ESR1, FTO, and UCP2 Genes Interact with Bariatric Surgery Affecting Weight Loss and Glycemic Control in Severely Obese Patients

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Published online: 1 July 2011
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Abstract
Background Significant variability in weight loss and glycemic control has been observed in obese patients receiving bariatric surgery. Genetic factors may play a role in the different outcomes.
Methods Five hundred and twenty severely obese patients with body mass index (BMI) ≥35 were recruited. Among them, 149 and 371 subjects received laparoscopic adjustable gastric banding (LAGB) and laparoscopic mini-gastric bypass (LMGB), respectively. All individuals were genotyped for five obesity-related single nucleotide polymorphisms on ESR1, FTO, PPARG, and UCP2 genes to explore how these genes affect weight loss and glycemic control after bariatric surgery at the 6th month.
Results Obese patients with risk genotypes on rs660339-UCP2 had greater decrease in BMI after LAGB compared to patients with non-risk genotypes (−7.5 vs. −6.0, p=0.02). In contrast, after LMGB, obese patients with risk genotypes on either rs712221-ESR1 or rs9939609-FTO had significant decreases in BMI (risk vs. non-risk genotype, −12.5 vs. −10.0 U on rs712221, p=0.02 and −12.1 vs. −10.6 U on rs9939609, p=0.04) and a significant amelioration in HbA1c levels (p=0.038 for rs712221 and p<0.0001 for rs9939609). The synergic effect of ESR1 and FTO genes on...
HbA1c amelioration was greater ($\sim 1.54\%$, $p$ for trend <0.001) than any of these genes alone in obese patients receiving LMGB.

Conclusions The genetic variants in the ESR, FTO, and UCP2 genes may be considered as a screening tool prior to bariatric surgery to help clinicians predict weight loss or glycemic control outcomes for severely obese patients.

Keywords ESR1 · FTO · UCP2 · Bariatric surgery · HbA1c

Introduction

Considerable evidence indicates that obesity is associated with numerous diseases and metabolic abnormalities which have high morbidity and mortality rates, such as type 2 diabetes, hypertension, dyslipidemia, coronary heart disease, and certain cancers [1, 2]. The incidence of type 2 diabetes mellitus and hyperglycemia is increasing all over the world, as well as among people of Han Chinese ethnicity in Taiwan [3]. Obese patients benefit greatly from any type of weight loss, whether resulting from lifestyle modification, oral medication, or bariatric surgery [4–8], but bariatric surgery is the sole method that has been proven to result in significant weight loss for severely obese patients [8, 9]. Gastric banding (restrictive type surgery) and gastric bypass (malabsorptive surgery) are the two most commonly performed bariatric surgeries worldwide [10]. Evidence has shown varied results in terms of weight loss and glycemic control after bariatric surgery among obese patients of different ethnicities [6, 11–15]. The high variation in responses to bariatric surgery might be partially explained by genetic effects [16]. However, there have been few studies exploring the interaction between bariatric surgery and genetic effects that might affect the efficacy of post-surgery weight loss and glycemic control, especially for Han Chinese ethnicity. Recently, a more comprehensive research has been performed to search the obesity genes in Chinese Han and explore the effect of these obesity genes on weight loss. Three genes (ESR1, FTO, and PPARγ) have been reported to associate with obesity and the efficacy of bariatric surgeries for Chinese Han [17, 18]. For the three genes, ESR1 is a ligand-activated transcription factor composed of several domains; FTO is a gene with unknown function, which was found widely expressed in fetal and adult tissues and with the highest expression level in the brain [19]. Uncoupling protein 2 (UCP2) is a cytosural one affecting the efficiency of energy metabolism [20, 21]. Moreover, a non-synonymous genetic variant (rs660339, also expressed as Ala55Val) on the UCP2 gene has been reported to interact with gastric banding and results in differences in efficiency of weight loss [16]. PPARγ encodes a nuclear receptor involved in adipocyte differentiation and acts as a lipid sensor participating in the regulation of energy storage and glucose and lipid homeostasis [22–24].

In this study, we aimed to explore the effects of four genes reported in previous studies on weight loss and glycemic control among severely obese patients receiving bariatric surgery [16–18].

Subjects and Methods

This was a multicenter study including three hospitals in Taiwan that recruited obese patients searching for bariatric surgery at any of three hospitals between May 2008 and April 2010. Patients ranging in age from 20 to 55 years old with a body mass index (BMI) equal to or greater than 35 kg/m² were enrolled and recommended for one of two bariatric procedures: laparoscopic adjustable gastric banding treatment (LAGB, using Lap-Band from Bioenterics Corp., Carpinteria, CA, USA) and laparoscopic mini-gastric bypass (LMGB). The study was performed with the approval of the ethics committee of Min-Sheng General Hospital, Taipei Medical University Hospital and Chang Jung University. All patients signed informed consent forms before entering this study and were followed up for at least 6 months after bariatric surgery.

Study Design

Five single nucleotide polymorphisms (SNPs) were selected which were reported to be significantly associated with severe obesity or bariatric surgery effectiveness in Chinese patients in the previous studies [16–18]. All the obese patients were genotyped for the five SNPs. The “rs” number of the five SNPs were rs712221 (on ESR1 gene), rs4684846 (on PPARγ gene), rs1822825 (on PPARγ gene), rs660339 (on UCP2 gene), and rs9939609 (on FTO gene), respectively.

gDNA Extraction and Genotyping

Genomic DNA was extracted from cells in the buffy coat layer using a modified phenol–chloroform method [25–27]. The quality of the DNA was assessed by the ratio of the 260- to 280-nm readings obtained by a spectrophotometer. DNA samples were quantified to ready for genotyping for five SNPs by the ABI TaqMan® SNP genotyping assays (Applied Biosystems, USA). The rule of TaqMan® is a real-time genotyping platform with the characteristics of high throughput and high accuracy. The sequence information of the five SNPs was retrieved from the dbSNP database (http://www.ncbi.nlm.nih.gov/SNP).
Statistical Analysis

The SAS 9.1.3 software has been applied in this analysis. *t* test and chi-square analysis were performed on descriptive data. The analysis of covariance (ANCOVA) model was performed to explore the association between gene and outcome variable. Subsequently, all of the shown *p* values were adjusted by multiple comparisons, based on 10,000 permutations. The outcome variables included the changes in HbA1c, blood glucose level, and BMI before and 6 months after bariatric surgery. The *p* value < 0.05 denotes significant difference.

Results

Of the total of 520 severely obese patients who qualified for surgical intervention, 149 patients (66 men/83 women) received LAGB surgery and 371 patients (105 men/266 women) received LMGB surgery. Before surgery, only the gender distribution showed significant difference between the LAGB and LMGB groups (Table 1).

Association Between Genetic Variants and Glycemic Control and Weight loss

In the first analysis, the results of allelic association analysis revealed that rs712221 (ESR1), rs9939609 (FTO), and rs660339 (UCP2) were associated with HbA1c reduction and weight loss in those patients undergoing bariatric surgery (data not shown). In the second risk genotype analysis, rs712221 and rs9939609 showed a recessive genetic effect; however, the rs660339 showed a dominant effect. The risk genotypes of rs712221, rs9939609, and rs660339 were “TT”, “AA”, and “CT/TT”, respectively (Tables 2 and 3). Furthermore, comparison showed that obese patients with a risk genotype (CT/TT) on rs660339 had more weight loss than those without the risk genotype (−7.5±3.8 vs. −6.0±3.1 U, *p* = 0.02) at the sixth month after undergoing LAGB (Table 2). Although the “T” allele showed a dominant effect on weight reduction, it did not show a good effect on glycemic control for patients at the sixth month after undergoing LAGB. Table 3 indicates that both of the rs712221 and rs9939609 were significantly associated with weight loss and improvement of glycemic control in obese patients after receiving LMGB. Severely obese patients carrying risk genotypes on rs712221 and rs9939609 had more weight loss than patients with no risk genotypes at the sixth month after undergoing LMGB (−12.5±3.1 vs. −10.0±3.3 U on rs712221, *p* = 0.02; −12.1±2.9 vs. −10.6±3.1 U on rs9939609, *p* = 0.04). Similarly, glycemic control after LMGB was better in those patients with risk genotypes than those carrying non-risk genotypes. Fasting blood glucose improved significantly to a greater target in patients with risk genotypes (reduced magnitude in blood glucose, −34.6±21.4 vs. −13.4±17.2 mg/dl on rs712221, *p* = 0.001; −38.7±12.9 vs. −9.3±19.1 mg/dl on rs9939609, *p* < 0.0001) than their non-risk genotype counterparts at the sixth month after LMGB (Table 3). With respect to HbA1c amelioration, patients with risk genotypes also showed a greater degree of amelioration in HbA1c levels than patients carrying non-risk genotypes at the sixth month after LMGB (reduced magnitude in HbA1c, −1.5±0.7% vs. −0.5±0.3% on rs712221, *p* = 0.038; −1.5±0.2% vs. −0.1±0.2% on rs9939609, *p* < 0.0001) (Table 3). Furthermore, the synergistic effect of two genetic variants (rs712221 on ESR1 and rs9939609 on FTO) showed the highest magnitude of weight loss at the sixth month post LMGB, when they simultaneously

Table 1: Characteristics of the 520 severely obese patients before and 6 months after bariatric surgery

<table>
<thead>
<tr>
<th></th>
<th>Before LAGB (n=149)</th>
<th>Before LMGB (n=371)</th>
<th><em>p</em> value</th>
<th>After LAGB (n=149)</th>
<th>After LMGB (n=371)</th>
<th><em>p</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD)</td>
<td>31.9±9.2</td>
<td>30.7±8.3</td>
<td>0.23</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Male/female</td>
<td>66/83</td>
<td>105/266</td>
<td>&lt;0.01</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>136.5±20.5</td>
<td>134.0±17.6</td>
<td>0.18</td>
<td>143.8±25.8</td>
<td>129.2±19.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>86.6±13.4</td>
<td>86.0±12.9</td>
<td>0.65</td>
<td>87.3±24.2</td>
<td>75.8±13.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.2±1.1</td>
<td>7.0±1.0</td>
<td>0.10</td>
<td>6.6±0.6</td>
<td>6.1±0.6</td>
<td>0.10</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>14.3±1.7</td>
<td>14.0±1.6</td>
<td>0.27</td>
<td>14.9±1.6</td>
<td>14.8±1.8</td>
<td>0.49</td>
</tr>
<tr>
<td>Blood glucose (mg/dl)</td>
<td>149.7±65.5</td>
<td>149.5±44.9</td>
<td>0.51</td>
<td>119.5±16.1</td>
<td>113.5±9.4</td>
<td>0.06</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>41.9±6.3</td>
<td>42.0±6.2</td>
<td>0.87</td>
<td>35.1±6.5</td>
<td>31.3±4.8</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data were expressed as mean ± SD (standard deviation). All *p* values were derived from the *t* test analysis, except the sex ratio, from chi-square analysis.

BMI, body mass index, LAGB, laparoscopic adjustable gastric banding, LMGB, laparoscopic mini-gastric bypass, HbA1c, glycated hemoglobin.
had both risk genotypes on rs712221 and rs9939609 (data not shown). Although greater weight loss and glycemic control amelioration were observed in the LMGB group than the LAGB group (Tables 2 and 3), weight loss did not show significant correlation with HbA1c amelioration (reduced blood glucose) \((r=0.03, p=0.65)\) for obese patients at the sixth month after LMGB (Table 4). In contrast, there was a significant correlation between weight loss and HbA1c amelioration \((r=0.40, p=0.024)\) in obese patients at the sixth month after receiving LAGB surgery (Table 4).

Synergistic Effect of Genetic Variants on Glycemic Control After LMGB

Focusing on glycemic control, our findings (Fig. 1) indicated that the amelioration of glycemic control possessed a linear trend with the increment of risk genotypes carried by severely obese patients \((p\text{ for trend}<0.0001)\) at the sixth month after LMGB. Severely obese patients who simultaneously carried two risk genotypes on rs712221-\textit{ESR1} and rs9939609-\textit{FTO} had

### Table 2

Changes in BMI and glycemic control for obese patients carrying risk (R) and non-risk (NR) genotypes in the sixth month after undergoing laparoscopic adjustable gastric banding (LAGB)

<table>
<thead>
<tr>
<th></th>
<th>ESR1 rs712221</th>
<th>FTO rs9939609</th>
<th>UCP2 rs660339</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R (TT)</td>
<td>R (AA)</td>
<td>R (CT/TT)</td>
</tr>
<tr>
<td>n</td>
<td>62</td>
<td>80</td>
<td>74</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>-6.9 (3.4)</td>
<td>-7.0 (3.6)</td>
<td>-7.5 (3.8)</td>
</tr>
<tr>
<td>p valuea</td>
<td>0.88</td>
<td>0.84</td>
<td>0.02</td>
</tr>
<tr>
<td>Blood glucose (mg/dl)</td>
<td>-25.1 (20.2)</td>
<td>-23.8 (21.8)</td>
<td>-23.0 (18.5)</td>
</tr>
<tr>
<td>p valueb</td>
<td>0.17</td>
<td>0.19</td>
<td>0.23</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>0.50 (0.45)</td>
<td>0.41 (0.37)</td>
<td>0.42 (0.34)</td>
</tr>
<tr>
<td>p valuea</td>
<td>0.15</td>
<td>0.73</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Data were expressed as mean (standard deviation)

\(BMI\): body mass index, \(HbA1c\): glycated hemoglobin, \textit{ESR1}: estrogen receptor 1, \textit{FTO}: fat mass and obesity-associated gene, \textit{UCP2}: uncoupling proteins 2

\* ANCOVA analysis adjusted for age, sex ratio, BMI, and HbA1c before LAGB

\* ANCOVA analysis adjusted for age, sex ratio, BMI, and blood glucose before LAGB

### Table 3

Change in BMI and glycemic control for obese patients carrying risk (R) and non-risk (NR) genotypes in the sixth month after undergoing laparoscopic mini-gastric bypass (LMGB)

<table>
<thead>
<tr>
<th></th>
<th>ESR1 rs712221</th>
<th>FTO rs9939609</th>
<th>UCP2 rs660339</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R (TT)</td>
<td>R (AA)</td>
<td>R (CT/TT)</td>
</tr>
<tr>
<td>n</td>
<td>118</td>
<td>233</td>
<td>225</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>-12.5 (3.1)</td>
<td>-12.1 (2.9)</td>
<td>-11.1 (3.6)</td>
</tr>
<tr>
<td>p valuea</td>
<td>0.02</td>
<td>0.04</td>
<td>0.59</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dl)</td>
<td>-34.6 (21.4)</td>
<td>-38.7 (12.9)</td>
<td>-23.8 (11.5)</td>
</tr>
<tr>
<td>p valueb</td>
<td>0.001</td>
<td>&lt; 0.0001</td>
<td>0.48</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>-1.5 (0.7)</td>
<td>-1.5 (0.2)</td>
<td>-0.34 (0.20)</td>
</tr>
<tr>
<td>p valuea</td>
<td>0.038</td>
<td>&lt; 0.0001</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Data were expressed as mean (standard deviation)

\* ANCOVA analysis adjusted for age, sex ratio, BMI, and HbA1c before LAGB

\* ANCOVA analysis adjusted for age, sex ratio, BMI, and blood glucose before LAGB

\(BMI\): body mass index, \(HbA1c\): glycated hemoglobin, \textit{ESR1}: estrogen receptor 1, \textit{FTO}: fat mass and obesity-associated gene, \textit{UCP2}: uncoupling proteins 2
more than threefold improvement in HbA1c levels than the those who had no risk genotype at the sixth month after LMGB surgery (reduced HbA1c for risk genotypes vs. non-risk genotype, −1.54±0.19% vs. −0.46±0.15%). We suggested that the genetic variant (rs9939609 on ESR1) seems to exhibit a stronger effect on HbA1c amelioration than rs712221 on ESR1 gene (Fig. 1).

Discussion

LAGB and vertical banded gastroplasty are among the most widely adopted restrictive type bariatric procedures and are safer and have less long-term complications than malabsorptive procedures, such as biliopancreatic bypass [28]. The current data showed a greater weight loss in LMGB compared with LAGB, which was similar to the results derived from a previous study [29], due to different surgery types. In our previous randomized trials, patients receiving LMGB had greater weight loss compared with patients receiving laparoscopic Roux-en-Y gastric bypass (LRYGBP) [30]. Lee et al. and Wang et al. [30, 31] also demonstrated that patients receiving LMGB had a lower rate of complications and mortality compared to patients receiving LRYGBP. Although LMGB is better at achieving both weight reduction and glycemic control than LAGB [5, 9, 11, 14], it is by no means an ideal procedure, because of its higher association with short-term morbidity and long-term complications. LAGB and LMGB currently are the most commonly performed bariatric surgical procedures; however the reported results for both procedures vary widely in terms of weight reduction and glycemic control [6, 12, 13, 32–36]. Some factors may potentially interact with bariatric surgery and result in highly variable outcomes in terms of weight loss and glycemic control afterwards. Much obesity research suggests that genes are strongly implicated in obesity and weight gain [17, 37, 38]. Evidence also shows that genes not only affect weight gain but also interact with other medical factors to influence weight loss and glycemic control [39–44].

In this study, although no difference in glycemic control was found between patients carrying risk genotypes and non-risk genotypes, the trend of improvement still showed a weak but significant correlation with weight loss in the LAGB group (r=0.4, p=0.024). Studies demonstrated that good glycemic control benefits from weight loss [45, 46]. We suppose that the glycemic improvement might result from weight loss, but the amplitude of weight loss was not sufficient for substantially improving glycemic control due to a short length of follow-up in the LAGB group. In this study, a greater improvement in glycemic control was observed in the LMGB group. Lee et al. [5] and Thomas et al. [12] suggest that LMGB may powerfully impair insulin action via gut hormone stimulation, not by the way of weight loss. This might explain why a significant correlation between weight loss and glycemic control had not been observed for the LMGB group. Moreover, the genetic effect may interact with gut hormone secretion, but the possible mechanism needs to be explored in further studies. With regard to the interaction between genes and LAGB surgery, this study has confirmed an association between weight reduction and rs660339 (Ala55Val) on exon 4 of the UCP2 gene, which is consistent with the results from our previous.

### Table 4 The correlation between BMI change and HbA1c amelioration in the sixth month after laparoscopic adjustable gastric banding (LAGB) and laparoscopic mini-gastric bypass (LMGB)

<table>
<thead>
<tr>
<th>Group</th>
<th>Pearson correlation coefficients (r)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAGB (n=149)</td>
<td>0.40</td>
<td>0.024</td>
</tr>
<tr>
<td>LMGB (n=371)</td>
<td>0.03</td>
<td>0.65</td>
</tr>
</tbody>
</table>

### Fig. 1

The synergistic effect of rs712221 (ESR1) and rs9939609 (FTO) on HbA1c amelioration in the sixth month after undergoing laparoscopic mini-gastric bypass (LMGB). NARG: obese patients carrying non-risk genotype in ESR1 and FTO genes, ESR1_RG: obese patients carrying one risk genotype at rs712221 of ESR1 gene, FTO_RG: obese patients carrying one risk genotype at rs9939609 of FTO gene, ESR1_RG + FTO_RG: obese patients carrying both risk genotypes at rs712221 and rs9939609 of ESR1 and FTO genes, respectively
study [16]. The UCP2 gene was previously found to be associated with resting energy expenditure, thermal effect of food, and 24-h substrate oxidation [47–49]. Buemann et al. [50] demonstrated a raised basal metabolic rate and energy expenditure during exercise in individuals carrying the “T” allele on rs660339 of UCP2 compared to those with the “C” allele. In this study, we found that patients carrying the “T” allele also had more efficient weight reduction after LAGB. In addition, another study has showed that this non-synonymous SNP has an impact on thyroid metabolism, increasing TSH release, and thereby affecting energy balance, body weight, and body composition during a period of high calorie diet [51]. Further studies are needed to unravel the underlying mechanism by which rs660339 affects weight loss after LAGB.

With regards to the interaction between genes and LMGB surgery, ANCOVA analysis showed that rs660339 did not have a significant association with weight loss and glycemic control. This result was similar to our previous results [16]. As previously mentioned, the UCP2 gene predominantly acts on thermogenic efficiency and resting energy metabolism [47–49, 52]; thus, a common variant of rs660339 might not substantially affect weight loss and glycemic control under the strongly physiological changes induced by LMGB due to LMGB as a malabsorptive procedure [53, 54]. This might explain why the rs660339-UCP2 did not significantly affect weight loss after LMGB.

The FTO gene has been found widely expressed in fetal and adult tissues, with the highest expression level in the brain [19]. This genetic variant (rs9939609 in FTO) is not only a newly discovered locus for fat-related anthropometric indices but has also been found in several ethnic groups and in association with diabetes [55], which are the reasons why we included this locus in this study. So far, augmented research has demonstrated that rs9939609 was obviously associated with loss of body weight and glycemic control [18, 44, 56], which is consistent with this study. Muller et al. demonstrated that the genetic variant of rs9969309 in FTO was not associated with weight loss by lifestyle intervention, but it might be associated with weight loss by bariatric surgery [56]. ESR1 is a ligand-activated transcription factor composed of several domains. ESR1 knockout mice had adipocyte hyperplasia and hypertrophy in white adipose tissue, which was accompanied by insulin resistance and glucose intolerance [55, 57, 58]. This study found that rs712221, a tag-SNP representing an LD block of approximately 7 kb in intron 2 of ESR1, was significantly associated with weight reduction and glycemic control. Further study of the molecular mechanism of rs712221 is needed to explore its action on gene expression and physiological status, such as weight loss and glycemic control. It is recommended that different types of bariatric surgery be tailored to patients according to evidence-based genetic predictors [59].

It was first demonstrated in a pharmaceutical study that gene variants may determine the outcome of treatment for obesity [60]. A recent study on gastric banding identified melanocortin-4 receptor gene variants and UCP2 gene variants as associated with binge eating and bariatric surgery, respectively [16, 60]. In this study, we demonstrated that the SNPs (rs712221-ESR1, rs9939609-FTO, and rs660339-UCP2) may be markers or potential predictors for the development of obesity and of the efficiency of weight loss and/or glycemic control after bariatric surgery. Although this study is limited by a lack of dietary data, Dias et al. and Ribeiro et al. denoted that the difference of dietary inputs was small among obese patients after receiving bariatric surgeries in 6 months [61, 62]. Furthermore, weight loss and physiological changes happened mostly during 6 months after surgery [14, 16, 63], and this is why we follow up for only 6 months. However, a longer period of follow-up is warranted in further studies.

These results may serve to motivate future attempts to search for multiple predictive genes and optimal treatment protocols for weight reduction tailored to suit individual needs. These three genetic variants may be a crucial target for clinicians hoping to incorporate genetic susceptibility testing into decisions about bariatric surgery to achieve better weight loss efficiency and glycemic control. These data also provide a useful message for patients considering surgical treatment for morbid obesity. Further studies are required on multiple candidate genes in the search and on environmental factors predictive of surgical outcomes in order to optimize outcomes from bariatric procedures for morbidly obese patients.

Conclusion

This study demonstrates that three SNPs on ESR1, FTO, and UCP2 genes were associated with the efficiency of weight loss and/or glycemic control after bariatric surgery and that the combined effects of ESR1 and FTO genes provide a greater effect (HbA1c amelioration, 1.54%) than any of these genes alone.

Acknowledgments We gratefully acknowledge that this study is partially based on the results derived from Dr. Wen-Hern Pan of Academia Sinica and LM Chuang of National Taiwan University Hospital. We also thank the researchers and subjects for their participation. The authors also have a great appreciation for Taipei Medical University Hospital, Min-Sheng General Hospital, and Chang Jung University. This project supported by the National Science Council, NSC 100-2320-B-309-001.

Conflict of Interest This paper is not currently being considered by other journals. All authors declare that they have no competing financial interests, agree to submit the paper to this journal, and transfer copyright to the publisher.
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