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Ala55Val Polymorphism on UCP2 Gene Predicts Greater Weight Loss in Morbidly Obese Patients Undergoing Gastric Banding

Hsin-Hung Chen[1,2]; Wei-Jei Lee, MD, PhD[3,4]; Weu Wang, MD[3,4]; Ming-Te Huang, MD[4]; Yi-Chih Lee, MHA[3]; Wen-Harn Pan PhD[1,2]

[1]Institute of Microbiology and Biochemistry, College of Life Science, National Taiwan University; [2]Division of Epidemiology and Genetics, Institute of Biomedical Sciences, Academia Sinica; [3]Division of Surgery and Medical Therapy, Department of Surgery, Min-Sheng General Hospital, National Taiwan University, Taipei; [4]Department of Surgery, Taipei Medical University Hospita, Taiwan

Background: Variability in weight loss has been observed from morbidly obese patients receiving bariatric operations. Genetic effects may play a crucial role in this variability.

Methods: 304 morbidly obese patients (BMI ≥39) were recruited, 77 receiving laparoscopic adjustable gastric banding (LAGB) and 227 laparoscopic mini-gastric bypass (LMGB), and 304 matched non-obese controls (BMI ≤24). Initially, all subjects were genotyped for 4 SNPs (single nucleotide polymorphisms) on UCP2 gene in a case-control study. The SNPs significantly associated with morbid obesity (*P*<0.05) were considered as candidate markers affecting weight change. Subsequently, effects on predicting weight loss of those candidate markers were explored in LAGB and LMGB, respectively. The peri-operative parameters were also compared between LAGB and LMGB.

Results: The rs660339 (Ala55Val), on exon 4, was associated with morbid obesity (*P*=0.049). Morbidly obese patients with either TT or CT genotypes on rs660339 experienced greater weight loss compared to patients with CC after LAGB at 12 months (BMI loss 12.2 units vs 8.1 units) and 24 months (BMI loss 13.1 units vs 9.3 units). However, this phenomenon was not observed in patients after LMGB. Although greater weight loss was observed in patients receiving LMGB, this procedure had a higher operative complication rate than LAGB (7.5% vs 2.8%; *P*<0.05).

Conclusion: Ala55Val may play a crucial role in obesity development and weight loss after LAGB. It may be considered as clinicians incorporate genetic susceptibility testing into weight loss prediction prior to bariatric operations.

Key words: Gene, UCP2, predictor, weight loss, gastric banding, mini-gastric bypass, morbid obesity, obesity surgery

Correspondence to: Dr. Wen-Harn Pan and Dr. Wei-Jei Lee, 128 Sec. 2, Academia Rd, Nankang, Taipei, 115 Taiwan, R.O.C. Fax: 886-2-27823047; e-mail: pan@ibms.sinica.edu.tw; wjlee_obessurg_tw@yahoo.com.tw

Introduction

Obesity is a pandemic health problem in both developed and developing countries.[1] Bariatric surgery is the only proven method that can produce sustained weight loss for morbid obesity.[2] Gastric banding (restrictive type surgery) and gastric bypass (restrictive plus malabsorptive surgery) are the two commonly performed bariatric surgeries worldwide.[3] Gastric banding is 10 times safer than gastric bypass and has less long-term sequelae. However, the reported average weight loss after banding is usually less and may vary in patients.[4] The reasons for high variability in response to bariatric surgery are currently unknown. An optimal outcome for the morbid obesity from bariatric operations may occur if the patients are better predicted preoperatively. This would be of great advantage, as prediction of successful treatment by bariatric surgery can avoid unnecessary adverse effects and costs.

Obesity and body weight change (weight gain/weight reduction) show moderate to high heritability,[5-7] suggesting potential genetic contributions

to these traits. Up to now, 29 candidate genes have been reported to be associated with either body weight change or long-term variations in obesity-related phenotypes.[7] Among them, the uncoupling proteins 2 (UCP2) is a cynosural one, affecting the efficiency of energy metabolism.[8,9]

UCP2 belongs to the family of mitochondrial transporter proteins, and it is in abundance in white fat tissue, immune-related tissues and pancreatic islets.[10,11] It increases the transport of protons (H^+) across the inner mitochondrial membrane; consequently, the formation of ATP from ADP is decreased with release of chemical energy as heat.[8-10,12] Therefore, the UCP2 gene is a plausible candidate gene for obesity and body weight change.

Two remarkably common single nucleotide polymorphisms (SNPs), -866A/G (in promoter region) and Ala55Val (in exon 4, also presented as rs660339) have been described in the UCP2 gene. Both of them have been associated with obesity (BMI, waist circumference),[13-15] resting energy expenditure,[16,17] body weight change,[14,18,19] and lipid metabolism.[9,20-22] In recent years, some studies have reported that the different efficiencies of weight loss were caused by the interactions between UCP2 gene and either dietary patterns or drugs.[18,23-26] Yet, there were few studies to explore the efficiencies of weight loss contributed by the interaction between UCP2 gene and bariatric operations. Furthermore, the associations between UCP2 gene and obesity-related phenotypes have not been carefully studied in Han Chinese. We have carried out systemically large scale studies to search for influential obese genes in Han Chinese (unpublished) prior to this study. Although the large-scale obesity study is still ongoing, primary results have partially revealed the positive associations between UCP2 gene and obesity in Han Chinese.

In the current report, we not only present the results on UCP2 gene derived from our ongoing obesity study, but also explore the relationship between UCP2 gene and body-weight change in patients who underwent bariatric surgery. Our attempt is the first in morbid obesity to search for weight-loss sensitive genetic variants within UCP2 gene after the patients underwent either one of the two bariatric surgeries, i.e., laparoscopic adjustable gastric banding (LAGB) and laparoscopic mini-gastric bypass (LMGB).

Methods

This is a collaborative study between W.H. Pan of Academic Sinica and W.-J. Lee of Min-Sheng General Hospital to search for influential genetic variants of UCP2 which caused different weight loss in morbidly obese subjects.

Patient Selection

Between July 1998 and May 2005, 304 patients with age range 20-55 years and body mass index (BMI) ≥39 kg/m^2 who underwent laparoscopic bariatric surgery at our center, were enrolled. Among them, 77 cases underwent LAGB, (Lap-Band®, Inamed/Allergan, Irvine, CA, USA)[27] and 227 cases underwent LMGB.[28] Patients were evaluated in a multidisciplinary and integrated medical team, including a surgeon, general physician, endocrinologist, psychiatrist, and dietician, with standardized protocol. All patients decided the type of the surgery after detailed explanation of the advantages and disadvantages of LAGB and LMGB. The study was performed with approval of the ethics committee of the Min-Sheng General Hospital. The matched non-obese controls (BMI ≤24) were selected from the Taiwan Han Chinese cell and genome bank database (http://ncc.sinica.edu.tw/). Signed informed consent was obtained from each participant before the study.

Study Design and Genotyping

We genotyped 304 cases (BMI ≥39) and 304 matched controls (BMI ≤24) for 4 SNPs (single nucleotide polymorphisms) within UCP2 gene, in order to search the SNPs significantly associated with morbid obesity (P<0.05). One SNP (C/T) on exon 4 (rs660339) and another variant in promoter -866G/A had been previously reported to be associated with obesity. Two additional SNPs, rs17132534 in intron 2 and rs643064 in 3'-untranslated (3'UTR) region were selected. The SNPs with P<0.05 were considered as the potential weight-change sensitive genetic variants. Subsequently, statistical analyses were carried out to explore its contribution to weight loss in morbidly obese patients receiving either LAGB or LMGB.

Genomic DNA was extracted from cells in the buffy coat layer. The quality of the DNA was assessed by the

ratio of the 260 nm to 280 nm readings obtained from the spectrophotometer. DNA samples were quantified to 2.5-3 ng /μl for multiplex PCR (polymerase chain reaction). Subsequently, the PCR products were genotyped for 4 SNPs by Multiplexed Homogeneous MassEXTEND(hME) Assay (SEQUENOM, San Diego, U.S.) in the National Genotyping Core in Taiwan (http://ngc.sinica.edu.tw/document.htm). The sequence-information of 4 SNPs (-866G/A, rs17132534, rs660339, rs643064) was retrieved from the dbSNP database (http://www.ncbi.nlm.nih.gov / SNP).

Statistical Analysis

Descriptive data are expressed as mean value ± s.d. The associations between genetic variants and morbid obesity were tested by the conditional logistic regression model and the adjusted *P*-values were calculated based on 10,000 random permutations. Comparison of peri-operative parameters were performed between LAGB and LMGB using *t*-test. The *P*-value <0.05 denotes the significant difference.

Results

From June 1998 to May 2005, 304 morbidly obese patients (116 men and 188 women, mean age 32.5 years; mean body weight 122.9 kg; mean BMI 44.7 kg/m^2) receiving laparoscopic bariatric surgeries in Min-Sheng General Hospital were recruited (227 individuals receiving LMGB and 77 individuals receiving LAGB). BMI values were in the range of 19-24 kg/m^2 with a mean of 23.2 kg/m^2 for the 304 sex and age matched non-obese controls (Table 1).

Table 1. Characteristics of patients

	Morbid Obesity (n = 304)	Non-obese Control (n = 304)
Age (mean ± SD)	32.5 ± 7.8	31.6 ± 8.6
Sex ratio (F:M)	188:116	188:116
Mean weight (kg)	122.9 ± 21.4	63.2 ± 1.9
BMI (kg/m^2)	44.7 ± 6.1	23.2 ± 0.7

BMI: body mass index

Association between Morbidly Obese and UCP2 Variants

The results revealed that only the rs660339 (C/T polymorphism), within UCP2 gene, was significantly associated with morbid obesity, and the risk-allele potentially associated with morbid obesity was 'T' allele exhibiting a dominant effect on morbid obesity. Table 2 indicates that the percentage of individuals carrying risk-genotypes (with either one or two 'T' alleles on rs660339) were 63.09% and 58.04% for the obese group and for controls, respectively (odds ratio = 1.17 for the risk genotypes, 95% CI = 1.08-1.71, $P = 0.049$).

The demographic and clinical data in morbidly obese patients carrying risk genotypes (with at least one 'T' allele) and those carrying non-risk genotype (with homozygous 'C' alleles) on rs660339 are summarized in Table 3. There were no significant differences in preoperative clinical data between morbidly obese patients with at least one 'T' allele and those without 'T' allele in genotypes distribution of rs660339.

Comparison of LAGB and LMGB

The peri-operative data of patients who received LAGB and LMGB, respectively, are shown in Table 4. The percentages of individuals carrying risk genotypes (with at least one 'T' allele) on rs660339 are 61% and 64.1% in the LAGB and LMGB group, respectively, and they were not significantly different between these two groups.

All patients had follow-up ≥1 year in this study. Weight loss was significantly greater in the LMGB group than in the LAGB group at all follow-up intervals (Figure 1). Both groups had a significant reduction in BMI and a significant improvement in obesity-related co-morbidities including blood pressure, hyperglycemia, blood lipids, uric acid and liver function (data not shown). Although greater weight loss was observed in the LMGB than the LAGB group (Figure 1), the LMGB group had a higher operative complication rate than LAGB (LMGB 7.5% vs LAGB 2.8%; $P<0.05$), (Table 4). Furthermore, no major complications were experienced in LAGB, but LMGB had a 3.1% major complication rate (none of the patients died in LMGB). The LMGB group also had a higher estimated intra-

Table 2. Allelic and genotypic distribution of the SNPs significantly associated with morbid obesity

SNP (Gene) rs660339 (UCP 2)	Morbid Obesity	Non-obese Control	Odds ratio	*P*-value
The allele frequency of risk-allele (T)	41.16%	36.5%	-	0.048
The percentage of individuals carrying risk-genotypes (CT/TT)	63.09%	58.04%	1.17	0.049

The data are analyzed by simple conditional logistic regression and all *P*-values were calculated based on 10,000 random permutations.

Table 3. Clinical data in obese patients carrying risk genotype (CT/TT) and those carrying non-risk genotype (CC) on rs660339 within UCP2 gene

	CT/TT	CC	*P*-value
Number	188(63.09%)	116(36.91%)	
Male/Female	72/116	44/72	0.746
Mean age (years)	31.1 ± 8.6	31.2 ± 9.0	0.946
Body weight (kg)	121.0 ± 19.2	123.4 ± 22.4	0.334
Surgery (LAGB:LMGB)	42:146	35:81	0.862
BMI (kg/m^2)	43.7 ± 5.1	44.9 ± 6.3	0.058
SBP (mmHg)	132.0 ± 15.7	135.7 ± 16.7	0.055
DBP (mmHg)	83.8 ± 11.8	85.7 ± 12.0	0.179
Glucose (mg/dl)	114.8 ± 40.1	117.4 ± 66.5	0.667
Total cholesterol (mg/dl)	199.9 ± 35.5	202.9 ± 34.2	0.478
Triglyceride (mg/dl)	204.3 ± 158.3	234.4 ± 193.6	0.147
Uric acid (mg/dl)	7.25 ± 1.70	7.40 ± 1.94	0.495
GOT (IU/L)	29.5 ± 20.5	30.7 ± 32.4	0.700
GPT (IU/L)	33.0 ± 30.5	35.6 ± 54.3	0.600
A1bumin (mg/dl)	4.48 ± 0.28	4.49 ± 0.30	0.892
WBC (103/ul)	8.25 ± 1.85	8.63 ± 2.14	0.103
Hemoglobin (g/dl)	13.9 ± 1.39	13.6 ± 1.4	0.052
MCV	88.2 ± 4.6	87.2 ± 6.7	0.159

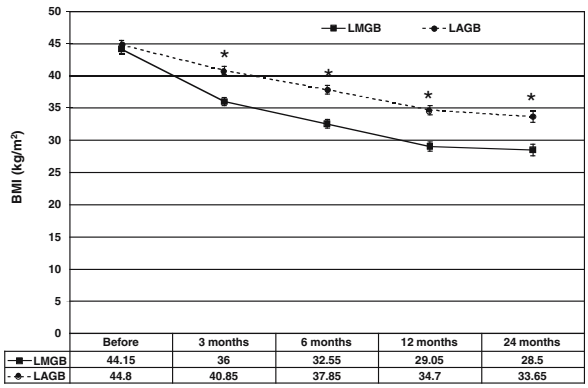
BMI: body mass index; SBP: systolic blood pressure; DBP; diastolic blood pressure; MCV: mean cellular volume; GOT: glutamic oxaloacetic transaminase); GPT: glutamic pyruvic transaminase; WBC: white blood cell count.

Table 4. Comparison of peri-operative parameters of patients undergoing laparoscopic adjustable gastric banding (LAGB) and laparoscopic mini-gastric bypass (LMGB)

	LAGB (total n = 77)	LMGB (total n = 227)	*P*-value
BMI (Before surgery)	44.8 ± 0.7	44.15 ± 0.7	NS
Age (years)	31.7 ± 9.1	30.7 ± 8.6	NS
Male % (n)	45.4 % (36)	35.6 % (80)	†NS
Mean operative time(min)	101.7 ± 37.4	103.5 ± 30.0	NS
Mortality	0	0	NS
Conversion rate	0	1(0.4%)	†NS
Intra-operative blood loss (ml)	16.9 ± 15.4	24.9 ± 15.5	<0.05
Early postoperative complication	2 (2.8%)	17(7.5%)	†
Major	0(0%)	7 (3.1%)	<0.05
Minor	2(2.8%)	10 (4.4%)	
Postoperative flatus passage (day)	1.0 ± 1.0	2.0 ± 1.2	<0.01
Analgesic use (units)	0.6 ± 1.1	2.2 ± 1.0	<0.049
Postoperative hospital stay (day)	3.0 ± 2.0	6.0 ± 5.2	<0.001

NS, not significant using *t*-test; †Chi-square test was carried out.

operative blood loss than the LAGB group in spite of similar mean operative duration in these two surgical procedures. Earlier postoperative flatus passage (LAGB 1.0 ± 1.0 days vs LMGB 2.0 ± 1.2 days; $P<0.05$) and shorter hospital stay (LAGB 3.0 ± 2.0 days vs LMGB 6.0 ± 5.2 days; $P<0.05$) were observed in the LAGB compared to the LMGB group. The LMGB group required a larger cumulative dose of analgesic medication (LMGB 2.2 ± 1.0 doses vs LAGB 0.6 ± 1.1 doses; $P<0.049$). The aforementioned results showed that although lesser weight loss was observed in patients receiving LAGB compared to patients receiving LMGB, LAGB is in general a safer operation than LMGB.



	Before	3 months	6 months	12 months	24 months
LMGB	44.15	36	32.55	29.05	28.5
LAGB	44.8	40.85	37.85	34.7	33.65

Figure 1. Change in BMI for patients after LAGB and LMGB. Mean change in BMI was compared between LMGB and LAGB by *t*-test at 4 follow-up intervals (*P<0.05). Bar denotes SE (standard error).

Genotyping and Success of Weight Reduction

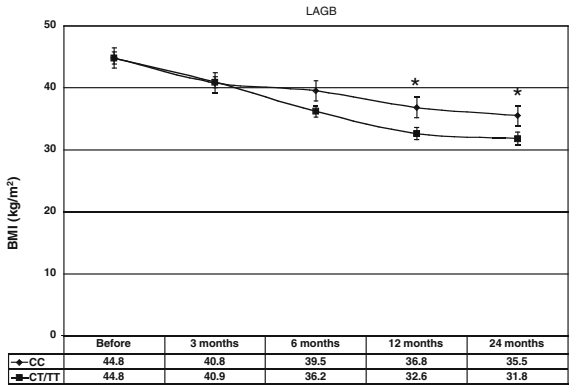
With regard to the genotypes of rs660339, morbidly obese patients receiving either LAGB or LMGB were divided into two subgroups (with and without 'T' allele). Figure 2 shows that morbidly obese patients with either one or two 'T' allele (risk genotypes) on rs660339 has a greater BMI loss than those with homozygous 'C' alleles (non-risk genotypes) at all four follow-up intervals in patients receiving LAGB. Mean units of BMI loss became statistically significant at 12 months (12.2 units in TT/CT genotype vs 8.1 units in CC genotype, P<0.003) and at 24 months (13.1 units in TT/CT genotype vs 9.3 units in CC genotype, P<0.03) after LAGB. However, this phenomenon has not been observed in the morbidly obese patients who received LMGB, as shown in Figure 3.

Discussion

This study has confirmed the association between obesity and rs660339 (also presented as Ala55Val) on exon 4 of UCP2 gene, consistent with that reported by Sui et al[29] and Zheng et al.[21] More importantly, the polymorphism rs660339 of UCP2 gene has a differential effect on the weight loss magnitude after LAGB, and therefore, may be used for patient selection for gastric banding. A 3.7 units greater drop in BMI was observed at the end of 2-year follow-up for those carrying at least one 'T' allele than for those with homozygous 'C' alleles on rs660339.

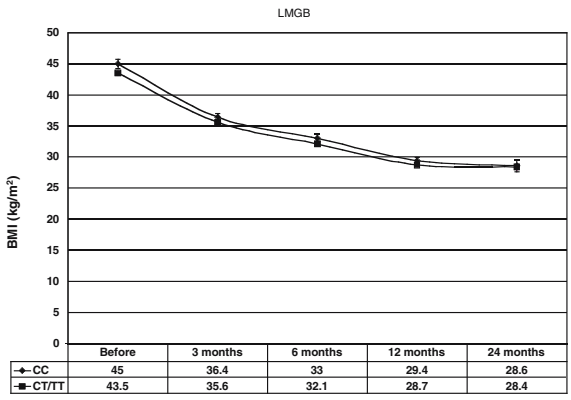
Among the most widely adopted bariatric operations, restrictive procedures including LAGB and vertical banded gastroplasty (VBG) are safer and have less long-term complications than malabsorptive procedures such as LMGB and biliopancreatic diversion.

In our previous randomized trials, patients after LMGB had a slightly better result compared to patients after laparoscopic Roux-en-Y gastric bypass (LRYGBP) at the end of the 1st and 2nd year (percentage of excess weight loss 64.9% after LMGB vs



	Before	3 months	6 months	12 months	24 months
CC	44.8	40.8	39.5	36.8	35.5
CT/TT	44.8	40.9	36.2	32.6	31.8

Figure 2. Change in BMI at differenct intervals after LAGB between patients carrying risk genotypes (CT/TT) and those carrying non-risk genotype (CC) on rs660339. Mean change in BMI was compared between LMGB and LAGB by *t*-test at 4 follow-up intervals (*P<0.05). Bar denotes SE (standard error).



	Before	3 months	6 months	12 months	24 months
CC	45	36.4	33	29.4	28.6
CT/TT	43.5	35.6	32.1	28.7	28.4

Figure 3. Change in BMI for patients after LMGB at different intervals between carrying risk genotypes (CT/TT) and carrying non-risk genotype (CC) on rs660339. There was no difference in BMI change between the two groups over 2 years at any of the 4 time-points; bar denotes SE (standard error).

58.7% after LRYGBP at the 1st year; 64.4% in LMGB vs 60.9% in LRYGBP at the 2nd year).[28] Moreover, operation time was shorter in LMGB than for LRYGBP (148 minutes for LMGB vs 205 minutes in LRYGBP, $P<0.05$).[28] Wang et al[30] also demonstrated that patients receiving LMGB had a lower complication rate and mortality rate compared to patients receiving LRYGBP. A steep learning curve was observed in LRYGBP: the conversion rate to an open operation varied from 0.8% to 11.8%, major complication rate from 3.3% to 15%, and late complication rate from 2.2% to 27%. Thus, we had adopted the simpler LMGB instead of LRYGBP.[28] We found that LMGB is a simpler and safer procedure that has no disadvantage compared with LRYGBP.

Although we believe that LMGB is better in many ways than LRYGBP, it is by no means an ideal procedure. Recently, we observed the higher related short-term morbidity and long-term complication rate of LMGB compared to LAGB.[28,30] Our operative data for LMGB in this study was similar to our previous report, which had a much higher major complication rate than LAGB.[30]

LAGB currently is the most commonly performed bariatric surgical procedure because of its safety. However, the reported results of weight reduction varied. International experience with the LAGB in Europe and Australia shows that weight loss continues even up to 5 years after surgery and stabilizes up to 9 years' follow-up.[31-36] The mean BMI reduction was about 8 to 9 units, but varied over a wide range. It is, therefore, very important for the bariatric surgeons to include appropriate patients for this procedure. We believe that individual patients should be tailored for different procedures according to evidence-based predictors.[37]

Some predictors for successful restrictive surgery or LAGB such as life-style and personality have been studied but with controversial results. Our previous study also found that *Helicobacter pylori* infection and gastric inflammation were negative predictors for weight loss after restrictive bariatric surgery.[38] Serum ghrelin levels were also found to be an important predictor in another study.[39]

Gene variants may determine the outcome of treatment of obesity, as first demonstrated in a pharmaceutical treatment study.[40] For bariatric surgery, a recent study found that melanocortin-4 receptor gene variants were associated with binge eating and influenced the treatment outcomes after gastric banding.[40] However, only 5.1 to 6.3% of the patients carried this gene variant. In the current study, we successfully demonstrated that the SNPs (rs660339), a common variant with ~ 60% of the population carrying at least one 'T' allele, may be a marker or potential variant for the development of obesity and for the efficiency of weight loss after bariatric surgery. If this finding is confirmed, a sizable number of people carrying the 'T' allele can be provided with information of a beneficial outcome of LAGB.

The UCP2 gene was previously found to be associated with resting energy expenditure, thermal effect of feeding, and 24-hour substrate oxidation.[16,19,22,41] Buemann et al[17] demonstrated a raised basal metabolic rate and energy cost of exercise in individuals carrying the 'T' allele in the SNP (rs660339), compared to those with 'C' allele. In this study, we found that the patients carrying the 'T' allele also had greater weight reduction when they were in an energy-deprived state after undergoing a LAGB, which may be similar to the energy-deprived state when people are subject to exercise training. On the other hand, another study showed that this non-synonymous SNP had an impact on thyroid metabolism, increasing TSH release, and thereby affecting energy balance, body weight, and composition during a period of high calorie diet.[42] Further studies are needed to unravel the underlying mechanism of rs660339 on weight loss after LAGB.

This study is limited by lacking data on dietary change and weight-control medication, so that we could not determine whether diet and medication may confound the findings. However, current results may serve to motivate future attempts to search for multiple predictive genes and the best treatment policy for weight reduction tailored to suit individual needs.

The rs660339 is a non-synonymous SNP with alanine (A) replacing with a valine (V) at codon 55 in UCP2 gene. Therefore, the rs660339 may be a crucial target for clinicians to consider as they incorporate genetic susceptibility testing into the weight-loss efficiency appraisal prior to bariatric surgery. This data is also relevant for patients who are considering surgical treatment for morbid obesity. In order to the best select the bariatric procedure for the morbidly obese patient, further studies are required on mechanism and on multiple candidate and novel genes,[38] as well as environmental factors predictive of the surgical outcomes.

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