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Study of seven single-nucleotide polymorphisms identified in East Asians for association with obesity in a Taiwanese population

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ABSTRACT

Objective: This study aimed to examine single-nucleotide polymorphisms (SNPs) of seven previously reported obesity genes in East Asians and to analyse their associations and synergistic effects on obesity in the Taiwanese population.

Design: Cross-sectional study.

Setting: One medical centre in northern Taiwan.

Participants: A total of 323 non-obese and 264 obese participants were recruited. The threshold for obesity in this study was a body mass index of ≥27 kg/m^2, as defined by the Ministry of Health and Welfare in Taiwan. The study was performed with the approval of the institutional review board of MacKay Memorial Hospital, Taipei, Taiwan (application number 12MMHIS106).

Outcome measures: We analysed the genotype distributions of seven SNPs localising to the *PPARγ2, GNB3, SDC3, ADRB2, FTO, PPARγ and ESR1* genes in obese and non-obese groups and then paired obesity-related SNPs to determine if they have synergistic effects on obesity.

Results: Analysis of the genotype distributions in obese and non-obese groups revealed only a significant positive correlation between an SNP in rs2282440-syndecan 3 (*SDC3*) and obesity in the Taiwanese population (p=0.006). In addition, the T/T genotype of *SDC3* was significantly associated with a larger waist and hip circumference, higher body fat percentage and lower high-density lipoprotein cholesterol. Moreover, the combination of the rs2282440-*SDC3T*/T genotype with the rs1801282-peroxisome proliferator-activated receptor-gamma2 gene (*PPARγ2*) G carrier genotype was strongly associated with obesity (OR=6.77).

Conclusions: We found that the rs2282440-*SDC3T*/T genotype is associated with obesity in the Taiwanese population. Furthermore, there is a synergistic effect of the high-risk alleles of the *SDC3* and *PPARγ2* genes on the obese phenotype in the Taiwanese population.

Trial registration number: 12MMHIS106; Results.

Strengths and limitations of this study

- This study allows comparison of genotype distributions of seven previously reported obesity-related genes in East Asians between obese and non-obese Taiwanese population.
- This is the first report describing the association of obesity with single-nucleotide polymorphisms (SNPs) in rs2282440-*SDC3* and the synergistic effect of SNPs in rs2282440-*SDC3* and rs1801282-*PPARγ2* on obesity in Taiwan.
- Cross-sectional study: The body mass index is not constant. Some participants who have been classified within the obese group at the time of study may fall within the non-obese group several months later.

INTRODUCTION

Obesity is a major worldwide health concern that predisposes individuals to a high risk of premature mortality, through an increased risk of chronic diseases, including type 2 diabetes mellitus, cardiovascular diseases, metabolic syndrome and cancer.[1] The proposed cut-off points of body mass index (BMI) for obesity are defined differently by Taiwan and the WHO. The Ministry of Health and Welfare in Taiwan has defined obesity as a BMI of ≥27 kg/m^2 and overweight as BMIs of ≥24 and <27 kg/m^2. According to the results of the National Health and Nutrition Examination Survey conducted in 1993–1996 and 2005–2008, the prevalence of overweight and obese adults among the Taiwanese population increased from 33% to 44%.[2] Among the top 10 leading causes of death in Taiwan, 8 were related to obesity, including cancer, heart disease, cerebrovascular disease, diabetes, chronic respiratory disease, chronic liver disease and cirrhosis, kidney disease and hypertension.[2] Therefore, obesity is a serious public health issue in Taiwan. Obesity is regarded as a complex multifactorial disease in which genes play a very important role. Genetic variations may predispose individuals to obesity by controlling the balance between energy intake and expenditure.[3 4]

Genetic factors in obesity have recently been estimated to account for 40–70% of population variance.[5 6] Large-scale genome-wide association studies (GWAS) have identified at least 58 genetic loci that are robustly associated with obesity-related traits.[7] The association of BMI, waist circumference and body fat with genetic variation were 16–85%,[8–12] 37–81%[13–15] and 35–63%,[16–19] respectively. Several genetic loci reported in GWAS have recently been studied to contribute to the development of obesity.[20 21] The majority of loci have been discovered through GWAS in populations of European ancestry, but a growing number of studies are now being performed in populations of non-European ancestry. However, there have been relatively limited studies on SNPs in obesity-related genes within the Taiwanese population.[22–27] We systematically reviewed PubMed-indexed studies for obesity-associated loci identified in East Asians[24–31] and selected seven SNPs to analyse their association with and synergistic effects on obesity in the Taiwanese population.

PARTICIPANTS AND METHODS

Study population

A population-based study was conducted consisting of 323 control (BMI <27 kg/m^2) and 264 study participants (BMI ≥27 kg/m^2), aged 20–65 years. The exclusion criteria were (1) pregnancy, (2) cancer, (3) secondary obesity, (4) hereditary disease (such as Prader-Willi syndrome or Bardet-Biedl syndrome) and (5) BMI <27 kg/m^2 following bariatric surgery or use of pharmacologic weight reduction agents. The study was approved by the institutional review board of MacKay Memorial Hospital, Taipei, Taiwan (application number 12MMHIS106). All patients signed informed consent forms before participating in this study. Height without shoes and body weight in light clothing were measured to the nearest 0.1 cm and 0.1 kg, respectively. Height was measured using a standard steel strip stadiometer, and weight was determined using a digital electronic scale. BMI was calculated as weight in kilograms divided by height in metres squared (kg/m^2). Waist circumference was measured at the midway point between the lower costal margin and the superior iliac crest in a horizontal plane with flexible anthropometric tape. Body fat was measured using a body composition analyser. The systolic and diastolic blood pressures and heart rate were recorded for all participants. Blood pressure was measured to the nearest 2 mm Hg using an appropriately sized cuff and a standard mercury sphygmomanometer in a sitting position by trained nurses. Participants took at least a 10 min rest before the measurement was taken. Blood samples were drawn with minimal trauma from the antecubital vein in the morning after an overnight fast. Biochemical markers, including total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting glucose, insulin, homeostatic model assessment-insulin resistance (HOMA-IR) and high-sensitive C reactive protein (hs-CRP), were analysed by a biochemical automated analyser (Beckman Coulter, California, USA).

Genotyping

Buccal swabs were collected from each participant using standard protocols, and DNA was isolated using the Isohelix Buccal DNA isolation kit (Cell Projects, Kent, UK) as per the manufacturer's instructions. DNA was then purified and concentrated using the DNA Clean and Concentrator kit (Zymo Research, Irvine, California, USA). The quality of isolated genomic DNA was checked using the agarose gel electrophoresis and quantified using spectrophotometry.

We systematically reviewed PubMed-indexed articles for previously identified obesity-related genes in East Asians and selected seven SNPs within the *PPARγ2*, *GNB3*, *SDC3*, *ADRB2*, *FTO*, *PPARγ* and *ESR1* genes.[24–31] All SNP genotyping was performed using the TaqMan SNP Genotyping assay. The primers and probes for the aforementioned SNPs were from the ABI Assay-on-Demand kit (ABI: Applied Biosystems, Foster City, California, USA). Reactions were carried out according to the manufacturer's protocol. The probe fluorescence signal detection was performed using the ABI *StepOnePlus* Real-Time PCR System.

Statistical analysis

SPSS (software V.21.0) was used for all statistical analyses. The categorical data were analysed using the χ^2 test, and differences for continuous variables were compared using Student's t-test to compare the characteristics of obese and non-obese participants. Genotype frequencies were evaluated for Hardy-Weinberg equilibrium using a χ^2 goodness-of-fit test. Analysis of covariance (ANCOVA) was used to compare clinical variable mean values, while adjusting for the covariates of age and gender. ORs and their 95% CIs were evaluated. Association between SNPs of candidate genes and obesity was tested via logistic regression analysis at the significance level of 5%. A Bonferroni correction was applied to adjust the significance level of multiple comparisons. The power to detect significant association was calculated by QUANTO software (http://biostats.usc.edu/software).

RESULTS

A comparison of characteristics between the study participants and control group is shown in table 1. Participants who were obese had significantly higher values for waist circumference, hip circumference, waist-to-hip ratio, body fat percentage, systolic and diastolic blood pressure, triglycerides, LDL-C, fasting glucose, blood insulin, HOMA-IR and hs-CRP than those in the control group. The association of obesity with SNPs in seven genes is shown in table 2. Analysis of the genotype distributions of the SNPs in obese and non-obese groups revealed a significant positive correlation between SNP in rs2282440-*SDC3* and obesity in the Taiwanese population

Table 1 Demographic and clinical characteristics of study participants

Characteristics	Control (BMI <27 kg/m^2, N=323, female %=74.0) Mean	SD	Obese (BMI ≥27 kg/m^2, N=264, female %=48.9) Mean	SD	p Value*
Age (years)	40.06	11.01	40.42	10.98	0.689
Height (cm)	162.05	7.59	166.58	8.74	<0.001
Weight (kg)	60.75	8.87	86.66	14.97	<0.001
BMI (kg/m^2)	23.07	2.35	31.14	4.27	<0.001
Waist circumference (cm)	73.91	8.34	97.09	13.43	<0.001
Hip circumference (cm)	92.93	5.42	108.42	10.24	<0.001
Waist-to-hip ratio	0.79	0.07	0.9	0.09	<0.001
Body fat (%)	28.86	5.89	37.27	9.3	<0.001
SBP (mm Hg)	118.09	13.7	131.77	17.84	<0.001
DBP (mm Hg)	74.27	10.12	82.25	13.03	<0.001
Heart rate (bpm)	75.95	13.11	76.98	13.29	0.349
Cholesterol (mg/dL)	193.99	37.66	199.53	37.84	0.078
Triglyceride (mg/dL)	86.24	49.01	147.38	110.86	<0.001
LDL-C (mg/dL)	114.49	33.98	123.51	32.57	0.001
HDL-C (mg/dL)	61.61	15.54	48.02	12.06	<0.001
Glucose (mg/dL)	88.78	12.41	103.2	32.26	<0.001
Insulin (μU/mL)	6.96	4.31	16.91	17.15	<0.001
HOMA-IR	1.56	1.09	4.61	6.08	<0.001
hs-CRP (mg/dL)	0.14	0.29	0.3	0.45	<0.001

BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment-insulin resistance; hs-CRP, high-sensitive C reactive protein; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.
*Independent t-test.

(p=0.006). Besides a higher BMI, the T/T genotype of *SDC3* was also significantly associated with a larger waist and hip circumference, higher body fat percentage and lower HDL-C (table 3). Furthermore, we examined the synergistic effects of rs2282440-*SDC3* with SNPs of the other genes on obesity. We performed an OR analysis by comparing the addition of minor or major alleles in the other genes to the *SDC3T*/T genotype versus their addition to the *SDC3* C/C+C/T genotypes. We found that there was a synergistic effect of the SNPs in rs2282440-*SDC3* and rs1801282-*PPARγ2* on obesity (table 4). Participants with concomitant rs2282440-*SDC3T*/T and 1801282rs-*PPARγ2* C/G genotypes had a higher risk of obesity (OR=6.77), larger waist circumference (OR=5.40), larger waist-to-hip ratio (OR=4.08), higher body fat percentage (OR=4.65) and higher serum triglycerides (OR=3.52). Finally, statistical power analysis revealed that the present study had 97.01% power, when using 0.25 as the allele frequency, 0.20 as the baseline disease risk and 2.0 in the effect size among obese and control participants in the complete sample population to detect associations of rs2282440-*SDC3* with obesity.

DISCUSSION

The prevalence of overweight and obese adults is increasing in Taiwan.[2] Obesity is an important worldwide public health issue, and a large number of potential obesity-associated genetic loci have been reported. To the best of our knowledge, this is the first report describing the association of obesity with an SNP in rs2282440-*SDC3* in Taiwan. One study revealed that the Arg16Gly polymorphism of *ADRB2* was significantly associated with obesity in Taiwanese female adolescents.[26] Another study found that three novel SNPs in *ESR1* and *PPARγ* resulted in a >5-fold risk of severe obesity in the Han Chinese population.[29] These SNPs (rs1042714-*ADRB2*, rs712221-*ESR1*, rs1822825-*PPARγ*) were included in our study; however, no significant differences were found in their genotype distributions between obese participants and non-obese controls. In addition, the rs5443-*GNB3* SNP did not exhibit a significant association with obesity in our study but was previously found to be correlated with obesity in the Taiwanese population according to a study by Hsiao *et al*.[24] Our study shows that among the seven obesity-related genes previously reported in East Asians, SNP in rs2282440-*SDC3* is the only one positively associated with obesity in the Taiwanese population. *SDC3* is expressed in the hypothalamic feeding centres and is involved in the regulation of energy balance. Furthermore, syndecan-3 protein expression in the hypothalamus is upregulated in response to food deprivation. *SDC3*-null mice responded to food deprivation with reduced reflex hyperphagia.[32] One study demonstrated that *SDC3*-null mice have reduced adipose content compared with wild-type mice. When given a high-fat diet, *SDC3*-null male and female mice exhibited a partial

Table 2 Association of obesity with SNPs in seven genes

Gene (SNP)	Genotype	Control		Obese			Adjusted model*		
		Count	Per cent	Count	Per cent	p Value†	OR	95% CI	p Value
PPARγ2 (rs1801282)	C/C	263	81.4	224	84.8	0.024	Reference		
	C/G	60	18.6	40	15.2		0.845	0.537 to 1.329	0.466
	G/G	0	0.0	0	0.0		NA	NA	NA
	G carrier	60	18.6	40	15.2		0.845	0.537 to 1.329	0.466
GNB3 (rs5443)	C/C	59	18.2	48	18.2	0.393	Reference		
	C/T	162	50.2	137	51.9		0.950	0.597 to 1.510	0.827
	T/T	102	31.6	79	29.9		0.901	0.547 to 1.486	0.684
	T carrier	264	81.8	216	81.8		0.931	0.600 to 1.445	0.749
SDC3 (rs2282440)	C/C	78	24.1	51	19.3	0.074	Reference		
	C/T	184	57.0	131	49.6		1.109	0.720 to 1.711	0.638
	T/T	61	18.9	82	31.1		2.016	1.221 to 3.327	0.006
	T carrier	245	75.9	213	80.7		1.339	0.887 to 2.023	0.165
ADRB2 (rs1042714)	C/C	247	76.5	213	80.7	0.923	Reference		
	C/G	73	22.6	46	17.4		0.737	0.481 to 1.129	0.161
	G/G	3	0.9	5	1.9		1.758	0.397 to 7.781	0.457
	G carrier	76	23.5	51	19.3		0.780	0.516 to 1.180	0.239
FTO (rs6499640)	G/G	206	63.8	181	68.6	0.698	Reference		
	G/A	104	32.2	77	29.2		0.852	0.589 to 1.223	0.396
	A/A	13	4.0	6	2.3		0.364	0.130 to 1.020	0.055
	A carrier	117	36.2	83	31.5		0.788	0.551 to 1.128	0.193
PPARγ (rs1822825)	G/G	113	35.0	89	33.7	0.037	Reference		
	G/A	163	50.5	142	53.8		1.140	0.787 to 1.651	0.489
	A/A	47	14.6	33	12.5		0.837	0.485 to 1.443	0.522
	A carrier	210	65.1	175	66.3		1.069	0.750 to 1.525	0.711
ESR1 (rs712221)	A/A	105	32.5	88	33.3	0.688	Reference		
	A/T	158	48.9	125	47.3		0.850	0.580 to 1.247	0.406
	T/T	60	18.6	51	19.3		0.892	0.548 to 1.452	0.645
	T carrier	218	67.5	176	66.6		0.862	0.601 to 1.236	0.418

*Logistic regression analysis adjusted for age and sex, and significant with the Bonferroni correction for multiple comparison.
†Hardy-Weinberg equilibrium using a χ^2 goodness-of-fit test with 1 degree of freedom.
NA, not available; SNP, single-nucleotide polymorphism.

Table 3 Comparison of clinical variables of SNPs in rs2282440-*SDC3*

Gene (SNP)	*SDC3* (rs2282440)				
Genotype	C/C and C/T (N=444)		T/T (N=143)		
Dependent variable	Mean	SE	Mean	SE	p Value
BMI (kg/m^2)	26.39	0.24	27.65	0.42	0.010
Waist circumference (cm)	83.46	0.68	87.05	1.21	0.010
Hip circumference (cm)	99.24	0.51	101.90	0.90	0.009
Waist-to-hip ratio	0.84	0.00	0.85	0.01	NS
Body fat (%)	32.19	0.38	34.04	0.68	0.018
SBP (mm Hg)	123.70	0.77	125.90	1.35	NS
DBP (mm Hg)	77.59	0.55	78.67	0.98	NS
Heart rate (bpm)	76.28	0.62	76.82	1.09	NS
Cholesterol (mg/dL)	196.50	1.74	196.30	3.07	NS
Triglyceride (mg/dL)	110.00	4.03	125.40	7.10	0.059
LDL-C (mg/dL)	118.50	1.57	118.60	2.78	NS
HDL-C (mg/dL)	56.17	0.66	53.41	1.17	0.040
Glucose (mg/dL)	94.64	1.12	97.20	1.97	NS
Insulin (μU/mL)	11.09	0.61	12.52	1.07	NS
HOMA-IR	2.83	0.21	3.24	0.37	NS
hs-CRP (mg/dL)	0.21	0.02	0.22	0.03	NS

BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment-insulin resistance; hs-CRP, high-sensitive C reactive protein; LDL-C, low-density lipoprotein cholesterol; NS, not significant; SBP, systolic blood pressure.
Analysis of covariance (ANCOVA): covariates are age and gender.

Table 4 Combined effects of SNPs in rs2282440-*SDC3* and rs1801282-*PPARγ2*

Characteristics	*SDC3* rs2282440	*PPARγ2* 1801282rs	OR	Upper 95% CI	Lower 95% CI	p Value*
BMI	C carrier	C/C	1.00			
	T/T	C/C	1.6	1.07	2.45	0.022
	T/T	G carrier	6.77	1.87	24.54	0.004
Waist circumference	C carrier	C/C	1.00			
	T/T	C/C	1.50	1.00	2.25	0.051
	T/T	G carrier	5.40	1.51	19.31	0.010
Waist-to-hip ratio	C carrier	C/C	1.00			
	T/T	C/C	1.56	1.00	2.45	0.049
	T/T	G carrier	4.08	1.49	11.18	0.006
Body fat (%)	C carrier	C/C	1.00			
	T/T	C/C	1.45	0.97	2.17	0.069
	T/T	G carrier	4.65	1.48	14.59	0.009
Triglycerides	C carrier	C/C	1.00			
	T/T	C/C	1.51	0.92	2.47	0.107
	T/T	G carrier	3.52	1.25	9.93	0.017

*Logistic regression adjusted for age and sex. BMI, body mass index; SNPs, single-nucleotide polymorphisms.

resistance to obesity due to reduced food intake in males and increased energy expenditure in females, relative to that of wild-type mice.[33] A strongly positive association of obesity with SNP in rs2282440-*SDC3* was also found in the Korean population.[30] Besides a higher BMI, our study also shows that an SNP in rs2282440-*SDC3* was significantly associated with larger waist and hip circumference, higher body fat percentage and lower HDL-C. Although evidence of *SDC3* in the regulation of energy balance has been published, few genetic studies concerning the association between *SDC3* and obesity have been reported. Marked ethnic difference is present in studies,[30 34] and this is the first report describing the association of *SDC3* and obesity in the Taiwanese population.

After we identified *SDC3* as an obesity-related gene in our population, we attempted to analyse whether it has synergistic effects with other genes on obesity. We found that the combination of SNPs in rs2282440-*SDC3* and rs1801282-*PPARγ2* resulted in an increased risk of obesity (OR=6.77; 95% CI 1.87 to 24.54). In our study, we identified no participants with the rs1801282-*PPARγ2* G/G genotype (Hardy-Weinberg equilibrium p value was 0.024). The rarity of the rs1801282-*PPARγ2* G/G genotype in the Taiwanese population has previously been noted in two other studies.[22 27] There were only 3 out of 663 participants with the rs1801282-*PPARγ2* G/G genotype in Hsiao's study and 0 out of 596 participants in Lei's study. *PPARγ* is a nuclear receptor that controls the transcription of genes involved in free fatty acid uptake and lipogenesis. *PPARγ2* is an isoform that is abundantly expressed in adipose tissue, and has been shown to play an important role in the regulation of insulin sensitivity and adipose tissue metabolism.[35] SNP rs1801282 (C→G) results in a Pro12Ala substitution in *PPARγ2*. A large number of studies assessing the association between this *PPARγ2* polymorphism and BMI have been reported with controversial results.[36] One meta-analysis revealed a higher BMI with an overall estimation of +0.065 kg/m^2 (95% CI 0.026 to 0.103, p=0.001) for homozygous and heterozygous carriers of the Ala allele of the *PPARγ2* gene in comparison to non-carriers.[36] Another study suggested that in the Taiwanese population, the Pro12Ala *PPARγ2* variant may contribute to fat accumulation and a higher BMI independent of type 2 diabetes mellitus. Additionally, carriers of the Ala12 allele have a 2.9 times (95% CI 1.5 to 5.5) higher chance of having a BMI of at least 25 kg/m^2.[27] Our study shows the distribution of polymorphisms in rs1801282-*PPARγ2* in non-obese and obese participants was not significantly different. However, the combination of homozygous T/T genotype in rs2282440-*SDC3* and heterozygous C/G genotype in rs1801282-*PPARγ2* resulted in an increased risk for obesity and obesity-related metabolic traits, such as waist circumference, waist-to-hip ratio, body fat percentage and higher serum triglycerides. Owing to previously described roles of *SDC3* in the feeding response and *PPARγ2* in adipocyte differentiation and insulin sensitivity, we postulate that the reason for the synergistic effect of SNPs in these genes on obesity may be the result of hyperphagia with increased fat accumulation. As this is the first report of synergism between SNPs in *SDC3* and *PPARγ2*, the true mechanism is still unclear and will require further studies for confirmation.

CONCLUSION

Although a large number of SNPs in obesity-related genes had previously been reported, there had been relatively a few studies in the Taiwanese population. We found that SNPs in rs2282440-*SDC3* were associated with obesity in the Taiwanese population. Furthermore, there was a synergistic effect of the high-risk alleles in the *SDC3* and *PPARγ2* genes on the obese phenotype in the Taiwanese population. Use of these SNPs as a potential biomarker for obesity risk in the Taiwanese population

could allow for potential early lifestyle modifications in those individuals with heritable risks.

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Contributors W-HH, L-CH, H-LC and Y-HL participated in the design of the study and interpretation of the data. W-HH, L-CH and H-YL helped to draft the manuscript. L-CH and Y-HL performed acquisition and statistical analyses. W-HH, L-CH and H-LC were responsible for participant screening. W-HH and H-YL contributed in revising drafts of the manuscript, and all authors had the approval of the final manuscript.

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