

ORIGINAL ARTICLE

Association of *MACROD2* gene variants with obesity and physical activity in a Korean population

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Abstract

Background: Obesity is a serious and common complex disease caused by the influence of genetic and environmental factors. Therefore, we aimed to evaluate the effect of genetic variants on obesity and the possibility of preventing obesity through physical activity using association analysis.

Methods: This study analyzed the association between obesity and variants in the *MACROD2* gene in the Korean association resource (KARE) cohort using logistic regression analysis. Linear regression analysis was performed for obesity-related phenotype traits including body mass index (BMI), body fat percentage (BFP), abdominal fat percentage (AbFP), and the waist-to-hip ratio (WHR). The level of physical activity was analyzed by dividing the participants into two groups according to the cutoff of one hour or more of daily intense activity.

Results: As a result, rs6079275 in the *MACROD2* gene had the highest significance in obesity and phenotypic characteristics. Minor allele carriers (CC, CG) of rs6079275 decreased the obesity risk (OR = 0.57, 95% CI = 0.40–0.82, $p = 2.34 \times 10^{-3}$) and showed a tendency to decrease the risk of BMI ($\beta = -0.312$, $p = 8.99 \times 10^{-4}$), BFP ($\beta = -0.482$, $p = 4.19 \times 10^{-3}$) and AbFP ($\beta = -0.0051$, $p = 5.96 \times 10^{-4}$). In addition, the participants with the minor allele (C) of rs6079275 had a reduced obesity risk with high physical activity (OR = 0.23, 95% CI: 0.14–0.93, $p = 0.036$).

Conclusions: This study demonstrated that variants in the *MACROD2* gene were correlated with obesity, phenotypic traits, and physical activity in the Korean population. Therefore, we suggest the possibility of preventing obesity by identifying this genetic variation and the interactive effect of lifestyle in Koreans.

KEYWORDS

genetic variant, *MACROD2*, obesity, physical activity, single-nucleotide polymorphism

1 | INTRODUCTION

According to a report from the Centers for Disease Control and Prevention (CDC), between 1999–2000 and 2017–2018,

the prevalence of obesity increased from 30.5% to 42.4%. In addition, the prevalence of severe obesity raised from 4.7% to 9.2% and was highest at 40–59 years compared to other age groups (Hales et al., 2020). Obesity is correlated with various

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diseases, especially type 2 diabetes, hyperlipidemia, hypertension, cardiovascular disease, and osteoarthritis (Dandona et al., 2004; Haslam & James, 2005). Obesity is indicated by the body mass index (BMI) and further evaluated by the waist-to-hip ratio (WHR), body fat percentage (BFP), and abdominal fat percentage (AbFP) (Gray & Fujioka, 1991; Purnell, 2000). In family studies, BMI was highly correlated with parental obesity, but it was difficult to distinguish whether these results were due to genetic or environmental factors (Lake et al., 1997). Silventoinen et al. (2016) demonstrated that genetic factors were important in variations in BMI by analyzing twin pairs to minimize the environmental factors. However, there are significant differences in BMI heritability estimates ranging from 31% to 90% (Min et al., 2013). Therefore, there is a limit to explaining obesity, which is spreading worldwide, by only the genetic background.

Adenosine diphosphate (ADP)-ribosylation is involved in immunity, transcription, the regulation of chromatin structure, insulin secretion, DNA repair, and RNA metabolism, particularly in response to diverse types of cellular stress (Butepage et al., 2015; Feijs et al., 2013; Jankevicius et al., 2013). The protein encoded by the MACRO domain 2 (*MACROD2*, OMIM: 611567) gene can reverse-regulate ADP-ribosylation by being involved in removing ADP-ribose from mono-ADP-ribosylated proteins (Feijs et al., 2020; Rosenthal et al., 2013). The *MACROD2* gene, which encodes a protein that performs various function in several biological processes, is located on human chromosome 20p12.1. Previous studies have reported that genetic variants in the *MACROD2* gene were related to hypertension, Crohn's disease, schizophrenia, and liver cancer (Fujimoto et al., 2016; Julia et al., 2013; Slavin et al., 2011; Xu et al., 2009). Another study discovered that the deletion of an exon in the *MACROD2* gene was closely related to obesity (Pettersson et al., 2017).

Obesity is a disease where adipose tissue accumulates abnormally due to genetic and lifestyle factors (Qi & Cho, 2008). The environmental factors include increased energy intake, reduced consumption of high-fiber foods, and physical inactivity due to a sedentary lifestyle (Burdette & Whitaker, 2005). Among them, physical activity has been demonstrated to promote maintenance of weight and reduce the risk of developing chronic diseases (Kim et al., 2018; Telford, 2007). However, the degree of improvement has been found to vary considerably among individuals due to genetic variants (Mori et al., 2009; Rankinen et al., 2006). Thus, identifying the interaction between environmental and genetic factors can be used to optimize individual treatment and the control of lifestyle-related diseases, and more effective and specific physical activities can be chosen.

Despite these studies, our current understanding of variants study falls far short of expectations in the *MACROD2* gene, obesity, and obesity-related phenotypes. Moreover, it is not known whether *MACROD2* genetic variants reduce an

individual's risk of obesity associated with physical activity. Therefore, we identified the correlation between SNPs in the *MACROD2* gene variants and obesity based on the Korean Genomic Epidemiology Study (KoGES) and then performed a comparative analysis of the correlation between physical activity and obesity-related SNPs.

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

This study was approved by the Institutional Review Board of the Korean National Institute of Health (KNIH) and Hoeso University (1041231170418-HR-056-02). The participants of this study were collected from the Ansan–Ansung cohorts in Korea as a portion of the Korean Genomic and Epidemiology Study (KoGES). In baseline study (2001–2002), a total of 10,038 peoples were recruited from the KoGES, and surveys were conducted biannually after the baseline survey to 2013–2014. The Korean Association Resource (KARE) project, also known as the Ansung and Ansan community-based cohort, performed a large-scale genome-wide genotyping analysis of 10,004 participants available for DNA analysis. Of these, 1196 were removed through genotype quality control, and the genotypes of 8842 participants aged 40–69 years were disclosed to the public domain. Detailed information on the KARE project has been described previously (Cho et al., 2009). The participants of this study were categorized as non-obese ($18.5 \leq \text{BMI} < 25 \text{ kg/m}^2$) or obese ($\text{BMI} \geq 30 \text{ kg/m}^2$) according to the World Health Organization (WHO) cut-off (World Health Organization, 2000). The genotype data used in this study were obtained by the Human Resources Bank of Korea Centers for Disease Control and Prevention (KBN-2017-046). All participants provided written informed consent.

2.2 | Basic characteristics and physical activity

The parameters measured in this epidemiological study were weight, height, waist, and hip circumferences. Body mass index [$\text{BMI} = \text{body weight (kg)}/\text{height (m}^2\text{)}$] was calculated by weight and height, and waist-to-hip ratios [$\text{WHR} = \text{waist measurement (cm)}/\text{hip measurement (cm)}$] were calculated by the circumference of the waist and hips. Tetrapolar bioelectrical impedance analysis using the Inbody 3.0 (Biospace, Seoul, Korea) determined body fat percentage (BFP) and abdominal fat percentage (AbFP). The basic characteristics of the study participants are described in Table 1. The level of physical activity was divided into two categories, low activity (<1 hour per day) and high activity (≥ 1 hour per day), depending upon

TABLE 1 Characteristics of participants in the Korean population

Characteristics	Quantitative trait analysis	Case-control analysis for obesity		
		Controls	Cases	<i>p</i> value*
Number of participants	7449	4355	327	
Gender [men (%)]	3025 (40.61)	2223 (51.04)	95 (29.05)	<0.001
Age (M years ± SD)	51.44 ± 8.79	51.55 ± 9.01	50.8 ± 8.2	0.142
Height (M cm ± SD)	160.42 ± 8.63	160.67 ± 8.49	157.86 ± 8.55	<0.001
Weight (M kg ± SD)	62.97 ± 10.15	58.47 ± 7.45	79.37 ± 8.86	<0.001
BMI (M kg/m ² ± SD)	24.42 ± 3.08	22.59 ± 1.61	31.8 ± 1.8	<0.001
Waist (M cm ± SD)	82.09 ± 8.66	78.17 ± 6.73	96.69 ± 7.27	<0.001
Hip (M cm ± SD)	93.5 ± 5.92	90.93 ± 4.62	104.04 ± 5.27	<0.001
WHR (M ± SD)	0.88 ± 0.07	0.86 ± 0.07	0.93 ± 0.07	<0.001
BFP (M ± SD)	26.5 ± 7.02	24.07 ± 6.22	36.71 ± 5.6	<0.001
AbFP (M ± SD)	0.9 ± 0.05	0.87 ± 0.03	0.99 ± 0.04	<0.001

Abbreviations: AbFP, abdominal fat percentage; BFP, body fat percentage; BMI, body mass index; M, mean value; SD, standard deviation; WHR, waist-to-hip ratio.

*Significant differences in characteristics between the cases and controls were determined by Student's *t* test.

the amount of time the adult engaged in intense activities per day (athletic sports, climbing, running, logging, agriculture, forestry, and mining).

2.3 | Genotyping

The genetic information was obtained from the Center for Genome Science, Korea National Institute of Health. Genomic DNA samples were separated from the peripheral blood of the participants and genotyped using the Affymetrix Genome-Wide Human SNP array 5.0 (Affymetrix). The genotyping was verified for accuracy through the Bayesian Robust Linear Modeling with the Mahalanobis Distance genotyping algorithm (Rabbee & Speed, 2006). The participants with low genotyping accuracy ($\leq 98\%$), high missing genotype call rates ($\geq 4\%$), high heterozygosity ($> 30\%$), and gender bias were excluded from the genotyping. This study selected three SNPs (rs6079275, rs6079272, and rs10470062) in the *MACROD2* gene (GenBank: NM_080676.6) connected with obesity. The location of the SNPs on the chromosome was confirmed by referring to National Center for Biotechnology Information (NCBI) human genome build 36 (hg18).

2.4 | Statistical analysis

Most statistical analyses were executed using PLINK version 1.9 (Purcell et al., 2007) and PASW Statistics version 18.0 (SPSS Inc). Logistic regression was used to analyze the association of obesity between the cases and controls by establishing the odds ratios (OR) and 95% confidence intervals (95% CI). The association analysis of

the quantitative traits related to obesity was performed using linear regression analysis. All association analyses were based on the dominant genetic model. All analyzes included age, area, and gender as covariates. Statistical significance was considered at *p* values of < 0.05 .

3 | RESULTS

3.1 | Characteristics of study participants

The KARE cohort included 7449 participants (3025 men and 4424 women; age 40–69 years) in this association analysis. The basic characteristics of the study participants are shown in Table 1. The 7449 participants were divided into obesity cases and the control group. As shown in Table 1, the mean and deviation of the phenotype characteristics were statistically different between the case and control groups by Student's *t* test. In the obesity case group, all obesity-related characteristics such as waist and hip circumference, BMI, WHR, BFP, and AbFP were increased compared to the control group. Specifically, the mean BMI value, an indicator of obesity, in the case group was 9.21 kg/m² higher than in the control group. Student's *t* test showed statistical significance between the obesity case group and the control group in all characteristics except age.

3.2 | Selected genetic variants from the KARE data

In the association study, the SNPs in the *MACROD2* gene were selected based on the KARE cohort. We performed logistic

and linear regression analyses of obesity and BMI on 341 SNPs in the *MACROD2* gene. As a result, 17 SNPs showed statistical significance for obesity (Table 2). Among them, SNPs rs6079275, rs6079272, rs10470062, and rs4814335 were highly associated with both obesity ($p = 2.34 \times 10^{-3}$, $p = 2.38 \times 10^{-3}$, $p = 5.27 \times 10^{-3}$, $p = 5.27 \times 10^{-3}$, respectively) and BMI ($p = 8.99 \times 10^{-4}$, $p = 1.29 \times 10^{-3}$, $p = 1.16 \times 10^{-3}$, $p = 8.24 \times 10^{-3}$, respectively). The odds ratio of SNP rs6079275, which showed the highest significance level, was 0.57 (95% CI 0.40–0.82) in obesity. The linear regression analysis of BMI, a representative indicator of obesity, also showed a tendency to decrease when a minor allele (C) was present.

3.3 | Association analysis between *MACROD2* gene variants and obesity

We investigated the correlation of the four SNPs (rs6079275, rs6079272, rs10470062, and rs4814335) with obesity-related traits such as BMI, BFP, AbFP, and WHR (Table 3). The association analysis showed significant correlations of rs6079275, rs6079272, and rs10470062 with BMI ($\beta = -0.312$, $p = 8.99 \times 10^{-4}$; $\beta = -0.302$, $p = 1.29 \times 10^{-3}$;

$\beta = -0.23$, $p = 1.16 \times 10^{-3}$), BFP ($\beta = -0.482$, $p = 4.19 \times 10^{-3}$; $\beta = -0.474$, $p = 4.81 \times 10^{-3}$; $\beta = -0.273$, $p = 0.032$), and AbFP ($\beta = -0.0051$, $p = 5.96 \times 10^{-4}$; $\beta = -0.0049$, $p = 8.46 \times 10^{-4}$; $\beta = -0.0026$, $p = 0.021$, respectively). However, there was no association between the WHR and the three variants in the *MACROD2* gene. Also, variant rs4814335 was only correlated with BMI ($\beta = -0.193$, $p = 8.24 \times 10^{-3}$).

3.4 | Association between rs6079275 in the *MACROD2* gene and physical activity

The rs6079275 variant in the *MACROD2* gene was significantly linked with exercise in the dominant model ($p = 0.036$). Among the minor allele carriers (CC, CG), the risk of obesity in participants with high activity was more than 2.5-fold lower than in participants with low activity, suggesting that a significant association between genotype and the level of physical activity decreased the risk (Figure 1). However, there was no statistical significance between individuals with a homozygous genotype in the major allele (G) and physical activity [OR = 0.75, 95% CI: 0.539–1.04, $p = 0.084$], although high physical activity tended to have a

TABLE 2 Association analysis of the SNPs in the *MACROD2* gene with BMI and obesity

No.	SNP	Minor allele	MAF	Function	BMI		Obesity	
					$\beta \pm SE$	p value	OR (95%CI)	p value
1	rs775106	A	0.260	Intron	0.133 \pm 0.072	0.065	1.30 (1.03–1.63)	0.027
2	rs7352992	C	0.376	Intron	-0.055 \pm 0.072	0.445	0.76 (0.61–0.96)	0.021
3	rs6079649	C	0.389	Intron	-0.195 \pm 0.073	7.25 $\times 10^{-3}$	0.75 (0.60–0.95)	0.015
4	rs6079391	A	0.139	Intron	0.234 \pm 0.080	3.7 $\times 10^{-3}$	0.73 (0.55–0.96)	0.025
5	rs6079275	C	0.087	Intron	-0.312 \pm 0.094	8.99 $\times 10^{-4}$	0.57 (0.40–0.82)	2.34 $\times 10^{-3}$
6	rs6079272	T	0.088	Intron	-0.302 \pm 0.094	1.29 $\times 10^{-3}$	0.58 (0.40–0.82)	2.38 $\times 10^{-3}$
7	rs6034091	A	0.039	Intron	0.277 \pm 0.133	0.037	1.60 (1.11–2.30)	0.012
8	rs4814335	A	0.389	Intron	-0.193 \pm 0.073	8.24 $\times 10^{-3}$	0.73 (0.58–0.92)	8.19 $\times 10^{-3}$
9	rs4814334	C	0.345	Intron	-0.164 \pm 0.071	0.021	0.77 (0.61–0.97)	0.024
10	rs444594	A	0.196	Intron	0.157 \pm 0.074	0.033	1.26 (1.00–1.59)	0.048
11	rs439451	T	0.387	Intron	-0.060 \pm 0.073	0.410	0.77 (0.61–0.96)	0.023
12	rs407097	T	0.380	Intron	-0.048 \pm 0.072	0.510	0.75 (0.60–0.95)	0.016
13	rs2193028	C	0.190	Intron	-0.155 \pm 0.074	0.038	0.76 (0.59–0.97)	0.030
14	rs193272	T	0.464	Intron	-0.011 \pm 0.078	0.890	0.78 (0.61–0.99)	0.043
15	rs1362512	A	0.398	Intron	-0.029 \pm 0.073	0.694	1.31 (1.03–1.67)	0.030
16	rs10485537	C	0.231	Intron	0.056 \pm 0.072	0.435	1.38 (1.10–1.73)	5.74 $\times 10^{-3}$
17	rs10470062	A	0.260	Intron	-0.230 \pm 0.071	1.16 $\times 10^{-3}$	0.72 (0.57–0.91)	5.27 $\times 10^{-3}$

Note: BMI used in the linear regression was adjusted for age, area, and gender. Odds ratios were calculated after adjusting for age, area, and gender. Both logistic and linear regressions were conducted using a dominant model.

MACROD2, MACRO domain-containing 2 (GenBank: NM_080676.6).

Abbreviations: β , regression coefficient; BMI, body mass index; CHR, chromosome; CI, confidence interval; MAF, minor allele frequency; OR, odds ratio; SE, standard error; SNP, single-nucleotide polymorphism.

TABLE 3 Association analysis of three SNPs in the *MACROD2* gene with obesity in the KARE study cohort

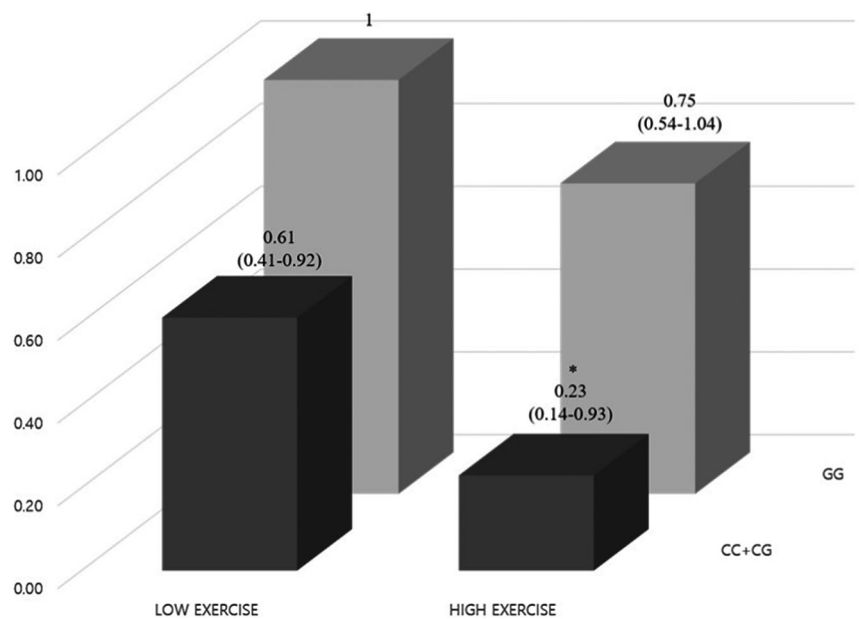
SNP	Minor allele	Phenotype	Dominant model	
			$\beta \pm SE$	<i>p</i> value
rs6079275	C	BMI	-0.312 ± 0.094	8.99×10^{-4}
		BFP	-0.482 ± 0.168	4.19×10^{-3}
		AbFP	-0.0051 ± 0.0015	5.96×10^{-4}
		WHR	-0.0022 ± 0.0019	0.235
rs6079272	T	BMI	-0.302 ± 0.094	1.29×10^{-3}
		BFP	-0.474 ± 0.168	4.81×10^{-3}
		AbFP	-0.0049 ± 0.0015	8.46×10^{-4}
		WHR	-0.0019 ± 0.0019	0.310
rs10470062	A	BMI	-0.230 ± 0.071	1.16×10^{-3}
		BFP	-0.273 ± 0.127	0.032
		AbFP	-0.0026 ± 0.0011	0.021
		WHR	-0.0017 ± 0.0014	0.231
rs4814335	A	BMI	-0.193 ± 0.073	8.24×10^{-3}
		BFP	-0.1811 ± 0.0131	0.167
		AbFP	-0.0021 ± 0.0011	0.072
		WHR	-0.00061 ± 0.0015	0.672

Note: The covariates contain age, area and gender in linear regression analysis.

MACROD2, MACRO domain-containing 2 (GenBank: NM_080676.6).

Abbreviations: β , regression coefficient; AbFP, abdominal fat percentage; BFP, body fat percentage; BMI, body mass index; SE, standard error; WHR, waist-to-hip ratio.

FIGURE 1 Risk of obesity according to physical activity and *MACROD2* rs6079275 genotypes. The relative OR (95% CI) of the dominant (CC + CG) and homozygous (GG) genotypes of *MACROD2* rs6079275 according to the level of physical activity. The reference allele was set up as a group with a homozygous major allele (GG). *p* values were adjusted for age, area, and gender as covariates. **p* < 0.05. OR, odds ratio; CI, confidence interval; *MACROD2*, MACRO domain-containing 2 (GenBank: NM_080676.6)



low odds ratio. These results suggest that physical activity was significantly related to the *MACROD2* rs6079275 genotype in Korean adults. In addition, gender, one of the covariates, indicated a significant association with obesity (Table S1). The associations between gender and obesity were clear in both the minor allele carriers (CC, CG) and the group with a homozygous major allele (GG).

4 | DISCUSSION

MACROD2-encoded protein domain, which is affinity to the ADP-ribose-binding domain, is said to play an important role in many biological processes (Butepage et al., 2015). Previous studies reported that the copy number variants of the *MACROD2* gene were related to brain disorders,

including schizophrenia, cerebral infarction, and brain volume in multiple sclerosis (Baranzini et al., 2009; DeBette et al., 2010; Xu et al., 2009). Interestingly, Pettersson *et al.* reported that the *MACROD2* gene was correlated with obesity through a copy number variant (CNV) analysis (Pettersson et al., 2017). The *MACROD2* gene was also linked to cardiovascular disease and hypertension (Kelly et al., 2013; Slavin et al., 2011; Zhu et al., 2010). These studies revealed that the *MACROD2* gene was closely related not only to obesity but also to various complex diseases.

Obesity is one of the biggest problems worldwide (Hossain et al., 2007) and is the predisposing factors for developing a variety of complex diseases and is very important in pathophysiology (Goodarzi, 2018; Sladoje et al., 2017). In this study, we explored whether genetic variants in the *MACROD2* gene were associated with obesity using a Korean cohort. As a result, 17 SNPs showed statistical significance, and we performed a correlation analysis between these genetic variants and obesity-related traits including BMI, BFP, AbFP, and WHR. Among them, three SNPs (rs6079275, rs6079272, and rs10470062) showed statistical significance in the obesity-related track, excluding WHR (Table 3). The results indicated that genetic variants in the *MACROD2* gene correlated with obesity in this Korean population. There have been studies on the relationship between *MACROD2* gene variants and BMI, but few papers have been published on the Korean population (Kichaev et al., 2019; Pulit et al., 2019).

Lifestyle factors as well as genetic factors are very significant in the development of obesity. Numerous studies have examined whether the association between physical activity and genetic variants influenced obesity risk (Cho et al., 2020; Rampersaud et al., 2008; Vimalaswaran et al., 2009). The present study focused on the genetic association between *MACROD2* gene variants and obesity and identified significant associations with physical activity. In this study, rs6079275 present in the intron of the *MACROD2* gene located on chromosome 20p12.1 was selected because it showed the highest level of significance with obesity. Our results showed that when compared to the participants with a homozygous genotype in the major allele (GG), minor allele carriers (CC, CG) had a 40% reduced risk of obesity, and high levels of physical activity lowered the risk by nearly 80%. In addition, high physical activity in individuals with a homozygous genotype in the major allele (GG) tended to have a lower OR, but higher OR than those of the minor allele carriers (CC, CG) with low physical activity, indicating that a lifestyle that includes physical activity is important in preventing obesity, but that genetic factors also have a large influence.

A previous study reported that a CNV caused by an exon deletion of the *MACROD2* gene was found in obese participants (Pettersson et al., 2017). However, since mothers of the participants with CNVs in the *MACROD2* gene were of

normal weight, this study suggested that the gene did not attribute to the obesity-related phenotype or that obesity may interact with genetic variants in the gene deletion region. In this study, unlike the previous study, the correlation between the *MACROD2* gene and obesity was analyzed using SNPs. The results showed that the *MACROD2* gene significantly lowered obesity risk (Table 2). Therefore, this study showed that variants in the *MACROD2* gene were associated with obesity. Association analysis with these genetic variants suggested the possibility that variants in the *MACROD2* gene would affect obesity even if it could not explain all the heritability of complex traits. However, the association analysis between obesity and diet could not be performed because there was no information on the standardized and controlled diet of the participants included in this study.

Chang *et al.* reported that the *MACROD2* gene regulated vascular adhesion protein-1 (VAP-1) by modulating adipogenesis (Chang et al., 2018). VAP-1 is a membrane-bound amine oxidase released into the circulatory system with high expression in mature adipocytes and vascular endothelium (Ambele et al., 2016; Bour et al., 2007; Foot et al., 2013; Sole & Unzeta, 2011). In addition, released VAP-1 is a significant marker and has been related to various diseases such as diabetes, inflammation, hypertension, hepatic steatosis, and kidney disease (Lin et al., 2008; Maciorkowska et al., 2015; Weston et al., 2015). A recent study reported a significant between *MACROD2* gene variants and hypertension (Ko & Jin, 2019). Another study reported an association between *MACROD2* gene variants and polycystic ovarian syndrome in Koreans and insulin sensitivity (Kim et al., 2019). Therefore, the *MACROD2* gene, which can regulate VAP-1, may affect obesity and various diseases.

5 | CONCLUSIONS

In summary, this study confirmed a significant association between *MACROD2* gene variants and obesity based on the Korean Genomic and Epidemiology Study. As a result, 17 SNPs showed a statistically significant correlation. Among them, three SNPs (rs6079275, rs6079272, and rs10470062) also showed statistical significance in obesity-related traits. In addition, a significant correlation was confirmed between SNP rs6079275, which is most associated with obesity, and physical activity. These results suggest that *MACROD2* gene variants can affect the pathogenesis of obesity and that lifestyle is important in preventing obesity. In conclusion, this study confirmed that genetic factors and environmental factors such as exercise work together in the occurrence of obesity. Especially, the fact that the state of the disease varies according to the intensity of exercise in relation to a specific genotype shows the importance of prophylactic suggestions for environmental factors that consider individual's genotype.

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CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

H.-R. K. and H.-S. J. were responsible for the design and conceptualization of the study, data collection, and analysis. Y.-B. E. was responsible for the design and conceptualization of the study, and funding acquisition. All authors contributed to the manuscript writing. All authors revised and approved the final manuscript.

ETHICS STATEMENT

This study was approved by the Institutional Review Board of the Korean National Institute of Health (KNIH) and Hoeso University (1041231170418-HR-056-02).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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