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/m², 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.

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/m² and overweight as BMIs of ≥24 and <27 kg/m². 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.3 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. Large-scale genome-wide association studies (GWAS) have identified at least 58 genetic loci that are robustly associated with obesity-related traits. The association of BMI, waist circumference and body fat with genetic variation were 16–85%, 37–81% and 35–63% respectively. Several genetic loci reported in GWAS have recently been studied to contribute to the development of obesity. 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. We systematically reviewed PubMed-indexed studies for previously identified obesity-related genes in East Asians 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/m²) and 264 study participants (BMI ≥27 kg/m²), 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/m² 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 using a standard steel strip at the height was measured using a standard steel strip station and was determined using a digital electronic scale. BMI was calculated as weight in kilograms divided by height in metres squared (kg/m²). 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. DNAs were 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 ESRI genes. 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 χ² 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 χ² 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.
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 SDC3C/C+C/T genotypes. We found that there was a synergistic effect of the SNPs in rs2282440-SDC3 and rs1801282-PPARγ on obesity (Table 4). Participants with concomitant rs2282440-SDC3T/T and 1801282rs-PPARγT2 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. 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. 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. 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. 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. 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 1** Demographic and clinical characteristics of study participants

| Characteristics | Control (BMI <27 kg/m², N=323, female %=74.0) | Obese (BMI ≥27 kg/m², N=264, female %=48.9) | 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/m²)     | 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 ± 5.88                                 | 37.27 ± 9.3                                   | <0.001   |
| SBP (mm Hg)     | 118.09 ± 13.7                                 | 131.77 ± 17.86                                | <0.001   |
| DBP (mm Hg)     | 74.27 ± 10.12                                 | 82.25 ± 13.06                                 | <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.

*p Independent t-test.
Table 2  Association of obesity with SNPs in seven genes

| Gene (SNP) | Genotype | Control | | Obese | | Adjusted model* | | OR | 95% CI | p Value  |
|-----------|----------|---------|---------|---------|---------|-----------------|---------|--------|---------|
|           |          | Count   | Per cent | Count   | Per cent | p Value† | OR | 95% CI | p Value  |
| PPARγ2    | 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      | C/C      | 59      | 18.2     | 48      | 18.2     | 0.393      | Reference |        |         |         |
|           | C/T      | 162     | 50.2     | 137     | 51.9     | 0.737      | 0.481 to 1.129 | 0.161  |
|           | T/T      | 102     | 31.8     | 79      | 29.9     | 1.758      | 0.937 to 2.102 | 0.155  |
| SDC3      | C/C      | 78      | 24.1     | 51      | 19.3     | 0.788      | 0.551 to 1.180 | 0.193  |
|           | C/T      | 184     | 57.0     | 131     | 49.6     | 1.221      | 0.909 to 1.523 | 0.179  |
|           | T/T      | 76      | 21.8     | 82      | 21.1     | 1.625      | 0.858 to 2.738 | 0.697  |
| ADRB2     | C/C      | 247     | 76.5     | 213     | 80.7     | 0.923      | Reference |        |         |         |
|           | C/T      | 73      | 22.6     | 46      | 17.4     | 0.737      | 0.481 to 1.129 | 0.161  |
|           | T/T      | 3       | 0.9      | 5       | 1.9      | 1.758      | 0.937 to 2.102 | 0.155  |
| FTO       | 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 | 0.655  |
|           | A carrier| 117     | 36.2     | 83      | 31.5     | 0.788      | 0.551 to 1.128 | 0.193  |
| PPARγ2    | 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      | 14.5     | 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      | 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 $\chi^2$ 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) | Genotype | SDC3 (rs2282440) | T/T (N=143) |
|------------|----------|-----------------|-------------|
|            |          | C/C and C/T (N=444) |               |
|            | Genotype | Mean     | SE    | Mean     | SE    | p Value  |
| BMI (kg/m²) |          | 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   | 3.84  | 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.

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resistance to obesity due to reduced food intake in males and increased energy expenditure in females, relative to that of wild-type mice. A strongly positive association of obesity with SNP in rs2282440-SDC3 was also found in the Korean population. 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 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 0.022). The rarity of the rs1801282-PPARγ2 G/G genotype in the Taiwanese population has previously been noted in two other studies. There were only 3 out of 615 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. 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. One meta-analysis revealed a higher BMI with an overall estimation of +0.065 kg/m² (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. 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/m². 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.

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

| Characteristics | SDC3 rs2282440 | PPARγ2 rs1801282 | OR    | Upper 95% CI | Lower 95% CI | p Value* |
|-----------------|----------------|------------------|-------|--------------|--------------|---------|
| BMI | C carrier | C/C | 1.00 | | | |
| | 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.

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

Acknowledgements The authors thank Ms Fang-Ju Sun for her professional assistance in biostatistics and Dr Betty C.C. Chang and Dr Victor T.G. Lin for editorial assistance.

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.

Funding This study was supported by the TCI Gene.

Competing interests None declared.

Patient consent Obtained.

Ethics approval MacKay Memorial Hospital.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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