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ORIGINAL RESEARCH

An Association Between *FNDC*5, *PGC*-1α Genetic Variants and Obesity in Chinese Children: A Case-Control Study

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Background: Fibronectin type III domain containing protein 5 (*FNDC5*) gene encodes irisin that regulates adipose tissue metabolism. Peroxide-proliferator-activated receptor γ coactivator 1α (*PGC-1α*) is a powerful promoter of mitochondrial biosynthesis and oxidative metabolism, which plays an important role in inducing heat production and energy consumption of brown fat. *PGC1-α* expression stimulated an increase in expression of *FNDC5*.

Purpose: The aims of this study were to analyze the association between *FNDC5, PGC-1α* genetic variants and overweight or obesity in Chinese children and adolescents.

Methods: A total of 198 children and adolescents with overweight or obesity and 198 children and adolescents with normal weight were screened according to gender and age 1:1. The healthy eating behaviors, moderate-to-vigorous physical activity time were surveyed using food frequency questionnaire and CLASS questionnaire, respectively. Genotypes of *FNDC5* and *PGC-1α* gene were detected using SNaPshot method.

Results: GT genotype of *FNDC*5 (rs16835198) increased the risk of overweight or obesity in boys (OR (95% CI): 1.68 (1.00, 2.93)) based on overdominant model; GG genotype of *FNDC*5 (rs16835198) decreased the risk of overweight or obesity in girls and boys (OR (95% CI): 0.45 (0.21,0.97), 0.45 (0.24, 0.83), respectively) based on dominant model; TT genotype of *FNDC*5 (rs16835198) increased the risk of overweight or obesity in girls based on recessive model (OR (95% CI): 2.46 (1.19, 5.05)), and based on the additive model (OR (95% CI): 3.82 (1.49, 9.80)). There was significant interaction between *FNDC*5 (rs16835198) and *PGC*-1α (rs3755863, rs8192678), healthy eating behaviors, moderate-to-vigorous physical activity time, interaction between *PGC-1α* (rs8192678) and moderate-to-vigorous physical activity time in the occurrence of overweight or obesity in Chinese children and adolescents.

Conclusion: *FNDC5* (rs16835198) played an independent or interactive role with *PGC*-1α (rs3755863, rs8192678), healthy eating behaviors, moderate-to-vigorous physical activity time in the occurrence of overweight or obesity in Chinese children and adolescents.

Keywords: children, adolescents, *FNDC*5, *PGC*-1α, gene polymorphism

Introduction

Childhood obesity has become one of the most important risk factors for chronic non infectious diseases, such as hyperlipidemia, hypertension, diabetes and metabolic syndrome, and is an important indicator for predicting obesity and risks of health in adulthood.[1–3] WHO reported that there were approximately 340 million children and adolescents aged 5–19 with overweight or obese worldwide.[4] Liu et al reported that the prevalence of overweight or obesity among Chinese children aged 6–18 years was high with 17.62% and 29.05% in boys, 17.57% and 18.04% in girls, respectively.[5] It was well known that overweight or obesity is the result of the interaction between genetic variants and unhealthy

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environmental factors (such as unhealthy eating behaviors, insufficient physical activity time, etc). Existing studies have shown that serum irisin and its genetic polymorphism are closely related to dyslipidemia and glucose metabolism, and may become a new target for the treatment of obesity and obesity-related metabolic diseases.[6]

Irisin is a new muscle/adipocytokine discovered in recent years to enhance fat burning and weight loss by increasing energy expenditure, improving glucose tolerance and inducing mitochondrial genetic expression.[7] Irisin is encoded by the fibronectin type III domain containing protein 5 (*FNDC*5) gene.[8,9] As a precursor of irisin, *FNDC5* is highly expressed in the heart, brain, liver and skeletal muscle, and is essential for maintaining metabolic homeostasis.[10,11] It has been reported that the levels of *FNDC5* mRNA in adipose tissue and circulating irisin negatively correlated with hyperglycaemia, triglycerides, visceral adiposity and extramyocellular lipid deposition.[12] Studies have shown that the wild GG genotype of *FNDC5* (rs16835198) is also significantly associated with increased fasting glucose levels in diabetic subjects.[13] However, other studies have shown that the TT genotype of *FNDC5* (rs16835198) is associated with several metabolic parameters in circulating serum, suggesting that both TT genotype and T allele may increase obesity susceptibility.[14] Remarkably, results of these study showed the SNPs of *FNDC5* gene correlated with obesity and glucose-lipid metabolism, which may be because it modulate the levels of serum irisin.[15,16]

Peroxide-proliferator-activated receptor γ coactivator 1α (*PGC-1α*) is a powerful promoter of mitochondrial biosynthesis and oxidative metabolism, and can induce high expression of brown fat cell uncoupling protein 1 (*UCP-1*), which plays an important role in inducing heat production and energy consumption of brown fat.[17] Two common SNPs of *PGC*-1α (rs8192678, rs3755863) were associated with obesity,[18] which may lead to the development of metabolic syndrome, but the effects may be small and depend on interactions of gene-gene and gene-environment. *PGC-1α* genetic variants may be one of the genetic causes of obesity in different periods of human life. The effects of genetic variants and interaction between *PGC-1α* and *FNDC5* genes on obesity in children and adolescents are still poorly understood. The purpose of the current study was to reveal the relationship between *FNDC5* (rs16835198), *PGC-1α* (rs8192678, rs3755863), healthy eating behaviors, moderate-to-vigorous physical activity time and overweight or obesity in Chinese children and adolescents based on the case-control study.

Material and Methods

Participants

A total of 198 overweight or obese participants aged 8–14 years were screened from two nine-year schools in Bengbu, Anhui Province, and 198 participants with normal weight were matched according to gender and age 1:1. Sample size calculation formula: $N = (Z_{\alpha/2} \times \sqrt{2p} + Z_{\beta}\sqrt{2(p_1 - p)(p_2 - p)/p})^2$, $p = (p_2 - OR \times p_1)/(1 - OR)$. p_1: Risk allele frequency of *FNDC5* (rs16835198) in normal weight group was 0.435; p_2: Risk allele frequency of *FNDC5* (rs16835198) in obesity group was 0.497; *OR*=1.33;[19] $Z_{\alpha/2}$=1.96, Z_{β}=1.282. The minimum effective sample size for overweight or obese participants was 162. This study was conducted according to the Declaration of Helsinki and approved by the Ethics Committee of Bengbu Medical College ([2015] No. 003). All parents or their guardians signed written informed consent.

Measurement of Morphological Development Indicators

During the measurement of body height and weight, participants had empty stomach and bladder, barefoot, took off their hats, and only wore underwear. Height was measured by a mechanical scale with height metre to the nearest 0.1 cm. Digital body weight scale was used to measure the body weight to the nearest 0.1 kg.

Criteria for Overweight or Obesity

Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$, and overweight or obesity was determined according to BMI Classification Standards for Overweight/Obesity Screening of Chinese School-age Children and adolescents.[20]

Survey on Dietary Behaviors and Physical Activity Time

Food frequency questionnaire was used to investigate the frequency of healthy eating behaviors, such as breakfast, eggs, milk, fresh vegetables, fruits and nuts. The frequency of each item was assigned 7 points for 7 times per week, 5 points

for 4–6 times per week, 2 points for 1–3 times per week, 0.5 points for 2 times per month, 0.25 points for 1 time per month and 0 points for never. The total score of healthy eating behaviors was divided into ≥ P_{75} and <P_{75}.[21]

Physical activity time was investigated by CLASS questionnaire,[22] and the time of moderate-to-vigorous physical activity time was divided into <60 min and ≥60 min.[23]

DNA Extraction and SNP Typing Detection

Medical professionals collected 3mL of fasting venous blood from the participants. DNA was extracted using the salting-out method. The national institute of environmental health sciences website (https://snpinfo.niehs.nih.gov/snpinfo/snptag.html) to determine the gene to be detected SNP. The SNP of *FNDC5* was rs16835198, the SNPs of *PGC-1α* were rs8192678, rs3755863. Genotype was performed using the SNaPshot method developed by ABI company. Table 1 contains the sequences of each primer that was used in the qPCR.

Statistical Analysis

IBM SPSS 23.0 software was used for statistical analysis. The data were described using proportion and mean ± standard deviation. *t*-test was used to compare the difference in the measurement variables between two groups. Chi-square test was used to compare the difference in proportion (%) between groups. Logistic regression model was used to analyze the associations between *FNDC5, PGC-1α* genetic variants and overweight or obesity in children and adolescents based on different genetic models (overdominant, dominant, recessive and additive model), after adjusting healthy eating behaviors and moderate-to-vigorous physical activity time. Generalized multifactor dimensionality reduction (GMDR) was used to analyze the interactions between *FNDC5* (rs16835198), *PGC-1α* (rs8192678, rs3755863), healthy eating behaviors, moderate-to-vigorous physical activity time in occurrence of overweight or obesity in children and adolescents. $P<0.05$ was statistically significant.

Results

Basic Information

A total of 396 primary and secondary school students aged 8–14 years were enrolled in this case-control study, including 234 boys (59.09%) and 162 girls (49.91%). The height, weight among overweight or obese children and adolescents were significantly higher than those among normal weight ($P<0.05$). However, the healthy eating behaviors and moderate-to-vigorous physical activity time were not significantly related to overweight or obesity in children and adolescents ($P>0.05$), as show in Table 2.

Association Between FNDC5, PGC-1α Polymorphisms and Overweight/Obesity in Children and Adolescents Based on Different Genetic Models

The distributions of SNPs of *FNDC5* and *PGC-1α* met the Hardy-Weinberg equilibrium. GT, TT genotypes and T allele frequencies of *FNDC5* (rs16835198) in overweight or obese children were significantly higher than those in normal weight children ($P<0.05$). TT genotype and T allele frequencies of *FNDC5* (rs16835198) in girls with overweight or obesity were higher than those in girls with normal weight ($P<0.05$). GT and TT genotype frequencies of *FNDC5*

Table 1 Sequences of Primers Used for the qPCR Reaction

Gene	Localization	Fragment Size	Primer Sequences
rs16835198	Upstream	376bp	TTGCCTCATAGAAACACTCACCAG
	Downstream		CCTACACAGCTAGACTTGGGATGT
rs3755863 and rs8192678	Upstream	477bp	CCACAGATTCAGACCAGTGCTAC
	Downstream		TGGAATATGGTGATCGGGAAC

Table 2 Association Between Healthy Eating Behaviors, Moderate-to-Vigorous Physical Activity Time and Overweight or Obesity Among Children and Adolescents

Variables	Total				Girls				Boys			
	Normal Weight (n=198)	Overweight or Obesity (n=198)	t/χ^2	*P*	Normal Weight (n=81)	Overweight or Obesity (n=81)	t/χ^2	*P*	Normal Weight (n=117)	Overweight or Obesity (n=117)	t/χ^2	*P*
Height (cm)	148.54±12.70	151.01±10.72	−2.10	<0.05	147.91±12.22	149.88±10.08	−1.12	0.27	148.97±13.06	151.80±11.13	−1.78	0.08
Weight (kg)	38.52±9.37	56.00±13.97	−14.62	<0.05	38.15±9.42	57.59±14.94	−9.91	<0.05	38.78±9.36	54.90±13.22	−10.77	<0.05
Healthy eating behaviors			0.01	0.90			1.11	0.29			0.35	0.55
$<P_{75}$	154 (77.8)	153 (77.3)			70 (86.4)	65 (48.1)			84 (72.0)	88 (75.0)		
$\geq P_{75}$	44 (22.2)	45 (22.7)			11 (13.6)	16 (56.3)			33 (28.0)	29 (25.0)		
Moderate-to-vigorous physical activity time			0.25	0.62			0.10	0.75			0.84	0.36
<60min	107 (54.0)	102 (51.5)			46 (56.8)	48 (59.3)			61 (52.1)	54 (46.2)		
≥60min	91 (46.0)	96 (48.5)			35 (43.2)	33 (40.7)			56 (47.9)	63 (53.8)		

(rs16835198) in boys with overweight or obesity were higher than those in boys with normal weight ($P<0.05$). Based on overdominant model, GT genotype of *FNDC5* (rs16835198) increased the risk of overweight or obesity in boys (OR (95% CI):1.68 (1.00, 2.93)). Based on dominant model, GG genotype of *FNDC5* (rs16835198) decreased the risk of overweight or obesity in total students, girls and boys (OR (95% CI): 0.45 (0.28,0.73), 0.45 (0.21,0.97) and 0.45 (0.24,0.83), respectively). Based on recessive model, TT genotype of *FNDC5* (rs16835198) increased the risk of overweight or obesity in girls (OR (95% CI): 2.46 (1.19, 5.05)). Based on additive model, TT genotype of *FNDC5* (rs16835198) increased the risk of overweight or obesity in total students and girls (OR (95% CI): 2.69 (1.48, 4.91) and 3.82 (1.49,9.80), respectively). However, *PGC-1α* (rs3755863, rs8192678) were not significantly associated with overweight or obesity in children and adolescents based on different genetic models, as shown in Table 3 and Figure 1.

Interactions of Gene (FNDC5, PGC-1α) Variants, Healthy Eating Behaviors, Physical Activity Time in Occurrence of Overweight or Obesity in Children and Adolescents

Generalized multifactor dimensionality reduction (GMDR) was used to explore the interaction of gene (*FNDC5, PGC-1α*) variants, healthy eating behaviors, physical activity time in the occurrence of overweight or obesity in children and adolescents. The results showed that the interaction between *FNDC5* (rs16835198) and *PGC-1α* (rs3755863, rs8192678), healthy eating behaviors, moderate-to-vigorous physical activity time was significant in the occurrence of overweight or obesity in children and adolescents ($P=0.01$). There was significant interaction between *PGC-1α* (rs8192678) and moderate-to-vigorous physical activity time in the occurrence of overweight or obesity in children and adolescents ($P=0.01$). As shown in Table 4 and Figure 2.

Discussion

Obesity has been a common and complex multifactorial disease, which leads to excessive fat accumulation under the combined action of environmental and genetic factors.[24,25] This study revealed the association between *FNDC5* (rs16835198), *PGC-1α* (rs3755863, rs8192678), eating behaviors, physical activity time and overweight or obesity in children and adolescents. There was significant association between *FNDC5* (rs16835198) and overweight or obesity, interaction between *FNDC5* (rs16835198) and *PGC-1α* (rs3755863, rs8192678), healthy eating behaviors, moderate-to-vigorous physical activity time, and interaction between *PGC-1α* (rs8192678) and moderate-to-vigorous physical activity time in the occurrence of overweight or obesity in children and adolescents.

The results of this study showed that healthy eating behaviors, moderate-to-vigorous physical activity time were not associated with overweight or obesity in sample children and adolescents. Traub et al[26] reported that skipping breakfast and increasing screen time were risk factors for overweight or obesity in children and adolescents. Raistenskis et al[27] found that obese children had less physical activity than those with normal weight, and sedentary lifestyle was not conducive to the health outcomes of children and adolescents.[28] Of course, some studies have shown that the relationships between eating behaviors, physical activity and obesity are not significant.[29] In addition, it can also be related to the memory bias of the subjective measurement method of eating behavior and physical activity time. This may also be due to the fact that obese children and adolescents have a higher awareness of healthy eating behaviors and physical activity, and intentionally improve their unhealthy eating behaviors or increase physical activity time to loss weight.

This study found that the SNP of *FNDC5* (rs16835198) was significantly associated with overweight or obesity in children and adolescents. T allele frequency of *FNDC5* (rs16835198) in overweight or obese children was higher than that in normal weight children. Based on different genetic models, the results showed that TT genotype of *FNDC5* (rs16835198) increased the risk of overweight or obesity in children and adolescents. Todendi et al[30] reported that TT genotype of *FNDC*5 (rs16835198) increased risk of obesity in South Brazilian children and adolescents. The studies showed that the obese adults with TT genotype of *FNDC*5 (rs16835198) had higher levels of total cholesterol (TC), triacylglycerol (TG) and low-density lipoprotein (LDL-C), lower levels of high-density lipoprotein (HDL-C).[14] Tang et al[31] reported that the interaction between *FNDC*5 (rs16835198) and BMI could affect fasting insulin level in Chinese population. However, the studies also showed that TT genotype of *FNDC*5 (rs16835198) was associated with decreased risk of T2DM, and G allele of *FNDC*5 (rs16835198) was associated with elevated insulin resistance in Egyptians with no effect on renal complications.[32,33] We knew that *FNDC*5 gene encode irisin that regulates adipose

Table 3 Associations Between FNDC5, PGC-1α Genetic Variants and Overweight or Obesity in Children and Adolescents Based on Different Genetic Models

Gene	SNP	Total				Girls				Boys			
		Normal Weight	Overweight / Obesity	χ^2	*P*	Normal Weight	Overweight / Obesity	χ^2	*P*	Normal Weight	Overweight / Obesity	χ^2	*P*
		(n=198)	(n=198)			(n=81)	(n=81)			(n=117)	(n=117)		
rs16835198	Genotype			11.76	<0.05			7.84	<0.05			6.92	<0.05
	GG	61 (30.8)	33 (16.7)			24 (29.6)	13 (16.0)			37 (31.6)	20 (17.1)		
	GT	98 (49.5)	110 (55.6)			42 (51.9)	39 (48.1)			56 (47.9)	71 (60.7)		
	TT	39 (19.7)	55 (27.8)			15 (18.5)	29 (35.8)			24 (20.5)	26 (22.2)		
	Allele			9.78	<0.05			7.73	<0.05			3.09	0.08
	G	220 (55.6)	176 (44.4)			90 (55.6)	65 (40.1)			130 (55.6)	111 (47.4)		
	T	176 (44.4)	220 (55.6)			72 (44.4)	97 (59.9)			104 (44.4)	123 (52.6)		
	Overdominant model			1.46	0.23			0.22	0.64			3.87	<0.05
	GT	98 (49.5)	110 (55.6)			42 (51.9)	39 (48.1)			56 (47.9)	71 (60.7)		
	GG+TT	100 (50.5)	88 (44.4)			39 (48.1)	42 (51.9)			61 (52.1)	46 (39.3)		
	Dominant model			10.94	<0.05			4.24	<0.05			6.7	<0.05
	GG	61 (30.8)	33 (16.7)			24 (29.6)	13 (16.0)			37 (31.6)	20 (17.1)		
	GT+TT	137 (69.2)	165 (83.3)			57 (70.4)	68 (84.0)			80 (68.4)	97 (82.9)		
	Recessive model			3.57	0.06			6.12	<0.05			0.1	0.75
	TT	39 (19.7)	55 (27.8)			15 (18.5)	29 (35.8)			24 (20.5)	26 (22.2)		
	GG+GT	159 (80.3)	143 (72.2)			66 (81.5)	52 (64.2)			93 (79.5)	91 (77.8)		
	Additive model			10.34	<0.05			7.62	<0.05			3.11	0.08
	GG	61 (61.0)	33 (37.5)			24 (61.5)	13 (31.0)			37 (60.7)	20 (43.5)		
	TT	39 (49.0)	55 (62.5)			15 (38.5)	29 (69.0)			24 (39.3)	26 (56.5)		
rs3755863	Genotype			2.14	0.34			2.05	0.36			2.65	0.27
	GG	63 (31.8)	65 (33.0)			32 (39.5)	25(30.9)			31 (26.5)	39 (33.3)		
	GA	92 (46.5)	100 (50.8)			34 (42.0)	43 (53.1)			58 (49.6)	59 (50.4)		
	AA	43 (21.7)	32 (26.2)			15 (18.5)	13 (16.0)			28 (23.9)	19 (16.2)		

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	Allele			0.74	0.39			0.32	0.57			2.49	0.11
	G	218 (55.1)	230 (58.1)			98 (60.5)	93 (57.4)			120 (51.3)	137 (58.5)		
	A	178 (44.9)	166 (41.9)			64 (39.5)	69 (42.6)			114 (48.7)	97 (41.5)		
	Overdominant model			1.01	0.32			2.01	0.16			0.02	0.90
	GA	92 (46.5)	102 (51.5)			34 (42.0)	43 (53.1)			58 (49.6)	59 (50.4)		
	GG+AA	106 (53.5)	96 (48.5)			47 (58.0)	38 (46.9)			59 (50.4)	58 (49.6)		
	Dominant model			0.01	0.91			1.33	0.25			1.31	0.25
	GG	63 (31.8)	64 (32.3)			32 (39.5)	25 (30.9)			31 (26.5)	39 (33.3)		
	GA+AA	135 (68.2)	134 (67.7)			49 (60.5)	56 (69.1)			86 (73.5)	78 (66.7)		
	Recessive model			1.99	0.16			0.17	0.68			2.16	0.14
	AA	43 (21.7)	32 (16.2)			15 (18.5)	13 (16.0)			28 (23.9)	19 (16.2)		
	GG+GA	155 (78.3)	166 (83.9)			66 (81.5)	68 (84.0)			89 (76.1)	98 (83.8)		
	Additive model			1.13	0.29			0.05	0.82			2.63	0.11
	GG	63 (59.4)	64 (66.7)			32 (68.1)	25 (65.8)			31 (52.5)	39 (67.2)		
	AA	43 (40.6)	32 (33.3)			15 (31.9)	13 (34.2)			28 (47.5)	19 (32.8)		
rs8192678	Genotype			2.96	0.23			3.82	0.15			3.12	0.21
	GG	62 (31.3)	60 (30.3)			31 (38.3)	21 (25.9)			31 (26.5)	39 (33.3)		
	GA	93 (47.0)	107 (54.0)			35 (43.2)	47 (58.0)			58 (49.6)	60 (51.3)		
	AA	43 (21.7)	31 (15.7)			15 (18.5)	13 (16.0)			28 (23.9)	18 (15.4)		
	Allele			0.51	0.47			0.81	0.37			2.8	0.09
	G	217 (57.3)	227 (57.3)			97 (59.9)	89 (54.9)			120 (51.3)	138 (59.0)		
	A	179 (42.7)	169 (42.7)			65 (40.1)	73 (45.1)			114 (48.7)	96 (41.0)		
	Overdominant model			1.98	0.16			3.56	0.06			0.07	0.79
	GA	93 (47.0)	107 (54.0)			35 (43.2)	47 (58.0)			58 (49.6)	60 (51.3)		

(*Continued*)

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Table 3 (Continued).

Gene	SNP	Total				Girls				Boys			
		Normal Weight	Overweight / Obesity	χ^2	*P*	Normal Weight	Overweight / Obesity	χ^2	*P*	Normal Weight	Overweight / Obesity	χ^2	*P*
		(n=198)	(n=198)			(n=81)	(n=81)			(n=117)	(n=117)		
	GG+AA	105 (53.0)	91 (46.0)			46 (56.8)	34 (42.0)			59 (50.4)	57(48.7)		
	Dominant model			0.05	0.83			2.83	0.09			1.31	0.25
	GG	62 (31.3)	60 (30.3)			31 (38.3)	21 (25.9)			31 (26.5)	39 (33.3)		
	GA+AA	136 (68.7)	138 (69.7)			50 (61.7)	60 (74.1)			86 (73.5)	78 (66.7)		
	Recessive model			2.39	0.12			0.17	0.68			2.71	0.10
	AA	43 (21.7)	31 (15.7)			15 (18.5)	13 (16.0)			28 (23.9)	18 (15.4)		
	GG+GA	155 (78.3)	167 (84.3)			66 (81.5)	68 (84.0)			89 (76.1)	99 (84.6)		
	Additive model			0.98	0.32			0.27	0.6			3.06	0.08
	GG	62 (59.0)	60 (65.9)			31 (67.4)	21 (61.8)			31 (52.5)	39 (68.4)		
	AA	43 (41.0)	31 (34.1)			15 (32.6)	13 (38.2)			28 (47.5)	18 (31.6)		

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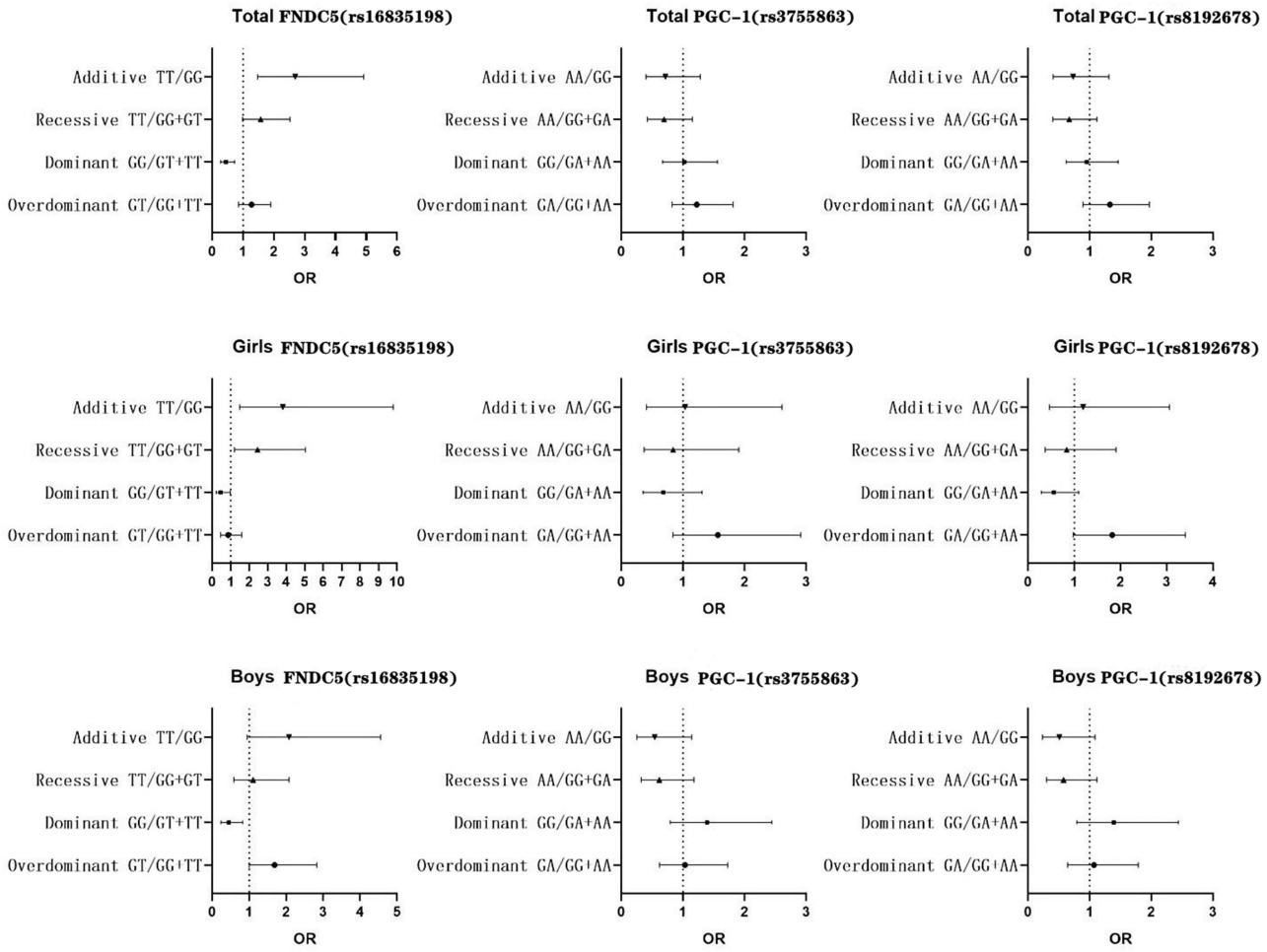

Figure 1 OR values of *FNDC5* (rs16835198) and *PGC-1α* (rs8192678, rs3755863) associated with overweight or obesity based on different genetic models.

tissue metabolism, and plays an important role in energy metabolism and obesity. Studies also demonstrated that irisin is not only a myokine but also an adipokine, with important autocrine and paracrine functions.[34] Luo et al[3] proposed that lack of irisin was associated with a poor browning response, glucose/lipid derangement, and decreased bone mass in mice. These may be a reasonable explanation for the association between T allele, TT genotype of *FNDC5* (rs16835198) and overweight or obesity.

In this study, the results of generalized multifactor dimensionality reduction (GMDR) showed that there was significant interaction between *FNDC5* (rs16835198) and *PGC-1α* (rs3755863, rs8192678) in the occurrence of

Table 4 Interaction of *FNDC5* (rs16835198), *PGC-1α* (rs3755863, rs8192678), Healthy Eating Behaviors, Moderate-to-Vigorous Physical Activity Time in Occurrence of Overweight or Obesity in Children and Adolescents

Model	Interaction	Tr.BA	Te.BA	CVC	*P*
1	rs16835198, rs3755863	0.59	0.57	10/10	0.01
2	rs16835198, rs8192678	0.59	0.56	10/10	0.01
3	rs16835198, healthy eating behaviors	0.57	0.55	10/10	0.01
4	rs16835198, moderate-to-vigorous physical activity time	0.57	0.55	10/10	0.01
5	rs3755863, rs8192678	0.54	0.5	10/10	0.95
6	rs3755863, healthy dietary behaviors	0.54	0.49	10/10	0.83

(*Continued*)

Table 4 (Continued).

Model	Interaction	Tr.BA	Te.BA	CVC	*P*
7	rs3755863, moderate-to-vigorous physical activity time	0.55	0.52	10/10	0.17
8	rs8192678, healthy dietary behaviors	0.55	0.54	10/10	0.05
9	rs8192678, moderate-to-vigorous physical activity time	0.55	0.55	10/10	0.01

Abbreviations: Tr.BA, Training Bal.Acc; Te.BA, Testing Bal.Acc; CVC, CV Consistency.

overweight or obesity in children and adolescents. Boström et al[35] showed that in mouse that *PGC1-α* expression in muscle stimulated an increase in expression of *FNDC5*. The level of *FNDC5* mRNA is increased in skeletal muscle in some exercise paradigms.[36] As a key regulator of energy metabolism, *PGC-1α* can not only regulate glucose metabolism

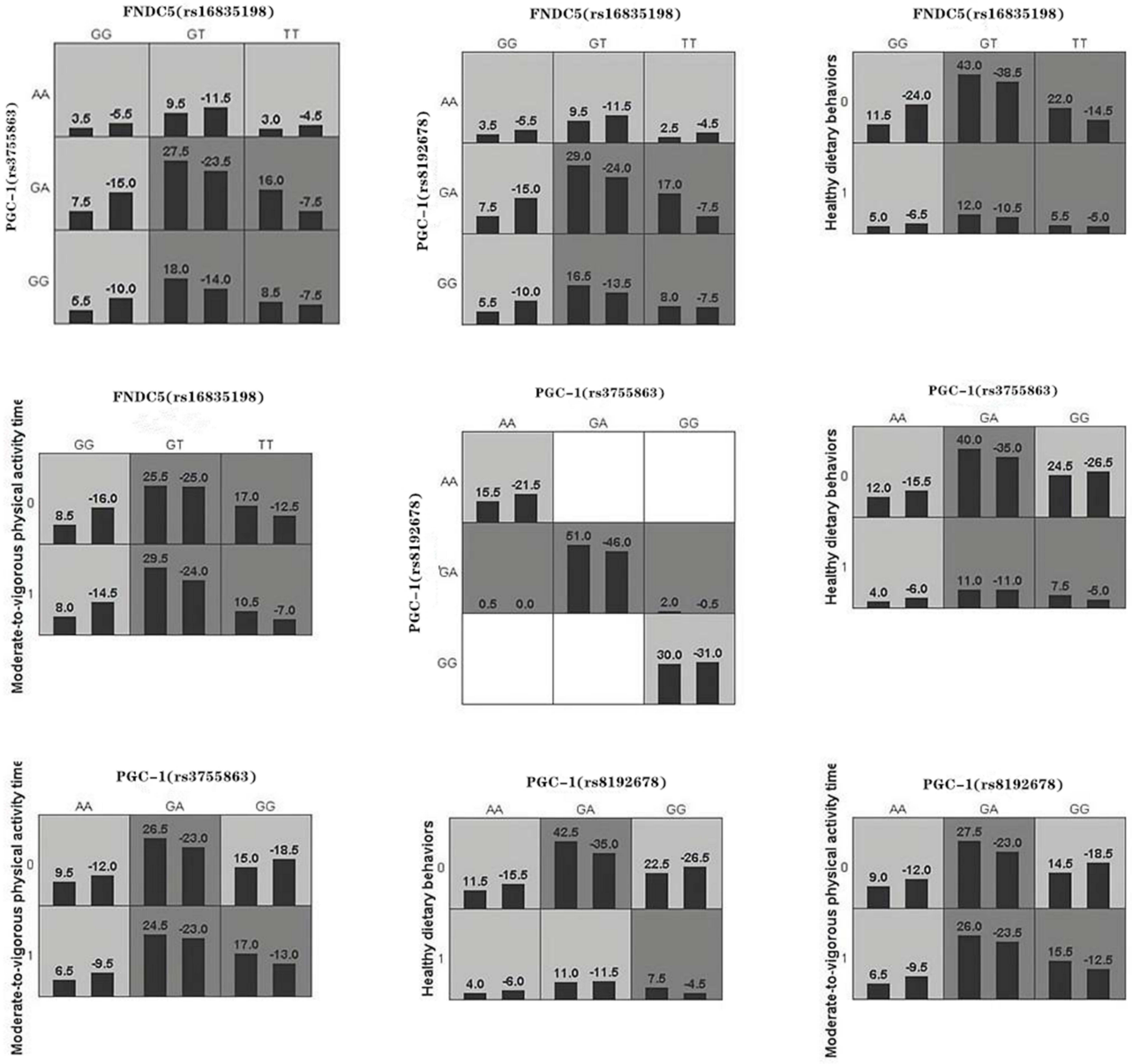

Figure 2 Combined action model of association between *FNDC5* (rs16835198), *PGC-1α* (rs8192678, rs3755863), healthy eating behaviors and healthy dietary behaviors, moderate-to-vigorous physical activity time and overweight or obesity in children and adolescents.

Notes: The left band of each small cell represents the total of positive integral, the right band represents the total of negative integral; dark gray cell represents high risk, light gray cell represents low risk.

in liver and muscle, but also regulate lipid oxidation and adipocyte differentiation. Studies suggest that *PGC-1α* can be a potential therapeutic target for various metabolic diseases.[37] Lin et al[38] demonstrated that A allele of *PGC-1α* (rs8192678) was an independent risk factor of nonalcoholic fatty liver disease in obese children and adolescents. These may be a reasonable explanation for the interaction between *FNDC5* (rs16835198) and *PGC-1α* (rs3755863, rs8192678) in the occurrence of overweight or obesity.

The results of this study showed that there was significant interaction between *FNDC5* (rs16835198) and healthy eating behaviors, moderate-to-vigorous physical activity time in the occurrence of overweight or obesity in children and adolescents, and the TT genotype of *FNDC5* (rs16835198) had the most significant effect. This shows that the children with TT genotype of *FNDC5* (rs16835198) are more likely to be obese if they have insufficient healthy eating behavior or moderate to high intensity physical activity. The *FNDC5* (rs16835198) variant may effect encoding of irisin, thus affecting role of irisin in energy metabolism. Studies showed that exercise increased levels of irisin in children, which may be more instrumental in mediating lipid metabolism.[39]

The interaction between *PGC-1α* (rs8192678) and moderate-to-vigorous physical activity time was significant in the occurrence of overweight or obesity in children and adolescents, and the GA genotype of *PGC-1α* (rs8192678) had the most significant effect. This means that the children with GA genotype of *PGC-1* (rs8192678) and insufficient physical activity are more likely to be obese. In a meta-analysis of the *PGC-1α* (rs8192678) variant, the A allele and AA genotype were suggested to be beneficial for athletic performance.[40] The study showed that the adolescents with A allele of *PGC-1α* (rs8192678) had higher TG than those with G allele of *PGC-1α* (rs8192678).[41] Some studies showed that *PGC-1α* gene regulated the induction of muscle adaptation training.[42] Endurance training can increase expression of *PGC-1α* mRNA.[43] However, the association between *PGC-1α* (rs8192678) and physical performance was not reproducible in different races and populations.[44] Eynon et al[45] found that the GG genotype of *PGC-1α* (rs8192678) was conducive to the increase in aerobic capacity. Yang et al reported that the G allele of *PGC-1α* (rs8192678) was associated with endurance performance, while the A allele of *PGC-1α* (rs8192678) was associated with power performance in Chinese Han Population.[46]

There were also some limitations. First, the subjective methods were used to measure healthy eating behaviors and physical activity time, which might have recall bias. Second, children suffering from obesity may increase their awareness of healthy eating behaviors and physical activities, so that they can change unhealthy eating behaviors or strengthen physical exercise. Third, we only studied Chinese children and adolescents, the generalizability to other ethnic groups was limited. Finally, the exact molecular mechanism of association between *FNDC5* (rs16835198) and childhood overweight or obesity remained to be elucidated.

Conclusion

This study showed that *FNDC5* (rs16835198) was significantly independently associated with overweight or obesity, and played an interactive role with *PGC-1α* (rs3755863, rs8192678), healthy dietary behaviors and moderate-to-vigorous physical activity time in the occurrence of overweight/obesity in Chinese children.

Abbreviations

GMD, Rgeneralized multi-factor dimensionality reduction method; *FNDC5*, fibronectin type III domain containing protein 5 gene; SNP, single nucleotide polymorphism; *PGC-1α*, Peroxide-proliferator-activated receptor γ coactivator 1α; *UCP-1*, uncoupling protein1; Tr.BA, Training Bal.Acc; Te.BA, Testing Bal.Acc; CVC, CV Consistency.

Data Sharing Statement

All data generated or analyzed during this study are not publicly available to maintain the privacy of the individuals' identities. The dataset supporting the conclusions is available upon request to the corresponding author.

Ethics Approval and Consent to Participate

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Medical Research Ethics Committee of Bengbu Medical College ([2015] NO.003). Written informed consent was obtained from parents or their guardians.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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