

Short communication

Genome-wide association study for the interaction between BMR and BMI in obese Korean women including overweight

Myoungsook Lee^{1,2§}, Dae Young Kwon³, Myung-Sunny Kim³, Chong Ran Choi¹, Mi-Young Park^{1,4} and Ae-jung Kim⁵

¹Research Institute of Obesity Science, Sungshin Women's University, 55, Dobong-ro 76ga-gil, Gangbuk-gu, Seoul 01133, Korea

²Department of Food and Nutrition, Sungshin Women's University, 55, Dobong-ro 76ga-gil, Gangbuk-gu, Seoul 01133, Korea

³Nutrition and Metabolism Research Group, Korea Food Research Institute, Gyenggi-do, 13539, Korea

⁴Institute of Health and Environment, Graduate School of Public Health, Seoul National University, Seoul 08826, Korea

⁵Graduate School of Alternative Medicine, Kyonggi University, Seoul 03746, Korea

BACKGROUND/OBJECTIVES: This is the first study to identify common genetic factors associated with the basal metabolic rate (BMR) and body mass index (BMI) in obese Korean women including overweight. This will be a basic study for future research of obese gene-BMR interaction.

SUBJECTS/METHODS: The experimental design was 2 by 2 with variables of BMR and BMI. A genome-wide association study (GWAS) of single nucleotide polymorphisms (SNPs) was conducted in the overweight and obesity (BMI > 23 kg/m²) compared to the normality, and in women with low BMR (< 1426.3 kcal/day) compared to high BMR. A total of 140 SNPs reached formal genome-wide statistical significance in this study ($P < 1 \times 10^{-4}$). Surveys to estimate energy intake using 24-h recall method for three days and questionnaires for family history, a medical examination, and physical activities were conducted.

RESULTS: We found that two *NRG3* gene SNPs in the 10q23.1 chromosomal region were highly associated with BMR (rs10786764; $P = 8.0 \times 10^{-7}$, rs1040675; 2.3×10^{-6}) and BMI (rs10786764; $P = 2.5 \times 10^{-5}$, rs10786764; 6.57×10^{-5}). The other genes related to BMI (*HSD52*, *TMA16*, *MARCH1*, *NRG1*, *NRXN3*, and *STK4*) yielded $P < 10 \times 10^{-4}$. Five new loci associated with BMR and BMI, including *NRG3*, *OR8U8*, *BCL2L2-PABPN1*, *PABPN1*, and *SLC22A17* were identified in obese Korean women ($P < 1 \times 10^{-4}$). In the questionnaire investigation, significant differences were found in the number of starvation periods per week, family history of stomach cancer, coffee intake, and trial of weight control in each group.

CONCLUSION: We discovered several common BMR- and BMI-related genes using GWAS. Although most of these newly established loci were not previously associated with obesity, they may provide new insights into body weight regulation. Our findings of five common genes associated with BMR and BMI in Koreans will serve as a reference for replication and validation of future studies on the metabolic rate.

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INTRODUCTION

The prevalence of overweight and obesity, a risk factor associated with the morbidity and mortality of several diseases, is increasing with epidemic proportions worldwide. Obesity, diagnosed on the basis of body mass index (BMI) or waist circumference (WC), derives from an imbalance between energy intake and energy expenditure; however, its underlying mechanisms are generally unclear [1-2]. Environmental factors play a crucial role in development of obesity, however, multiple twin and family studies have shown that genetic factors also have an important contribution to the etiology of obesity. Many genetic loci associated with obesity have been demonstrated; however, these loci can explain only a narrow portion of the genetic variances for obesity [2]. Genetic variants associated

with "common polygenic obesity" have been widely studied through candidate gene approaches and genome-wide linkage studies. However, the candidate gene approach has failed for several reasons, including too small study samples, lack of adjustment for multiple testing, and insufficient replication. On the other hand, with high-throughput genotyping and the Human Genome Project, genome-wide linkage studies have established several methods for discovery of obesity susceptibility genes. In genome-wide linkage studies, the whole genome of individuals is scanned to investigate the linkage of chromosomal regions with obesity and associated traits [3].

Genome-wide association study (GWAS) recently demonstrated several single nucleotide polymorphisms (SNPs) associated with both BMI and obesity susceptibility loci, located in or near genes such as fat mass and obesity-associated protein (*FTO*), melano-

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[§] Corresponding Author: Myoungsook Lee, Tel. 82-2-920-7211, Fax. 82-2-920-2078, Email. mlee@sungshin.ac.kr

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cortin receptor 4 (*MC4R*), transmembrane protein 18 (*TMEM18*), glucosamine-6-phosphate deaminase 2 (*GNPDA2*), brain-derived neurotrophic factor (*BDNF*), neuronal growth regulator 1 (*NEGR1*), SH2B adapter protein 1 (*SH2B1*), mitochondrial carrier homolog 2 (*MTCH2*), and potassium channel tetramerization domain containing 15 (*KCTD15*) in Europeans as well as in different ethnic populations [2,4-11]. Many of these genes are involved in many biological pathways and expressed in numerous tissues, including the central nervous system [2]. Some of the new obesity genes (*FTO*, *MC4R*, *TMEM18*, *GNPDA2*, *SH2B1*, *KCTD15*, and *BDNF*) are expressed in the hypothalamus and are involved in a crucial center for energy balance and regulation of appetite [10]. In addition, meta-analyses of GWAS for obesity-related traits, including BMI and waist-hip ratio (WHR), have identified many regions of the genome associated with obesity [1]. Few studies to confirm the associations of BMI-associated loci with central obesity have been conducted. Because the crucial role of central obesity, as assessed by WC, is more strongly associated with the risk of hypertension, type 2 diabetes, cardiovascular diseases (CVD), and cancer than with obesity, it is necessary to determine whether BMI-associated loci can significantly predict central obesity [4]. In addition, as the accumulation of abdominal fat is a risk factor for CVD and type 2 diabetes, understanding mechanisms involved in regulation of fat accumulation and visceral fat mass is important in understanding obesity [3]. Obesity associated with fat mass is usually measured using BMI or WC. WC and WHR are also related to intra-abdominal fat content and central obesity, rather than BMI [1].

Imbalance between energy expenditure and energy intake causes excessive fat accumulation, leading to an increase in the number and/or size of fat cells [12]. Basal metabolic rate (BMR) is the minimum energy required to retain the physiological functions of the body while awake. BMR accounts for approximately 45% to 70% of total energy expenditure in most healthy adults and is directly affected by age, sex, body surface area, body composition, genetic composition, pregnancy, and hormonal status [13-14]. Thus, estimating BMR is important for establishing strategies for obesity prevention programs [2]. For several years, numerous predictive equations for BMR have been developed in different populations. Many studies have reported on the influence of ethnicity on BMR, however, their results have been inconsistent [13-14]. Several GWAS on BMI, WC, WHR, extreme obesity phenotypes, and BMI-adjusted WHR in ethnic groups have been published; however, GWAS of BMR and BMI has not yet been confirmed in Korean women. To investigate the differences of the eating behavior and obesity-related life pattern between women with obesity and healthy control subjects, we conducted a survey using the 24-h recall method and a questionnaire.

SUBJECTS AND METHODS

Study population

The study population consisted of 77 Korean female participants aged 18-34 years who were recruited between May and July 2012. This study was approved by the ethics committee of Sungshin Women's University (SSWU IRB 2012-003). The study included completion of anthropometrics, questionnaires (family

history, a medical examination, and physical activities), and dietary intakes. Written informed consent was obtained from all participants. Subjects with BMI > 25 kg/m² and WC > 85 cm² were included. Subjects with vascular disease (e.g., myocardial infarction or stroke), disturbances of lipid metabolism, acute or chronic renal failure, and impaired hepatic function were excluded. Those taking diabetes medication or diet pills were also excluded. A total of 77 participants who fulfilled all requirements were divided into four groups including high vs. low BMR according to median value of BMR, 1426.3 kcal/day, and low BMI (< 23 kg/m²) vs. high BMI (> 23 kg/m²).

Measurement of anthropometric parameters and BMR

Anthropometry was performed for weight, height, BMI, BMR, WC, hip, lean body mass, fat mass, percent of fat mass, and WHR. WC was measured midway between the lowest rib and the superior border of the iliac crest at the end of normal expiration using an inelastic measuring tape to the nearest 0.1 cm. BMR measurement was performed using a MedGem[®] metabolic analyzer (Microlife USA, Dunedin, FL), a handheld indirect calorimeter used for its accuracy and portability in clinical settings, which is becoming popular in research studies as a screening tool and a criterion measure of RMR. This device is used for calculation of RMR using fluorescent quenching of ruthenium in the presence of oxygen and the modified Weir equation with an assumed RQ of 0.85 for estimation of carbon dioxide production [15].

Questionnaires

Six divisions of general questionnaires were conducted; general question, family history, nutritive conditions with eating habits, weight-control history, exercise and diet intakes with eating pattern. Questions about age, smoking status, and drinking status were included as general questions, and questions on hypertension, diabetes, myocardial infarction, angina, stroke, and cancer (stomach, lung, breast, etc.) were inspected for the family history. Assessments of habitual diet intake, including the number of starvation periods per week, intake of fast-food, carbonated drink, coffee, snack, and dietary (food, health, nutritional) supplement, and number of times eating-out were performed. Environmental data, including weight control methods, degree of physical activity such as hard, normal, and light exercise were acquired through the questionnaires. Dietary intakes with three days recall methods were collected and analyzed using Can Pro 4.0 software.

GWA Genotyping

Samples were analyzed on Affymetrix Genome-Wide Human SNP array 6.0 in the DNALink (Songpa-gu, Seoul, Korea). Affymetrix Genome-Wide Human SNP array 6.0 comprises 906,600 genome-wide SNPs and 946,000 copy number variations. Approximately 500ng of genomic DNA was digested with two restriction enzymes, NSP I and Sty I, and processed according to the Affymetrix protocol. The digested segments were ligated to enzyme specific adaptors which incorporate a universal PCR priming sequence. PCR amplification using universal primers was performed in a reaction optimized for amplification of fragments between 200-1,100 base pairs. A fragmentation step

then reduced the PCR product to segments of approximately 25-50 bp, which were then end-labeled using biotinylated nucleotides. The labeled product was then hybridized to a chip, washed, and detected. Images were analyzed using GeneChip Operating System software (Affymetrix, Santa Clara, CA, USA). For the data obtained from the chip, internal quality control measures were used: the QC call rate (Dynamic Model algorithm) always exceeded 86% and heterozygosity on the X chromosome correctly identified the gender of the individual. Genotype calling was performed using the Birdseed v2 algorithm.

Statistical analysis

For the analysis of GWAS data, the subjects were divided into two groups: high BMR and low BMI (control group) vs. low BMR and high BMI (case group). Continuous variables were expressed as mean \pm SD, and differences between groups were assessed using Student's t-test. Categorical variables were represented as percentages and tested using the χ^2 test. Hardy-Weinberg equilibrium (HWE) was assessed using the χ^2 test. A P value > 0.05 was considered significant. In addition, all datasets were filtered to exclude samples or SNPs with $> 5\%$ missing values, variants with $< 5\%$ minor allele frequency, and samples deviating from the HWE, using PLINK, whole genome data analysis tool set. Quantitative trait association analyses for BMR and BMI in the 77 overweight women (BMR < 1426.3 kcal/day and BMI > 23 kg/m²) and normal-weight control subjects (BMR > 1426.3 kcal/day and BMI < 23 kg/m²) were performed. BMI and BMR were analyzed as continuous traits, separately in obese and normal-weight subjects, with linear regression in PLINK, using dominant, codominant, and recessive models. Genotype and allele frequencies were compared between groups using the chi-square test, the

Cochran Armitage trend test, or the Jonckheere-Terpstra test as appropriate. Data analysis was performed using SAS software version 9.1.3 (SAS Inc., Cary, NC, USA) and PLINK. [16].

RESULTS

Clinical characteristics of the study population

A total of 77 subjects were enrolled in the current study. Table 1 shows the clinical characteristics of the study population. The subjects were divided into several groups: normal vs. overweight according to BMI and low vs. high BMR. The mean BMR value was 1452.9 ± 141.4 kcal/day and the mean BMI was 23.6 ± 4.5 kg/m² in all subjects. In the BMR groups, subjects with a high BMI had significantly higher BMR than those with a low BMI ($P < 0.001$). Significant differences in BMI, BMR, waist measurement, hip measurement, lean body mass, and body fat mass were observed in each group according to BMR or BMI (Table 1). Blood TG and TC did not differ among the four groups.

Genome-wide association study

We performed systematic quality control steps on the raw genotype data and obtained 904,085 SNPs; SNPs with a minor allele frequency of $< 1\%$, a call rate of $< 95\%$, and a significant deviation from Hardy-Weinberg equilibrium in controls ($P < 1 \times 10^{-7}$) were excluded. SNPs likely to be false-positive associations due to wrong clustering were also excluded. After quality control, 710,315 and 710,679 SNPs were included in BMR and BMI study. The Manhattan plot of $-\log_{10}(P\text{-value})$ from the GWAS and imputation analysis against the chromosome position showed that no genetic loci reached genome-wide significance with the threshold P -value of 1×10^{-7} (Fig. 1). For identification of susceptible loci associated with BMR, a two-step discovery

Table 1. Demographic characteristics of the study subjects according to BMR and BMI

Variables	Low BMR (N = 39)		High BMR (N = 38)		P-values ²⁾
	Low BMI (N = 34)	High BMI (N = 5)	Low BMI (N = 6)	High BMI (N = 32)	
Anthropometrics					
Age (year)	22.5 \pm 2.0 ^a	26.8 \pm 5.2 ^b	20.8 \pm 0.7 ^a	21.4 \pm 1.5 ^{a1)}	< 0.001
BMI (kg/m ²)	20.1 \pm 1.9 ^a	24.4 \pm 1.5 ^b	21.1 \pm 1.1 ^a	27.6 \pm 3.6 ^c	< 0.001
BMR (kcal/day)	1,345.8 \pm 66.1 ^a	1,348.6 \pm 55.6 ^a	1,532.4 \pm 101.8 ^b	1,568.0 \pm 114.4 ^b	< 0.001
Waist (cm)	70.3 \pm 6.5 ^a	77.2 \pm 6.8 ^b	78.6 \pm 5.9 ^b	86.0 \pm 7.7 ^c	< 0.001
WHR	0.79 \pm 0.03 ^a	0.85 \pm 0.03 ^b	0.78 \pm 0.02 ^a	0.88 \pm 0.05 ^b	< 0.001
SBP (mmHg)	104.0 \pm 6.8	108.0 \pm 4.4	108.3 \pm 2.5	107.5 \pm 10.6	NS
DBP (mmHg)	67.7 \pm 3.9	72.0 \pm 4.4	69.1 \pm 2.0	68.7 \pm 7.4	NS
LBM (kg)	35.5 \pm 2.5 ^a	37.9 \pm 2.6 ^a	41.4 \pm 4.0 ^b	43.1 \pm 4.7 ^b	< 0.001
Body fat mass (kg)	14.2 \pm 3.6 ^a	20.0 \pm 3.1 ^b	16.2 \pm 2.9 ^{ab}	27.4 \pm 7.4 ^c	< 0.001
LBM/fat ratio	2.69 \pm 0.89 ^b	1.92 \pm 0.25 ^a	2.61 \pm 0.41 ^b	1.64 \pm 0.30 ^a	< 0.001
Blood lipids					
TG (mg/dl)	92.7 \pm 43.7	115.6 \pm 40.0	65.5 \pm 28.3	118.0 \pm 64.2	NS
TC (mg/dl)	235.1 \pm 79.7 ^{ab}	253.2 \pm 40.4 ^b	184.8 \pm 53.2 ^a	222.0 \pm 50.5 ^{ab}	NS
Diet intakes per day					
Energy intakes (Kcal)	1,631 \pm 449.8	1,614.8 \pm 369.36	1,499.8 \pm 457.8	1,666.6 \pm 484.2	NS
Vit E (mg)	9.9 \pm 2.9 ^a	14.85 \pm 9.3 ^b	9.9 \pm 3.8 ^a	12.5 \pm 5.2 ^{ab}	0.044

¹⁾ Mean \pm SD

²⁾ P-values; statistical differences among 4 groups, NS; non-significant differences

BMI: body mass index; BMR: basal metabolic rate; WHR: waist-hip ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; LBM: lean body mass; TG: triglyceride; TC, total cholesterol.

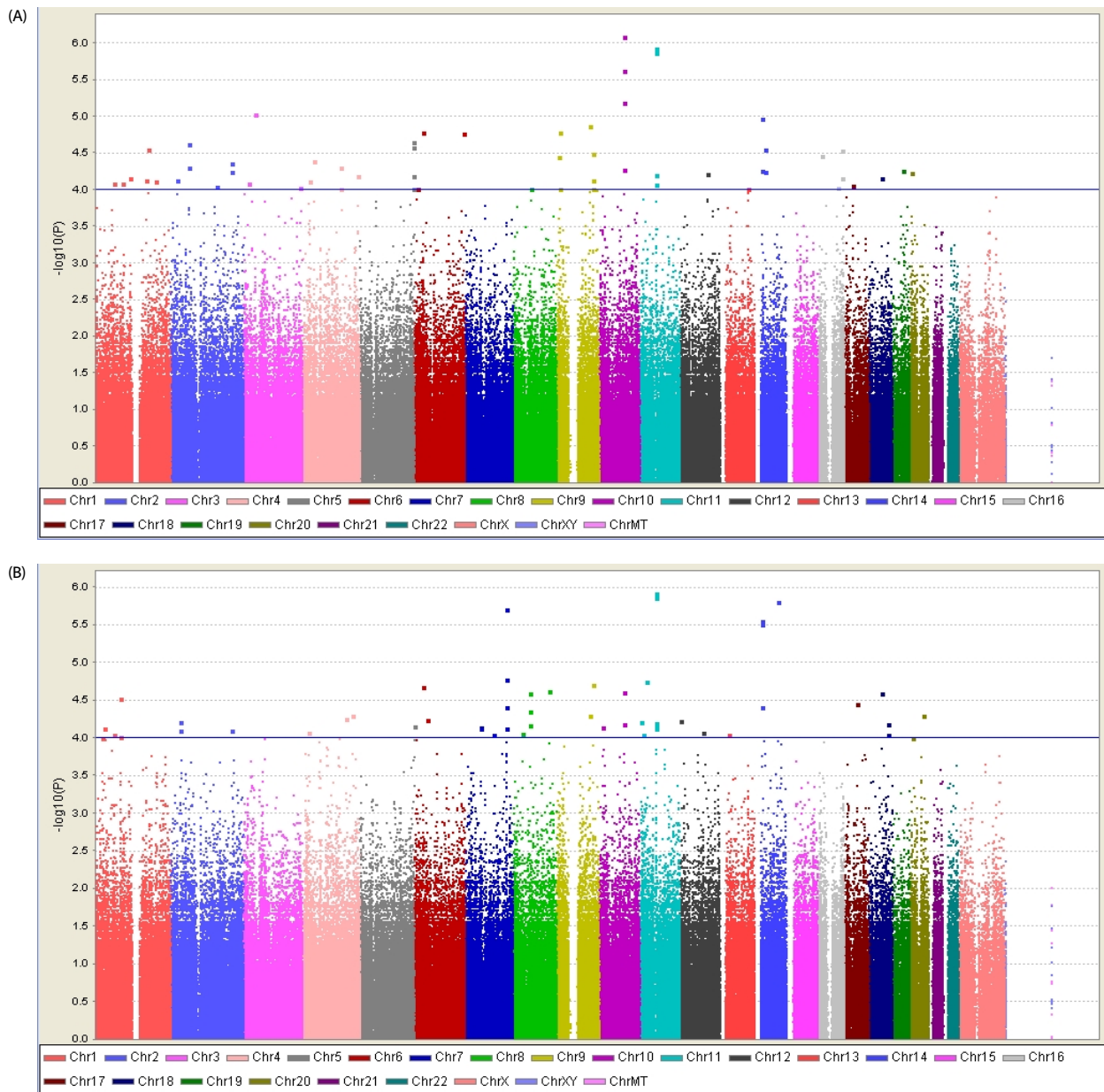


Fig. 1. The Manhattan plot for the genome-wide association study (GWAS) of obesity in the Korean female subjects. This plot is based on $-\log_{10}(P\text{-value})$ from GWAS and imputation analysis against chromosome position; each color represents a different chromosome. Blue horizontal line indicates the suggestive association threshold, $P=1 \times 10^{-4}$. (A) BMR and (B) BMI in these study subjects.

design was applied in the Korean female subjects. In an initial discovery step based on the sample of 77 female subjects, we selected all loci with a P value of $< 10^{-4}$ using continuous variables; 239 loci associated with BMR satisfied this criterion. In a second analysis, we attempted to replicate the strongest SNP association in the groups divided according to BMR and BMI. Using continuous variables, 118 SNPs in the whole chromosome including the *NRG3* and *PTPRD* regions reached our current threshold for genome-wide significance (data not shown). The subjects were divided into two groups: high-BMR and low-BMI (control group) vs. low-BMR and high-BMI (case group). In the second analysis, 49 additional loci including

rs1018484 in *NRG3* and a locus (rs11228758) at chromosome 11 in the intron of olfactory receptor, family 8, subfamily U, member 8 (*OR8U8*; GenBank NW_003871073) reached genome-wide significance (Tables 2 and 3). A total of 140 SNPs reached formal genome-wide statistical significance in this study ($P < 1 \times 10^{-4}$). First, *NRG3* gene SNP (rs10786764) in the 10q23.1 chromosomal region was highly associated with both BMR ($P = 8.0 \times 10^{-7}$) and BMI ($P = 8.0 \times 10^{-7}$), and *NRG3* gene SNP (rs1040675), also a gene commonly associated with BMR and BMI even though it was not as strong as rs10786764 in the linkage disequilibrium (LD) plot (Fig. 2). The *FGGY* gene SNP rs6676078 also reached genome-wide significance ($P = 8.3 \times$

Table 2. Summary of BMR-associated genes SNPs showing a P -value of $< 1 \times 10^{-4}$ in Korean female subjects

Phenotype	Chr	SNP	SNP type	Gene Symbol	Gene name	Major	Minor	MAF ¹⁾	Position	P -value ²⁾
BMR ¹⁾	1	rs6587854	Intron	FGGY	FGGY carbohydrate kinase domain containing	C	T	T = 0.380	59895534	$8.32 \times 10^{-5\#}$
		rs6676078	Intron			A	G	G = 0.379	59894984	$8.32 \times 10^{-5\#}$
	9	rs1484073	Flanking	PTPRD	protein tyrosine phosphatase, receptor type, D	C	A	A = 0.435	180135579	$9.56 \times 10^{-5*}$
		rs10759099	Intron			C	T	T = 0.453	9908492	$9.55 \times 10^{-5\#}$
	10	rs12348066	Flanking	NRG3	neuregulin 3	C	T	T = 0.457	9910028	$1.65 \times 10^{-5+}$
		rs1018484	Intron			C	T	T = 0.444	83665670	$6.51 \times 10^{-6*}$
		rs1040675	Intron			T	C	C = 0.444	83665764	$2.34 \times 10^{-6*}$
		rs10786764	Intron			G	C	C = 0.460	83677486	$8.01 \times 10^{-7*}$
		rs10883921	Intron			C	A	A = 0.427	83685802	$5.24 \times 10^{-5*}$
		rs11191757	Intron			T	G	G = 0.444	83667910	$6.51 \times 10^{-6*}$
		rs3918483	Flanking			A	C	C = 0.470	83668440	$6.51 \times 10^{-6*}$
		rs6584402	Intron			A	G	G = 0.470	83663215	$6.51 \times 10^{-6*}$
		rs7917690	Flanking			A	G	G = 0.417	83660737	$6.51 \times 10^{-6*}$
		rs11228758	Flanking			T	C	C = 0.303	56508476	$6.32 \times 10^{-5\#}$
	11	rs17151047	Flanking	OR8U8	olfactory receptor, family 8, subfamily U, member 8	C	T	T = 0.343	56503873	$8.47 \times 10^{-5\#}$
		rs2187511	Flanking			C	G	G = 0.283	56306853	$1.16 \times 10^{-6\#}$
		rs658845	Flanking			C	T	T = 0.284	56294275	$1.34 \times 10^{-6\#}$
	14	rs12882406	Flanking	BCL2L2-PABPN1	BCL2L2-PABPN1 readthrough	G	C	C = 0.457	23795976	$5.53 \times 10^{-5\#}$
		rs2268330	Flanking	PABPN1 SLC22A17	poly(A) binding protein, nuclear 1 solute carrier family 22, member 17	C	G	G = 0.299	23795976	$1.07 \times 10^{-5\#}$
	14	rs10872876	Intron	NPAS3	neuronal PAS domain protein 3	G	C	C = 0.292	33915724	$2.81 \times 10^{-5\#}$
		rs4981191	Intron			G	A	A = 0.294	33916616	$5.63 \times 10^{-5\#}$
	16	rs7194394	Intron	PKD1L2	polycystic kidney disease 1-like 2	T	C	C = 0.299	81238818	$6.99 \times 10^{-5*}$
		rs7194443	Intron			T	C	C = 0.299	81238889	$2.93 \times 10^{-5*}$
	18	rs16978179	Intron	SETBP1	SET binding protein 1	T	C	C = 0.094	42386553	$6.99 \times 10^{-5*}$
		rs2277710	Intron			T	C	C = 0.149	42372487	$6.99 \times 10^{-5*}$

¹⁾ BMR: basal metabolic rate; MAF: minor allele frequency.

²⁾ P -values; Statistical differences among 4 groups. * Dominant, # Recessive, # Allele, § Co-dominant

Table 3. Summary of BMI-associated genes SNPs showing a P -value of $< 1 \times 10^{-4}$ in Korean female subjects.

Phenotype	Chr	SNP	SNP type	Gene Symbol	Gene name	Major	Minor	MAF ¹⁾	Position	P -value ²⁾
BMI ¹⁾	1	rs3902349	Intron	HSD52	uncharacterized LOC729467	T	C	C = 0.390	59601998	$8.93 \times 10^{-5\#}$
		rs4912386	Intron	T	C	C = 0.310	59599712	$8.93 \times 10^{-5\#}$		
	4	rs12500221	Flanking	TMA16,MARCH1	translation machinery associated 16 homolog	A	G	G = 0.348	164436103	$5.07 \times 10^{-5+}$
		rs3816244	Intron			A	G	G = 0.392	164427985	$5.07 \times 10^{-5+}$
	7	rs10234581	Intron	DGKI	diacylglycerol kinase, iota	T	C	C = 0.465	137404781	$1.93 \times 10^{-6+}$
		rs12056089	Flanking			T	C	C = 0.377	137399820	$3.94 \times 10^{-5+}$
		rs1424372	Intron			C	T	T = 0.494	137414396	$7.44 \times 10^{-5+}$
		rs3800637	Intron			T	C	C = 0.469	137403432	$1.65 \times 10^{-5+}$
		rs3800649	Intron			G	A	A = 0.229	137424509	$7.37 \times 10^{-5\#}$
		rs6957797	Intron			C	T	T = 0.488	137425301	$7.4 \times 10^{-5+}$
		rs10087434	Intron			T	C	C = 0.387	31983067	$8.84 \times 10^{-5+}$
		rs10808322	Intron			C	G	G = 0.325	31970656	$8.84 \times 10^{-5+}$
	8	rs12056821	Intron	NRG1	neuregulin 1	T	G	G = 0.268	31966653	$8.84 \times 10^{-5+}$
		rs1481757	Intron			C	T	T = 0.310	31967958	$8.84 \times 10^{-5+}$
		rs6468082	Intron			C	G	G = 0.354	31962508	$8.84 \times 10^{-5+}$
	10	rs1040675	Intron	NRG3	neuregulin 3	T	C	C = 0.443	83665764	$6.57 \times 10^{-5*}$
		rs10786764	Intron			G	C	C = 0.459	83677486	$2.50 \times 10^{-5*}$
	11	rs11228758	Flanking	OR8U8	olfactory receptor, family 8, subfamily U, member 8	T	C	C = 0.303	56508476	$6.25 \times 10^{-5\#}$
		rs17151047	Flanking			C	T	T = 0.343	56503873	$7.53 \times 10^{-5\#}$
		rs2187511	Flanking			C	G	G = 0.282	56306853	$1.18 \times 10^{-6\#}$
		rs658845	Flanking			C	T	T = 0.283	56294275	$1.38 \times 10^{-6\#}$
		rs12882406	Flanking			BCL2L2-PABPN1,	BCL2L2-PABPN1 readthrough	G	C	C = 0.457
	14	rs2268330	Flanking	PABPN1,	poly(A) binding protein, nuclear 1	C	G	G = 0.298	23795976	$3.83 \times 10^{-5\#}$
		rs4982753	Flanking	SLC22A17	solute carrier family 22, member 17	C	T	T = 0.284	23814569	$3.09 \times 10^{-6+}$

Table 3. continued

Phenotype	Chr	SNP	SNP type	Gene Symbol	Gene name	Major	Minor	MAF ¹⁾	Position	P-value ²⁾
	14	rs17835706	Intron	NRXN3	neurexin 3	C	G	G = 0.200	79209409	$1.54 \times 10^{-6\#}$
		rs746459	Intron			G	A	A = 0.242	79210894	$1.54 \times 10^{-6\#}$
	20	rs16989563	Intron	STK4	serine/threonine kinase 4	A	G	G = 0.030	43605961	$5.10 \times 10^{-5*}$
		rs2071834	Intron			C	T	T = 0.029	43629193	$5.10 \times 10^{-5*}$

¹⁾ BMI: body mass index; MAF: minor allele frequency

²⁾ P-values; Statistical differences among 4 groups. * Dominant, # Recessive, # Allele, § Co-dominant

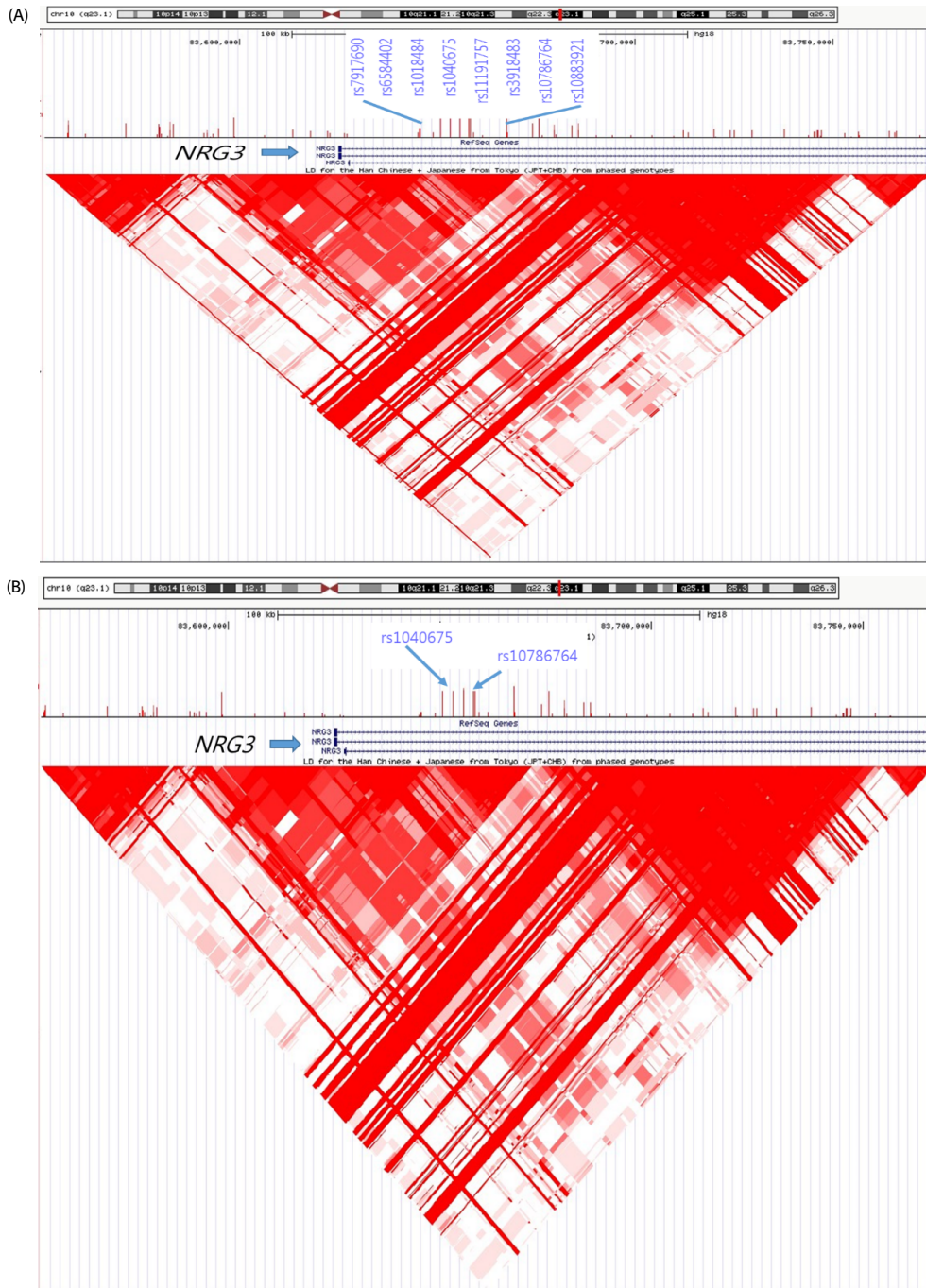


Fig. 2. Linkage Disequilibrium Plot figure of NRG3 gene SNPs (rs10786764 and rs1040675), black arrow on chromosome 10, in obese Korean women including overweight. The darker red in each diamond shape, stronger LD in association with BMR (A) and BMI (B).

10^{-5}). The *TNR*, *B3GNT2*, *FZD7*, *OR2Y1*, *MGAT1*, *NPAS3*, *PKD1L2*, and *SETBP1* genes showed weaker associations ($P < 1 \times 10^{-5}$) with BMR. Seven other genes associated with BMI (*HSD52*, *TMA16*, *MARCH1*, *DGKI*, *NRG1*, *NRXN3*, and *STK4*) yielded $P < 10 \times 10^{-4}$. The five common genes associated with both BMR and BMI were *NRG3*, *OR8U8*, *BCL2L2-PABPN1*, *PABPN1*, and *SLC22A17* ($P < 1 \times 10^{-4}$).

Dietary intake and physical activity assessments using a questionnaire

We conducted a questionnaire investigation, including items on dietary intake and physical activity in all subjects. We found that total energy intakes (Kcal/day) including carbohydrate, protein, lipid, vitamin, and minerals did not differ among the 4 groups except vit E intakes (Table 1). Higher Vit E intakes were observed in high BMI than in low BMI, with no significant difference between low BMR and high BMR. However, significant differences in habitual eating behavior, trial of weight control, number of starvation periods per week, and family history were observed between the low BMR and high BMR groups. Sixteen women (41.0%) with low BMR skipped a meal four or five times per week; however, nine subjects (23.6%) with high BMR often went hungry ($P = 0.014$). In the low BMR group, 33.3% of the women had been working on their weight, while only 3.3% in the high BMR group were making a desperate effort to watch their weight. ($P = 0.005$). From questions about the family history of gastric cancer, it was found that women in the high BMR have higher family history rates than subjects in the low BMR group ($P = 0.013$).

DISCUSSION

Twenty two genes/chromosome regions that reached genome-wide association significance ($P < 1 \times 10^{-4}$, 44 SNPs) in this GWAS were investigated. Five common genes (*NRG3*, *OR8U8*, *BCL2L2-PABPN1*, *PABPN1*, and *SLC22A17*) yielded $P < 1 \times 10^{-5}$ in the BMR and BMI groups. From the questionnaire investigation, differences in items including family history and food intake were observed between the low BMR and high BMR groups. These findings provide new insights into the genetic etiology of obesity in relation to BMR and BMI. Recently, common variations of fat mass and obesity-related genes, including *FTO*, *MC4R*, and *TMEM18*, have been consistently associated with obesity traits and BMI in GWAS [17-18]. GWAS have identified approximately 40 SNPs showing a significant association with BMI, a widely used measurement of adiposity. However, only eight of these associations have been verified by follow-up GWAS using more complicated evaluations of adiposity. Among these eight, an SNP close to the *FTO* gene has been studied for discovery of its function, while the remaining seven SNPs adjacent to, or within, the *NEGR1*, *TMEM18*, *ETV5*, *FLJ35779*, *LINGO2*, *SH2B1*, and *GIPR* genes are less well reported than *FTO*, particularly in connection with obesity. Some reports did not demonstrate the putative mechanism associating the *FLJ35779* and *LINGO2* genes with obesity. All of these genes are expressed in the brain, and *SH2B1* and *GIPR* have been directly linked to appetite regulation. *SH2B1* is an enhancer of intracellular signaling in the JAK-STAT pathway, and *GIPR* is the receptor for an appetite-linked

hormone (GIP) produced by the alimentary tract. *NEGR1*, *ETV5*, and *SH2B1* have suggested roles in neurite outgrowth; therefore, SNPs within these genes may influence the energy balance circuitry. These functions may contribute to their effects on the obese phenotype [19-21].

However, these genes and functions have shown association with BMI only, not BMR. Thus far, GWAS have confirmed at least 50 loci associated with BMI, WHR, body fat percentage, and extreme obesity. Some of these have been demonstrated to replicate in non-white populations and in children and adolescents. Despite the many new findings, the sizes of the established loci are small, and they can explain only a narrow portion of the inter-individual variations in BMI. In addition, most of these newly discovered loci were not previously linked to obesity [19]. From this study, we supposed that the new loci associated with BMR and BMI in obese Korean women might be associated with *NRG3*, *OR8U8*, *BCL2L2-PABPN1*, *PABPN1*, and *SLC22A17* genes. However, these genes and their functions related to obesity, BMR, and BMI have not yet been reported. The neuregulin 3 (*NRG3*) gene located at 10q22-q24 is involved in multiple psychiatric disorders including cognitive impairment [22]. As recently reported, genetic polymorphisms and haplotypes in the *NRG3* gene may play a role in Alzheimer disease; however, *NRG3* was not associated with BMR and BMI [23]. The current study shows a different result. *OR8U8* is located in a cluster of seven olfactory receptor genes, previously associated with odor perception. Among these genes, for the first time, an SNP in the *OR7G3* gene (rs10414255) was also found to be associated with adiposity and eating behaviors [22]. In the study by Choquette et al., *OR8U8*, an olfactory receptor gene, was found to be associated with obesity and/or BMI; this result should be considered as potential new speculation on the effects of polymorphisms in olfactory receptor genes on eating behaviors and obesity, and should be further studied in other populations. However, our study found a different result.

Recently, the overexpression of solute carrier family 22 member 17 (*SLC22A17*) was found to be an independent prognostic factor involved in the aggressive behavior of endometrial carcinoma cells [24]. The organic cation transporter (*OCT*, *SLC22*) family is a family of polyspecific transmembrane proteins involved in the uptake or excretion of many cationic drugs, toxins, and endogenous metabolites in many tissues. Two novel rat *SLC22* genes, *SLC22A17* (*BOCT1*) and *SLC22A23* (*BOCT2*), were recently cloned and characterized. However, some reports showed that although these novel family members have conserved sequence elements like the other OCT members, these proteins were unable to transport typical substrates as the *SLC22* family, and another possible function of *SLC22A17* was suggested [25]. The *SLC22* family has not yet been associated with obesity and/or BMI; however, further studies and experiments are needed in order to test this novel hypothesis.

In the current study we investigated the eating behavior and lifestyle of the low BMR and high BMR groups, and BMR- and BMI-related genes were identified. Subjects with a high BMR had a higher rate of family history of gastric cancer and higher coffee intake, as well high quantities of protein and vitamin

E intake, compared to those with a low BMR. Interestingly, the number of starvation periods per week and the trial of weight control in the subjects with low BMR were higher than in those with a high BMR. Because they have a high BMI, women with a low BMR are more likely to be overweight, thus this population may need to watch their weight. Therefore, understanding the genetic causes of obesity susceptibility by investigating BMR- and BMI-related genes may reveal some of the underlying mechanisms leading to the prevention and possible treatments of obesity in the future. Despite the limitation of small number of subjects in this study because of economics, several common BMR- and BMI-related genes were discovered using GWAS. Although most of these newly established loci were not previously associated with obesity, they may provide new insights into body weight regulation. Further studies in gene discovery and function are needed in order to increase our understanding of obesity.

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