

Discussion

Our study supports a link between *IL6-R* gene variation and obesity and MetS in the Taiwanese adolescent population. Genetic association was more predominant in girls. This information may be helpful for physicians in early detection of at-risk subjects, who would be more likely to develop diabetes and/or CVD.

In studies in humans, circulating IL-6 concentrations are positively correlated with obesity (Fried *et al.*, 1998). Circulating IL-6R concentrations are also associated with obesity (Pecoits-Filho *et al.*, 2002), implying that genetic variants in the *IL6-R* gene may play an important role in the development of obesity. A nonsynonymous Asp358Ala genetic variant of the *IL6-R* gene rs8192284 has been identified both in Western and Asian countries. Previous studies found that the *IL6-R* genetic variant, the rs8192284 polymorphism, positively correlated with obesity (Wolford *et al.*, 2003; Esteve *et al.*, 2006), and subjects with the major allele (A allele or Asp allele) had higher adiposity than non-A carriers (or Ala/Ala). However, those results were inconsistent with those of other studies (Hamid *et al.*, 2004; Wang *et al.*, 2005; Song *et al.*, 2007; Qi *et al.*, 2007; Jiang *et al.*, 2010). Ethnicity, allelic frequency, sample size, and adiposity index measurement may explain the discrepancy. A possible reason for the link between *IL6-R* genetic variants and obesity may be the elevated circulating IL-6 concentrations. This hypothesis is based on the observation that the genetic *IL6-R* variant, the rs8192284 SNP, modulates IL-6 levels by causing splicing of IL-6R to sIL-6R, affecting the development of obesity (Müllberg *et al.*, 1994). Our study also supports a correlation between rs8192284 genetic variants and obesity. However, this correlation was only observed in girls. To the best of our knowledge, this is the first study to link this genetic variant to gender-specific obesity. We found a better correlation to WC than to BMI. Conversely, the C allele or CC genotype had higher adiposity in our study, which is in contrast to the majority of previous studies. This observation is difficult to explain. Because obesity is influenced by genetic and environmental factors, epigenetic effects of obesity may play a role. This is supported by one study, in which the *IL6-R* D358A polymorphism appeared to interact with energy intake and affect abdominal obesity in Japanese men, without influencing adiposity (Song *et al.*, 2007). Additionally, age group contributed to the effect. However, according to a

TABLE 3. CLINICAL CHARACTERISTICS OF METABOLIC SYNDROME IN TAIWANESE CHILDREN BY GENOTYPE

	AA	AC	CC	ANOVA, p-value		
				p ^a	p ^b	p ^c
Boys (n=451)	(n=170)	(n=221)	(n=60)			
BMI (kg/m ²)	20.7±3.8	21.3±4.2	20.5±3.7	0.17	0.29	0.24
WC (cm)	71.0±9.6	72.9±11.2	70.0±9.4	0.07	0.14	0.22
SBP (mm Hg)	119.1±15.6	117.2±14.5	118.8±15.2	0.42	0.68	0.29
DBP (mm Hg)	68.3±11.8	68.0±11.7	68.4±10.5	0.97	0.88	0.88
TG (mg/dL)	70.7±35.3	69.6±33.6	59.4±20.7	0.09	<0.05	0.31
HDL-C (mg/dL)	48.8±10.4	50.3±12.3	50.3±10.8	0.41	0.69	0.17
FPG (mg/dL)	88.9±7.8	89.0±8.5	88.9±6.8	0.99	0.95	0.95
Girls (n=474)	(n=160)	(n=235)	(n=79)			
BMI (kg/m ²)	19.9±3.1	20.2±3.5	20.0±3.6	0.77	0.88	0.52
WC (cm)	66.5±7.6	67.8±7.8	68.3±8.0	0.13	0.27	<0.05
SBP (mm Hg)	112.6±14.5	112.9±13.0	112.4±11.8	0.95	0.82	0.90
DBP (mm Hg)	67.7±12.4	68.2±10.8	67.4±9.8	0.84	0.67	0.83
TG (mg/dL)	67.7±26.2	70.7±30.3	73.0±37.8	0.60	0.39	0.18
HDL-C (mg/dL)	52.7±11.7	51.4±11.7	49.6±10.1	0.14	0.10	0.11
FPG (mg/dL)	88.0±8.7	88.2±7.6	87.5±6.8	0.78	0.51	0.96

Data are presented as mean±SD.

p<0.05 is considered to be statistically significant.

p^a, AA versus AC versus CC; p^b, (AA + AC) versus CC; p^c, AA versus (AC + CC).

recent study using dual-energy X-ray absorptiometry for the measurement of body fat content, this genetic SNP did not play a role in adiposity in a population of young adult men (Andersson *et al.*, 2010). This is comparable to our study results, in which obesity was not associated with the genetic

TABLE 5. LOGISTIC REGRESSION ANALYSES OF METABOLIC SYNDROME IN TAIWANESE CHILDREN WITH THE A/C ALLELE OF INTERLEUKIN-6 RECEPTOR rs8192284

TABLE 4. MULTIPLE REGRESSION ANALYSES OF METABOLIC SYNDROME IN TAIWANESE CHILDREN WITH THE A/C ALLELE OF INTERLEUKIN-6 RECEPTOR rs8192284

Sex	Variable	Model 1			Model 2		
		β	seβ	p	β	seβ	p
Male	(n=451)						
	BMI	0.083	0.274	0.76	0.104	0.272	0.70
	Waist	0.099	0.716	0.89	0.131	0.707	0.85
	SBP	-0.571	1.031	0.58	-0.673	1.014	0.51
	DBP	-0.025	0.794	0.98	-0.099	0.776	0.90
	TG	-4.271	2.263	0.06	-3.831	2.253	0.09
	HDL-C	0.892	0.784	0.26	0.791	0.780	0.31
	Fasting glucose (mg/dL)	0.008	0.551	0.99	0.039	0.548	0.94
Female	(n=474)						
	BMI	0.076	0.223	0.73	0.098	0.223	0.66
	Waist	0.988	0.511	0.05	1.100	0.502	<0.05
	SBP	-0.032	0.878	0.97	-0.097	0.878	0.91
	DBP	-0.056	0.737	0.94	-0.022	0.739	0.98
	TG	2.818	2.000	0.16	2.627	1.996	0.19
	HDL-C	-1.482	0.756	0.05	-1.414	0.755	0.06
	Fasting glucose (mg/dL)	-0.163	0.526	0.75	-0.092	0.512	0.86

p<0.05 is considered to be statistically significant.

A allele is the comparison group. Model 1: univariate analysis; Model 2: adjusted for age, cigarette smoking, alcohol drinking, and puberty status.

Variable		Model 1		Model 2	
		OR	95% CI	OR	95% CI
Male (n=451)					
Adiposity	C vs. A	1.06	0.72–1.55	1.09	0.74–1.61
BMI	C vs. A	1.04	0.69–1.58	1.08	0.71–1.64
Waist	C vs. A	1.15	0.75–1.77	1.20	0.78–1.85
SBP	C vs. A	0.72	0.45–1.15	0.72	0.45–1.15
DBP	C vs. A	1.06	0.69–1.62	1.08	0.70–1.66
TG	C vs. A	0.67	0.42–1.07	0.73	0.45–1.17
HDL-C	C vs. A	0.80	0.52–1.24	0.83	0.54–1.30
Fasting glucose	C vs. A	0.82	0.53–1.26	0.84	0.55–1.31
MetS ¹	C vs. A	0.61	0.30–1.24	0.63	0.31–1.29
MetS ²	C vs. A	0.61	0.30–1.24	0.63	0.31–1.29
Female (n=474)					
Adiposity	C vs. A	1.38	0.95–2.02	1.43	0.98–2.10
BMI	C vs. A	1.40	0.92–2.14	1.40	0.91–2.14
Waist	C vs. A	1.54	1.01–2.34	1.58	1.03–2.41
SBP	C vs. A	0.76	0.50–1.16	0.75	0.49–1.15
DBP	C vs. A	1.10	0.75–1.62	1.11	0.75–1.62
TG	C vs. A	1.37	0.93–2.02	1.38	0.94–2.03
HDL-C	C vs. A	1.49	1.01–2.18	1.49	1.01–2.18
Fasting glucose	C vs. A	0.83	0.56–1.21	0.83	0.56–1.22
MetS ¹	C vs. A	2.19	1.15–4.18	2.15	1.12–4.13
MetS ²	C vs. A	2.39	1.26–4.51	2.40	1.26–4.55

p<0.05 is considered statistically significant. A allele is the comparison group.

Model 1: univariate analysis; Model 2: adjusted for age, cigarette smoking, alcohol drinking, and puberty status. MetS was divided into two groups according to the different criteria used for adiposity (MetS¹ and MetS²), with respect to abnormal BMI and WC.

OR, odds ratio; CI, confidence interval.

variant in the study's male population, supporting a gender difference in the genetic association with obesity. This possibly reflects the gender-related difference of IL-6 levels in different genotypes, which was found in a previous study (Jiang *et al.*, 2010).

Circulating IL-6 concentrations have been shown to be a good predictor for further T2D development (Pradhan *et al.*, 2001). One study showed that, although the serum IL-6R levels in diabetic patients are not elevated, their serum IL-6/IL-6R complex levels are significantly higher than those in healthy subjects (Kado *et al.*, 1999). It has been suggested that IL-6 has an important role on the development of obesity- and T2D-related IR. IL-6 impairs insulin action in the target organ, including liver, muscle, and adipose tissue. Further, this effect is closely correlated with the circulating IL-6 concentrations. The effect of IL-6 on glucose homeostasis is complex through both central and peripheral mechanisms (Fève and Bastard, 2009). Therefore, the genetic variant of the *IL-6R* gene is also a candidate predictor for T2D or the prediabetes trait, MetS. In our study, we did not enroll diabetic subjects because we were studying the adolescent population. We explored a possible genetic association between the *IL-6R* gene and MetS and its components. Aside from obesity, we found that borderline lower TG concentrations in boys and lower HDL-C levels in girls were correlated with genetic variants (C allele and CC genotype). Our results revealed that there was a different trend in TG and HDL-C among genotypes in both genders. This finding is interesting but difficult to explain. Without gender consideration, the results were similar to previous studies, in which lower TG (Esteve *et al.*, 2006; Jiang *et al.*, 2010) and HDL-C levels (Jiang *et al.*, 2010) were observed in the C-allele carriers. However, the genetic association with MetS components was not observed in the other studies (Wolford *et al.*, 2003; Hamid *et al.*, 2004; Song *et al.*, 2007). Additionally, our results showed that in girls, the highest prevalence of MetS was associated with the CC genotype and the lowest with the AA genotype. These results were in contrast to findings by Esteve *et al.* (2006) and Jiang *et al.* (2010), in which subjects with the CC genotype had a decreased MetS prevalence, suggesting a protective role in MetS development. It is also interesting that, in the study by Jiang *et al.* (2010), CC carriers had lower TG and HDL-C concentrations with a lower prevalence of MetS. This may imply different impacts of TG and HDL-C on the development of MetS. Our study's data also imply that gender effects might contribute to the differences in MetS prevalence because female CC genotype carriers had lower HDL-C and higher TG levels, which was in contrast to what was observed for boys. MetS prevalence was more common in girls with the CC genotype and in boys with the AA genotype, although it did not reach statistical significance. These findings are similar to those in a Japanese study, in which only a male population was enrolled (Song *et al.*, 2007). In addition to playing a role in obesity, the IL-6 gene can also disturb glucose and lipid metabolism, as shown by an animal study (Wallenius *et al.*, 2002). One possible reason for the discrepancy in results between our study and other studies may be explained by age- and gender-related factors, largely because most previous studies were evaluated in an adult population with gender specification. There are gender and age differences in the circulating IL-6 concentration (Ferrucci *et al.*, 2005; O'Connor *et al.*, 2007), which may impact the findings linking genotype with phenotype of MetS

components (trend of TG and HDL-C) and MetS development in adolescents in both genders. Several studies have suggested that the *IL-6R* genetic variant is associated with circulating IL-6R (Rafiq *et al.*, 2007; Reich *et al.*, 2007) and IL-6 levels (Qi *et al.*, 2007; Jiang *et al.*, 2010). The elevation of adipocytokine enhances lipolysis and inhibits the activity of lipoprotein lipase, leading to elevation of TG levels (Hardardottir *et al.*, 1994). Interestingly, in observations by Jiang *et al.* (2010), carriers of minor alleles (C allele or CC genotype) were protected from developing MetS, even if they had higher IL-6 levels. Therefore, the age- and gender-specific role of *IL-6R* SNP in the pathophysiology of MetS needs to be further investigated.

There are some strengths and weaknesses in the present study. This is the first study to evaluate the genetic effect of the *IL-6R* variants on obesity and MetS and its components in adolescents, taking gender specification into account. We found that gender differences were associated with MetS. However, several limitations to our study should be addressed. First, we did not measure the circulating IL-6 and IL-6R concentrations, which would have allowed us to explore possible explanations for the different results in other studies. The issue is worthy of further investigation, especially with gender consideration. Second, we cannot report on the exact lifestyle patterns of our subjects, which may influence MetS characteristics. Finally, the relatively small sample sizes may attenuate the power of our study. A study with greater scale, gender specification, and ethnic variation would help to clarify these concerns.

In summary, we demonstrated that the *IL-6R* genetic variant, rs8192284, is significantly associated with characteristics of MetS, predominantly in female adolescents. There may be a possible gene-gender interaction of the *IL-6R* polymorphism with MetS in Taiwanese adolescents. Further hormone evaluation and longitudinal follow-up would be necessary to explore this association in more detail. Accumulation of such information could suggest ways to optimize prevention of MetS development.

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Author Disclosure Statement

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