Association of protein tyrosine phosphatase 1B gene polymorphism with the effects of weight reduction therapy on bodyweight and glycolipid profiles in obese patients

Hajime Yamakage1, Yousuke Konishi1, Kazuya Muranaka1, Kikuko Hotta2, Yoshihiro Miyamoto3, Hiroko Morisaki4, Takayuki Morisaki5, Noriko Satoh-Asahara1*

1Department of Endocrinology, Metabolism and Hypertension Research, Clinical Research Institute, National Hospital Organization Kyoto Medical Center, Kyoto, Japan, 2Laboratory of Pathophysiology and Pharmacotherapeutics, Faculty of Pharmacy, Osaka Ohtani University, Osaka, Japan, 3Open Innovation Center, National Cerebral and Cardiovascular Center, Osaka, Japan, 4Department of Medical Genetics, Sakakibara Heart Institute, Tokyo, Japan, and 5Division of Molecular Pathology, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan

Keywords
Obesity, Protein tyrosine phosphatase 1B, Weight reduction therapy

*Correspondence
Noriko Satoh-Asahara
Tel.: +81-75-641-9161
Fax: +81-75-645-2781
E-mail address: nsatoh@kuhp.kyoto-u.ac.jp

J Diabetes Investig 2021; 12: 1462–1470
doi: 10.1111/jdi.13492

Clinical Trial Registry
University Hospital Medical Information Network Clinical Trials Registry UMIN000023740

ABSTRACT

Aims/Introduction: Weight reduction therapy is the primary treatment to prevent complications of obesity, such as lifestyle diseases and cardiovascular disease; however, to date, useful methods and genetic factors for predicting the outcomes of weight reduction therapy in obese patients have not been established. Protein tyrosine phosphatase 1B (PTP1B), a negative regulator for insulin and leptin signaling, potentially modulates glucose and energy homeostasis. This study aimed to investigate the contribution of PTPN1 polymorphisms on weight reduction and diabetes in obese Japanese patients.

Materials and Methods: PTPN1-tagged single-nucleotide polymorphisms (SNPs) rs3787348 and rs6067484 were genotyped in 447 obese Japanese patients from the general population. In this prospective cohort study, all obese patients underwent a 3-month weight reduction therapy with lifestyle modifications, as recommended by guidelines.

Results: In obese patients (male/female 196/251, age 50–15 years, body mass index [BMI] 32–6 kg/m2), the minor allele appeared at a frequency of 45.5% in rs3787348 SNP of the PTPN1 gene. The T allele of rs3787348 was significantly associated with a higher BMI (P = 0.041 in the additive model). The patients with the T allele in SNP rs3787348 of PTPN1 had significantly smaller reductions in BMI, bodyweight and waist circumference levels during weight reduction therapy (BMI G/G, -1.9 – 0.2; G/T, -1.5 ± 0.1; T/T, -1.2 ± 0.1; P = 0.001 in the additive model).

Conclusions: Our findings show that the SNP rs3787348 in PTPN1 was associated with the effects of weight reduction therapy on BMI and waist circumference among obese Japanese patients.

INTRODUCTION

Obesity is a worldwide issue and a major risk factor for cardiovascular disease (CVD), dyslipidemia, hypertension, insulin resistance, type 2 diabetes and cancer1. Weight reduction therapy is essential for the management of obesity, and can decrease obesity-related metabolic sequelae and CVD complications2,3. We previously reported the beneficial effects of short-term weight reduction with diet and exercise guidance on arterial stiffness, serum oxidative LDL, and cystatin C, all of which are CVD and chronic kidney disease risk factors4–6.

Genetic factors contribute to the development of obesity, and to date, several candidate gene studies and genome-wide association studies using observational cohorts have shown that hundreds of genetic variants and loci are associated with body mass index (BMI)7,8. In a recent genome-wide association study...
of BMI in a Japanese population, 85 loci were found to be significantly associated with obesity\(^7\). However, the contribution of genetic variants to efficient weight loss in response to weight reduction therapy remains unknown.

The ubiquitously expressed protein tyrosine phosphatase 1B (PTP1B), encoded by the \(PTPN1\) gene, dephosphorylates phototyrosine residues of the active insulin receptor, which consequently downregulates insulin signaling\(^8,9\). PTP1B also inhibits leptin signaling through the dephosphorylation of Janus kinase 2 and signal transducer and activator of transcription 3\(^10\). The disruption of the \(PTPN1\) gene in mice results in increased insulin sensitivity and resistance to diet-induced obesity, and enables the normalization of blood glucose levels\(^12,13\). The in vitro inhibition of PTP1B improves adipocyte energy storage and insulin sensitivity, and the PTP1B inhibitor provides a prolonged reduction in bodyweight (BW) and glycemic parameters in overweight patients with type 2 diabetes\(^14-16\).

Taken together, these data illustrate the crucial role of PTP1B in the insulin and leptin pathways, and show that abnormal PTP1B activity might lead to insulin resistance, and thereby to type 2 diabetes and obesity.

In humans, \(PTPN1\) maps to chromosome 20q13.13, which also contains a major human quantitative trait locus for obesity and type 2 diabetes, thus further supporting \(PTPN1\) candidacy in type 2 diabetes and obesity\(^17,18\). Several previous studies have found convincing associations of genetic variants of \(PTPN1\) with type 2 diabetes in two independent studies of white Americans, and with insulin sensitivity and fasting glucose in Hispanic Americans\(^19,20\). However, a meta-analysis involving the largest number of European case-control samples was unable to replicate this association for any single SNP or haplotype\(^21\).

In addition, several previous studies have shown that \(PTPN1\) variants were associated with obesity in French people\(^22,23\). However, among Pima Indians, SNPs within \(PTPN1\) were unlikely to have a major role in the etiology of type 2 diabetes or obesity\(^24\). Accordingly, the results of the association of \(PTPN1\) polymorphisms with diabetes and obesity differ slightly in different populations, and no studies have yet reported on the contributions of \(PTPN1\) gene polymorphisms on obesity and diabetes in Japanese populations. Furthermore, although weight reduction therapy is essential for the management of obesity, little is known about the genetic contribution to weight reduction therapy in obese individuals, and no studies have shown whether \(PTPN1\) genotypes affect longitudinal changes in BW and glycolipid metabolism during weight reduction therapy in obese patients. The present study aimed to determine the association of \(PTPN1\) gene polymorphisms with weight reduction and the risk of diabetes in obese Japanese patients.

### MATERIALS AND METHODS

#### Study design

In the present prospective cohort study, 447 overweight or obese Japanese outpatients were consecutively enrolled in the outpatient clinic at the National Hospital Organization Kyoto Medical Center during the period from April 2005 to March 2011. Obese patients were defined as those with a BMI ≥25 kg/m\(^2\), based on the guidelines of the Japan Society for the Study of Obesity (JASSO)\(^6,25\). The exclusion criteria were as follows: a previous history of CVD; other vascular diseases; apparent renal disease; severe liver dysfunction; or secondary obesity due to endocrine disorders, such as Cushing syndrome, polycystic ovary syndrome, acromegaly and hypothyroidism. None of the patients had received anti-obesity drugs. The study protocol was approved by the ethics committee for human research at the Kyoto Medical Center (approval number: 05-27, 09-10), and all participants provided written informed consent. This study adhered to the STROBE checklist (Appendix S1).

#### Data collection and laboratory measurements

Height and BW were measured, and BMI was calculated as the weight in kilograms divided by height in meters squared; BMI was used as an index of obesity. The primary outcome in this study was BMI. Waist circumference (WC) was measured to the nearest 0.1 cm at the level of the umbilicus with participants in the standing position at the end of expiration while breathing gently\(^3-5\). The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were each measured twice with an automatic electronic sphygmomanometer (BP-103i II; Nippon Colin, Komaki, Japan). Blood was obtained from the antecubital vein in the morning after an overnight fast, and was used to determine fasting plasma glucose (FGP), glycosylated hemoglobin A1c (HbA1c; National Glycohemoglobin Standardization Program), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) levels according to standard procedures\(^3\). Immunoreactive insulin (IRI) was measured with an enzyme immunoassay (Tosoh, Tokyo, Japan)\(^3-5\). The insulin resistance index was assessed by the homeostasis model assessment (HOMA-R)\(^6\). Serum levels of leptin and adiponectin were determined as previously described. The adiponectin levels were measured with enzyme-linked immunosorbent assays (Otsuka Pharmaceutical, Tokyo, Japan). The leptin levels were determined using a radioimmunoassay (Linco Research, St. Charles, MO, USA)\(^3-5\).

#### DNA preparation and SNP genotyping

Genomic DNA was prepared using BioRobot EZ1 (QIAGEN, Valencia, CA, USA) from blood samples collected from each participant. High-throughput genotyping of the \(PTPN1\)-tagged SNPs (rs3787348 and rs6067484) was carried out using TaqMan SNP Genotyping Assays (Applied Biosystems, Foster City, CA, USA). We selected two \(PTPN1\)-tagged SNPs (rs3787348 and rs6067484) with reference to the study by NJ Spencer-Jones et al.\(^26\) The polymerase chain reaction primers and TaqMan probes were purchased from Applied Biosystems and optimized according to the manufacturer’s protocol\(^27\). Water blanks were installed on each plate and evaluated as a negative control to guarantee accuracy.
Weight reduction therapy
All obese patients were subjected to weight reduction therapy through lifestyle modifications, which included reducing energy intake and increasing physical activity for 3 months. All patients who underwent weight reduction therapy were instructed to maintain the same levels of energy intake and physical activity for the entire period, as recommended by the Japan Atherosclerosis Society’s Guidelines for the Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases. The diet therapy prescribed consisted of 25 kcal/kg of ideal BW per day. The participants consumed a diet in which carbohydrates comprised 60% of the total energy intake, fats comprised 20–25% and protein comprised 15–20%. They were also instructed to exercise for >30 min at a moderate intensity at least 3 days/week. In the present study, all patients were instructed to follow our weight reduction protocol, and checked the treatment period. To ensure adherence to the weight reduction therapy during this period, we interviewed and instructed all the patients on our weight reduction protocol, and checked the patients’ daily records in our outpatient clinic every month. We measured the metabolic parameters for each patient before and after the 3-month weight reduction therapy. Smoking habits and prescribed drugs were not altered.

Statistical analysis
To observe the difference in the mean change in BMI between the PTPN1-tagged SNPs (rs3787348), and based on information from prior reports describing the respective genotype proportions (approximately 30% of participants were G/G, 50% were G/T and 20% were T/T), all obese patients were G/G, 31.0 ± 0.6; G/T, 31.8 ± 0.3; T/T, 32.6 ± 0.4 kg/m²; P = 0.041 in the additive model). The T allele of rs3787348 tended to be associated with increased HbA1c levels, but this trend was not significant (G/G, 6.3 ± 0.1; G/T, 6.5 ± 0.1; T/T, 6.7 ± 0.1%; P = 0.064, q-value >0.999 in the additive model). However, the T allele of rs3787348 did not show any significant associations with BW, WC, SBP, DBP, FPG, IRI, HOMA-R, TC, TG, HDL-C, LDL-C, leptin or adiponectin (Table 2).

Table S1 presents the results of the association analysis of the tagged SNP of rs6067484 with metabolic parameters, adjusted for age and sex. No significant association was observed for rs6067484.

Effects of bodyweight reduction therapy
Table 1 presents the characteristics of the 447 obese patients who underwent weight reduction therapy at baseline and at 3 months. Of the 447 patients, 248 (55.5%) successfully reduced their BW by >3%. BW, BMI, WC, SBP, DBP, FPG, HbA1c, IRI, HOMA-R, TC, TG, HDL-C and leptin were significantly decreased 3 months after the weight reduction therapy (P < 0.05). HDL-C and adiponectin levels were significantly increased 3 months after the weight reduction therapy (P < 0.01; Table 1). The use of prescribed drugs was not altered.

Association analysis of PTPN1-tagged SNPs with changes in metabolic parameters after weight reduction therapy
Table 3 presents the results of the association analysis of the PTPN1-tagged SNPs (rs3787348) with the changes in metabolic parameters adjusted for age, sex and baseline value of
Table 1 | Baseline clinical characteristics of obese patients

|                        | Baseline | 3-month | P-value |
|------------------------|----------|---------|---------|
| n                      | 447      |         |         |
| Sex (male/female)      | 196/251  |         |         |
| Age (years)            | 500 ± 140|         |         |
| Bodyweight (kg)        | 845 ± 195| 808 ± 189| <0.001 |
| BMI (kg/m²)            | 3.21 ± 0.6| 3.07 ± 0.5| <0.001 |
| Waist circumference (cm)| 103.1 ± 14.0| 99.5 ± 13.2| <0.001 |
| Systolic blood pressure (mmHg) | 14.2 ± 19.3| 13.51 ± 16.7| <0.001 |
| Diastolic blood pressure (mmHg) | 8.52 ± 12.5| 8.18 ± 10.9| <0.001 |
| Fasting plasma glucose (mmol/L) | 6.6 ± 2.2| 6.2 ± 1.8| <0.001 |
| HbA1c (%)              | 6.5 ± 1.3| 6.2 ± 1.0| <0.001 |
| HbA1c (mmol/mol)       | 47.5 ± 14.2| 44.2 ± 10.9| <0.001 |
| IRI (pmol/L)           | 86 (53–155)| 79 (46–145)| 0.004 |
| HOMA-R                 | 3.9 (2.2–8.1)| 3.5 (1.8–7.2)| 0.001 |
| Total cholesterol (mmol/L) | 5.4 ± 1.0| 5.1 ± 0.9| <0.001 |
| Triglyceride (mmol/L)  | 1.7 (1.2–2.5)| 1.3 (0.9–1.9)| <0.001 |
| HDL cholesterol (mmol/L) | 1.4 ± 0.4| 1.5 ± 0.4| 0.003 |
| LDL cholesterol (mmol/L) | 3.3 ± 0.8| 3.0 ± 0.6| <0.001 |
| Leptin (ng/mL)         | 132 (68–231)| 109 (57–183)| <0.001 |
| Adiponectin (µg/mL)    | 6.1 (4.5–9.3)| 6.6 (4.8–9.5)| 0.004 |

Proportion (n, %)

With hypertension: 286, 64.0%  
With diabetes: 173, 38.7%  
With dyslipidemia: 334, 74.7%  
Taking calcium: 80, 17.9%  
Taking ACE/ARB: 103, 23.0%  
Taking antidiabetic medication: 106, 23.7%  
Taking statin: 99, 22.1%  
rs3787348 (n, %)  
G/G: 90, 20.1%  
G/T: 227, 50.8%  
T/T: 130, 29.1%  
Minor allele frequency (%): 45.5  
rs6067484, n (n, %)  
A/A: 368, 82.3%  
A/G: 77, 17.2%  
G/G: 2, 0.5%  
Minor allele frequency (%): 9.1

Data are expressed as the mean ± standard deviation, median (interquartile range), or the number and percentage of patients. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; HbA1c, glycosylated hemoglobin A1c; HDL, high-density lipoprotein; HOMA-R, homeostasis model assessment ratio; IRI, immunoreactive insulin; LDL, low-density lipoprotein.

dependent variables. After the 3-month weight reduction therapy, patients with the T allele in rs3787348 showed less significant decreased levels of BMI, BW and WC (ΔBMI: G/G, −1.9 ± 0.2; G/T, −1.5 ± 0.1; T/T, −1.2 ± 0.1 kg/m²; P = 0.001; ΔBW: G/G, −5.1 ± 0.5; G/T, −4.1 ± 0.2; T/T, −3.1 ± 0.3 kg; P = 0.001, q-value = 0.014; ΔWC: G/G, −5.2 ± 0.7; G/T, −4.1 ± 0.4; T/T, −2.9 ± 0.4 cm; P < 0.001, q-value = 0.013).

Additionally, patients with the T allele in rs3787348 showed nominal associations with decreased levels of TC and leptin (ΔTC: G/G, −0.4 ± 0.1; G/T, −0.3 ± 0.1; T/T, −0.2 ± 0.1 mmol/L; P = 0.034, q-value = 0.238; Δleptin: G/G, −3.9 ± 0.7; G/T, −3.4 ± 0.8; T/T, −1.1 ± 0.8 ng/mL; P = 0.011, q-value = 0.103 in the additive model). The T allele of rs3787348 was associated with a trend toward reduced lowering of FPG, HbA1c and LDL-C, although this trend was not statistically significant. Conversely, the T allele of rs3787348 did not show any significant associations with ΔSBP, ΔDBP, ΔIRI, ΔHOMA-R, ΔTG, ΔHDL-C and Δadiponectin (Table 3).

Table 4 represents the results of the association analysis of the PTPN1-tagged SNPs (rs6067484). The A allele in rs6067484 was only nominally associated with reduced lowering of levels of WC (ΔWC: A/A, −4.0 ± 0.4; A/G, −2.2 ± 0.7; G/G, −0.5 ± 1.5 cm; P = 0.030, q-value = 0.210 in the additive model; Table 4). However, the A allele of rs6067484 did not show any significant associations with other parameter changes.

**DISCUSSION**

In the present study, we found that the PTPN1 polymorphism rs3787348 was significantly related to the beneficial effects in weight reduction and obesity-related metabolic changes (WC, TC and leptin levels) through weight reduction therapy in obese Japanese patients. This is the first report of PTPN1 SNPs in Japanese individuals, and it is also the first report examining the association of rs3787348 in the PTPN1 gene with obesity and weight loss. The detection of gene polymorphisms involved in weight loss and obesity-related metabolic changes might help identify specific targets for nutritional interventions to achieve significant weight loss.

Initially, in obese patients, the T allele of rs3787348 in PTPN1 is significantly associated with a higher BMI; however, no significant association was observed in the SNP rs6067484 in PTPN1. The PTPN1 gene encodes PTP1B, which is an enzyme that negatively regulates the signaling pathways of insulin and leptin, two hormones that are involved in the central regulation of energy balance. Thus, evidence has accumulated reflecting a crucial role of PTP1B in the insulin and leptin pathways, which suggests that abnormal PTP1B activity could lead to insulin resistance, and thus to type 2 diabetes and obesity. In humans, the PTPN1 gene is located on 20q13, a region that is located to type 2 diabetes and obesity. The present results showed that the T allele of rs3787348 in PTPN1 was significantly associated with a higher BMI. Previous case-control studies of French individuals reported that other SNPs of the PTPN1 gene, which differed from the SNP rs378748 that we examined, were associated with obesity. Thus, there have been no reports on significant associations of rs3787348 in PTPN1 with obesity; therefore, the present study is the first report on a significant relationship between the PTPN1 SNP
### Table 2 | Association analysis of PTPN1 tag single-nucleotide polymorphism of rs3787348 with baseline metabolic parameters

| rs3787348 | G/G | G/T | T/T | P-value | q-value |
|-----------|-----|-----|-----|---------|---------|
| Sex (male/female) | 36/54 | 96/131 | 64/66 |         |         |
| Age (years) | 481 ± 1.4 | 500 ± 0.9 | 513 ± 1.2 | 0.041 | >0.999 |
| BMI (kg/m²) | 31.8 ± 0.3 | 32.6 ± 0.4 | 32.6 ± 0.4 | 0.163 | >0.999 |
| Bodyweight (kg) | 825 ± 1.7 | 840 ± 0.8 | 855 ± 1.0 | 0.165 | >0.999 |
| Waist circumference (cm) | 101.3 ± 1.5 | 102.6 ± 0.7 | 103.9 ± 0.9 | 0.971 | 0.971 |
| Systolic blood pressure (mmHg) | 142.2 ± 2.1 | 142.2 ± 1.0 | 142.3 ± 1.3 | 0.028 | 0.927 |
| Diastolic blood pressure (mmHg) | 850 ± 1.3 | 852 ± 0.7 | 854 ± 0.8 | 0.357 | 0.833 |
| Fasting plasma glucose (mmol/L) | 64 ± 0.3 | 66 ± 0.1 | 67 ± 0.2 | 0.064 | >0.999 |
| HbA1c (%) | 6.3 ± 0.1 | 65 ± 0.1 | 67 ± 0.1 | 0.157 | >0.999 |
| HbA1c (mmol/mol) | 45.3 ± 1.0 | 475 ± 1.0 | 49.7 ± 1.1 | 0.809 | 0.944 |
| ln HOMA-R | 1.6 ± 0.1 | 1.4 ± 0.1 | 1.5 ± 0.1 | 0.050 | 0.906 |
| Total cholesterol (mmol/L) | 54 ± 0.1 | 54 ± 0.1 | 54 ± 0.1 | 0.867 | 0.934 |
| Triglyceride (mmol/L) | 2.0 ± 0.1 | 2.1 ± 0.1 | 2.1 ± 0.1 | 0.022 | 0.880 |
| HDL cholesterol (mmol/L) | 1.4 ± 0.03 | 1.4 ± 0.02 | 1.5 ± 0.02 | 0.020 | 0.945 |
| LDL cholesterol (mmol/L) | 3.3 ± 0.1 | 3.3 ± 0.1 | 3.3 ± 0.1 | 0.045 | 0.980 |
| ln Leptin (ng/mL) | 2.50 ± 0.06 | 2.51 ± 0.08 | 2.55 ± 0.08 | 0.027 | 0.945 |
| ln Adiponectin (µg/mL) | 1.77 ± 0.06 | 1.87 ± 0.04 | 1.88 ± 0.05 | 0.027 | 0.966 |

Data are presented as the mean ± standard error of the mean. General linear model analysis was performed to test for associations between PTPN1 genotypes and each parameter after adjusting for age and gender. *q-value: Benjamini–Hochberg procedure for secondary outcomes. BMI, body mass index; HbA1c, glycosylated hemoglobin A1c; HDL, high-density lipoprotein; HOMA-R, homeostasis model assessment ratio; IRI, immunoreactive insulin; LDL, low-density lipoprotein; ln, log transformation.

### Table 3 | Association analysis of PTPN1 tag single-nucleotide polymorphism of rs3787348 with changes of metabolic parameters at 3-month

| rs3787348 | G/G | G/T | T/T | P-value | q-value |
|-----------|-----|-----|-----|---------|---------|
| ΔBMI (kg/m²) | −1.9 ± 0.2 | −1.5 ± 0.1 | −1.2 ± 0.1 | 0.001 | − |
| ΔBodyweight (kg) | −0.5 ± 0.5 | −0.4 ± 0.2 | −0.3 ± 0.3 | 0.001 | 0.014* |
| ΔWaist circumference (cm) | −0.5 ± 0.3 | −0.4 ± 0.2 | −0.3 ± 0.3 | 0.001 | 0.014* |
| ΔSystolic blood pressure (mmHg) | −0.2 ± 0.7 | −0.1 ± 0.6 | −0.1 ± 0.6 | 0.001 | 0.014* |
| ΔDiastolic blood pressure (mmHg) | −0.6 ± 1.1 | −0.5 ± 1.1 | −0.4 ± 1.1 | 0.001 | 0.014* |
| ΔFasting plasma glucose (mmol/L) | −0.7 ± 0.2 | −0.5 ± 0.1 | −0.3 ± 0.1 | 0.001 | 0.014* |
| ΔHbA1c (%) | −0.3 ± 0.1 | −0.2 ± 0.1 | −0.1 ± 0.1 | 0.001 | 0.014* |
| ΔHbA1c (mmol/L) | −3.3 ± 1.1 | −2.2 ± 1.1 | −1.1 ± 1.1 | 0.051 | 0.286 |
| ΔIRI (pmol/L) | −20 ± 21 | −16 ± 9 | −16 ± 13 | 0.025 | 0.924 |
| ΔHOMA-R | −1.8 ± 1.4 | −0.7 ± 0.5 | −1.7 ± 0.9 | 0.632 | 0.804 |
| ΔTotal cholesterol (mmol/L) | −0.2 ± 0.1 | −0.1 ± 0.1 | −0.1 ± 0.1 | 0.034 | 0.238 |
| ΔTriglyceride (mmol/L) | −0.6 ± 0.1 | −0.5 ± 0.1 | −0.4 ± 0.1 | 0.001 | 0.014* |
| ΔLDL cholesterol (mmol/L) | 0.02 ± 0.02 | 0.03 ± 0.01 | 0.02 ± 0.01 | 0.001 | 0.014* |
| ΔLeptin (ng/mL) | −0.3 ± 0.1 | −0.2 ± 0.1 | −0.1 ± 0.1 | 0.001 | 0.014* |
| ΔAdiponectin (µg/mL) | 0.1 ± 0.3 | 0.3 ± 0.2 | 0.1 ± 0.5 | 0.058 | 0.775 |

Data are presented as the mean ± standard error of the mean. General linear model analysis was performed to test for associations between PTPN1 genotypes and changes of each parameter after adjusting for age, sex and baseline value of dependent variables. Changes from baseline conditions to those at 3 months were abbreviated as Δ. *q-value: Benjamini–Hochberg procedure for secondary outcomes. *p-value < 0.05. BMI, body mass index; HbA1c, glycosylated hemoglobin A1c; HDL, high-density lipoprotein; HOMA-R, homeostasis model assessment ratio; IRI, immunoreactive insulin; LDL, low-density lipoprotein.
Table 4  Association analysis of PTPN1 tag single-nucleotide polymorphism of rs6067484 with changes of metabolic parameters at 3 months

| rs6067484 | A/A      | A/G      | G/G      | P-value | q-value |
|-----------|----------|----------|----------|---------|---------|
| AΔBMI (kg/m²) | −1.4 ± 0.1 | −1.3 ± 0.2 | −1.1 ± 0.4 | 0.398   | —       |
| AΔBodyweight (kg) | −3.8 ± 0.2 | −3.3 ± 0.5 | −2.8 ± 1.0 | 0.351   | 0.578   |
| AΔWaist circumference (cm) | −4.0 ± 0.4 | −2.2 ± 0.7 | −0.5 ± 1.5 | 0.030   | 0.210   |
| AΔSystolic blood pressure (mmHg) | −3.7 ± 3.8 | −6.9 ± 7.7 | −10.1 ± 15.8 | 0.706   | 0.824   |
| AΔDiastolic blood pressure (mmHg) | −3.8 ± 0.5 | −2.5 ± 1.1 | −1.3 ± 2.3 | 0.292   | 0.545   |
| AΔFasting plasma glucose (mmol/L) | −0.05 ± 0.1 | −0.2 ± 0.2 | 0.0 ± 0.4 | 0.184   | 0.515   |
| AΔHbA1c (%) | −0.03 ± 0.1 | −0.4 ± 0.1 | −0.4 ± 0.2 | 0.513   | 0.718   |
| AΔHbA1c (mmol/L) | −3.2 ± 0.9 | −4.3 ± 1.1 | −4.2 ± 2.1 | —       | —       |
| AΔIRI (pmol/L) | −18 ± 8 | −4 ± 15 | −10 ± 37 | 0.240   | 0.517   |
| AΔHOMA-R | −1.6 ± 0.5 | −0.5 ± 1.0 | −0.7 ± 3.9 | 0.150   | 0.467   |
| AΔTotal cholesterol (mmol/L) | −0.03 ± 0.1 | −0.3 ± 0.1 | −0.3 ± 0.2 | 0.869   | 0.936   |
| AΔTriglyceride (mmol/L) | −0.05 ± 0.1 | −0.4 ± 0.1 | −0.2 ± 0.2 | 0.198   | 0.504   |
| AΔHDL cholesterol (mmol/L) | 0.03 ± 0.01 | 0.05 ± 0.02 | 0.07 ± 0.05 | 0.452   | 0.666   |
| AΔLDL cholesterol (mmol/L) | −0.02 ± 0.1 | −0.2 ± 0.1 | −0.2 ± 0.1 | 0.950   | 0.936   |
| AΔLeptin (ng/mL) | −3.0 ± 0.5 | −3.3 ± 1.1 | −3.1 ± 1.8 | 0.989   | 0.989   |
| AΔAdiponectin (µg/mL) | 0.3 ± 0.2 | 0.1 ± 0.3 | 0.2 ± 1.0 | 0.281   | 0.562   |

Data are presented as the mean ± standard error of the mean. General linear model analysis was carried out to test for associations between PTPN1 genotypes and changes of each parameter after adjusting for age, sex and baseline value of dependent variables. Changes from baseline conditions to those at 3 months were abbreviated as A. *p*-value: Benjamini–Hochberg procedure for secondary outcomes. BMI, body mass index; HbA1c, glycosylated hemoglobin A1c; HDL, high-density lipoprotein; HOMA-R, homeostasis model assessment ratio; IRI, immunoreactive insulin; LDL, low-density lipoprotein.

rs3787348 and obesity. Additionally, the T allele of rs3787348 in PTPN1 showed a tendency to be associated with higher HbA1c levels in the present study, although this relationship was not significant. One previous study showed a higher frequency of the G allele of the rs3787348 SNP in PTPN1 in type 2 diabetes patients than in control individuals among white individuals. The other study reported that insulin sensitivity was lower in the G allele of the rs3787348 SNP in Hispanic Americans. A meta-analysis including 7,883 European individuals did not replicate these previous associations. We carefully carried out weight reduction therapy in accordance with the Japan Society for the Study of Obesity guidelines, and carefully assessed records of nutritional status, daily meals, daily steps and daily BW changes for each consultation in the outpatient clinic. To our knowledge, there have been several interventional studies on weight reduction therapy through metabolic surgery and low-energy diets, but there have been few observational longitudinal studies on weight reduction therapy through fundamental diet and exercise therapy based on guidelines. A longitudinal study reported that the melanocortin-4 receptor gene, which is a key protein regulating energy balance and adiposity, was associated with postpartum weight reduction and glycemic changes among women with prior gestational diabetes. Mutations in the beta-3 adrenergic receptor were related to the response to lifestyle interventions in obese individuals and patients with impaired glucose tolerance in the Japan Diabetes Prevention Program. The polymorphisms of several genes, such as the UCP1 gene and genes of the renin–angiotensin system, were reported to be associated with the effects of a short-term diet intervention. However, no studies have examined the relationship of the polymorphisms of PTPN1 with response to weight reduction therapy; therefore, the present study is the first to show a significant relationship between the SNPs of PTPN1 and the effects of weight reduction therapy. Because PTP1B is involved in insulin and leptin signaling, the T allele of rs3787348 in PTPN1 might
cause further insulin resistance and leptin resistance, thus accumu-
lating adipose tissue, which might make it difficult to lose bodyweight and serum leptin. Conversely, the G allele of rs3787348 in the PTPNI gene might not result in the accumulation of adipose tissue and thus is not resistant to weight reduction. In addition, the T allele of rs3787348 was associated with the smaller reduction of WC, which represents central obesity and metabolic syndrome. As PTP1B is involved in energy balance, and is an important signal for insulin and leptin, the present results are noteworthy for weight management and the prevention of CVD in obese patients.

A 3% reduction in weight is the minimum requirement to improve health hazards and obesity-related risk factors, such as hypertension, and glucose and lipid metabolism, in obese and overweight people in Japan36. The present study showed that 3–5% reductions of initial BW in all genotypes of the PTPNI SNP rs3787348 were observed. The G allele of rs3787348 in PTPNI had a tendency to show greater decreases in TC, LDL-C, FPG and HbA1c; conversely, the T allele of the SNP rs3787348 in PTPNI was resistant to decreases in cholesterol and glucose parameters. These differences of reductions in lipid and glucose profiles might be due to differences in weight reductions. In addition, because PTP1B is involved in insulin signaling, the larger decreases in lipid and glucose profiles in the G allele of rs3787348 in PTPNI might be due to directly enhanced insulin and leptin signaling by improving PTP1B action. Furthermore, the inactivation of PTPNI with antisense oligonucleotides regulates the expression of genes involved in lipogenesis, such as SREBP1, suggesting that PTP1B might play a role in lipid metabolism14. These detailed mechanisms for improving glycolipid metabolism through rs373847 mutations must be examined in the future. Several cross-sectional studies have shown that PTPNI SNPs are related to obesity and obesity-related complications, such as diabetes, dyslipidemia, hypertension, metabolic syndrome and coronary atherosclerosis33–39. Therefore, as PTPNI gene polymorphisms affected the degree of weight reduction and improvement of complications, such as glycolipid metabolism, in the present study, our results might contribute to future personalized medicine, such as more rigorous interventions with diet and exercise programs for obese patients with the T allele of rs3787348 in the PTPNI gene.

The present study had some limitations. The examination of PTPNI polymorphisms was limited to just two tagged SNPs. The two tagged SNPs that we examined (rs3787348 and rs6067484) do not cover the regions of exons 1, 9 and 10 of the 10 exons of PTPNI; accordingly, they do not cover the entire PTPNI gene region. In the future, SNPs that cover the entire PTPNI gene must be considered. The observation period during which weight reduction therapy was carried out was short. However, most obese individuals regain BW during long-term weight reduction treatment due to environmental and psychosocial factors40. Therefore, it might be appropriate to examine the degree of weight loss during a 3-month period, as in the present study. Although the records of daily meals, steps and changes in BW were checked in the outpatient clinic, detailed energy balance and metabolism were not measured. Furthermore, a long-term prospective cohort study with a larger sample size must be carried out in individuals of various ethnicities to clarify the involvement of PTPNI polymorphisms and the clinical significance of the rs3787348 SNP in PTPNI for weight reduction therapy in obese patients. In the future, the potential functional implication of the SNP rs3787348 of the PTP1B gene must be elucidated.

In conclusion, the present study has provided the first evidence that a PTPNI polymorphism (rs3787348) was significantly associated with weight reduction and the improvement of glycolipid metabolism through weight reduction therapy in obese patients. These findings imply that the PTPNI polymorphism can be used as a clinical predictor of the efficacy of weight reduction and cardiovascular risks in obese patients. These results might help develop precision medicine for obese patients according to their genetic predisposition, which would lead to an improvement in the quality of medical care for the prevention of lifestyle diseases and CVD in a super-aging society.

ACKNOWLEDGMENTS
We thank Minako Inamura M.D., Ph.D. (University of the Ryukus) for valuable discussions. We thank Enago (www.enago.jp) for the English language review. This work was supported in part by Grant-in-Aid for Scientific Research (C) to HY (JSPS KAKENHI Grant Number JP19K07905), Research Activity start-up to YK (19K21525), Scientific Research (B) (JP18H02737) and Exploratory Research to NS-A (JP18K19769), from the Japan Society for the Promotion of Science. This study was also supported in part by a grant from TANITA Healthy Weight Community Trust to NS-A; a grant from Suzuken Memorial Foundation to NS-A; and a grant from the National Hospital Organization for clinical research to NS-A (H26–GENE–03). The funders had no role in data collection, analysis, decision to publish or preparation of the manuscript.

DISCLOSURE
The authors declare no conflict of interest.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Association analysis of PTPNI tag single-nucleotide polymorphism of rs6067484 with metabolic parameters.
Appendix S1 | STROBE Statement – checklist of items that should be included in reports of observational studies.