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Genetic variants in vitamin D metabolism-related genes and body mass index: Analysis of genome-wide scan data of $\approx 7\,000$ Chinese women

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Abstract

Vitamin D deficiency has been consistently associated with obesity. However, it is unclear whether vitamin D deficiency is the cause or consequence of obesity. We investigated this question by evaluating the association between genetic variants in vitamin D metabolism pathway genes and obesity-related traits. Using directly genotyped and imputed data from a genome-wide association (GWA) study of 6,922 women aged 25–70 years, we examined the association of 198 SNPs in vitamin D pathway genes (*CYP27A1*, *CYP27B1*, *CYP24A1*, *CYP2R1*, *GC*, and *VDR*) with body mass index (BMI) and body weight. Per allele beta () estimates were calculated for this association using linear regression models, controlling for age, square of age, menopausal status, and sample sets. Overall, only two SNPs (rs2248359 in *CYP24A1* and rs10832313 in *CYP2R1*) had a nominally significant association with BMI and weight ($P=0.02$ for both) with no variation observed by menopausal status, physical activity, or dietary energy intake. None of the SNPs examined in the *VDR* gene were associated with BMI or weight. Our findings suggest that common genetic variations in vitamin D pathway genes do not play a major role in obesity among Chinese women.

Keywords

genetic variants; body mass index; body weight; obesity; vitamin D pathway; genome-wide association study; women; China

Introduction

Obesity is an epidemic worldwide and a potential risk factor for many chronic health conditions and diseases including cancer.^{1,2} Obesity and high BMI have been shown to be related to vitamin D deficiency (low level of circulating 25-hydroxyvitamin D:

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Conflicts of Interest

The authors declare no conflicts of interest.

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25(OH)D),^{2,3} which may partially explain the role of obesity in the risk of cancer.⁴ The direction of the associations between circulating 25(OH)D and obesity is unknown. Lower levels of 25(OH)D may cause obesity.⁵ On the other hand, obesity may cause low levels of 25(OH)D because of its volume of distribution according to body size and amount of adipose tissue.^{5,6} Studies have found associations between vitamin D pathway gene polymorphisms and circulating 25(OH)D level.^{7–9} Genetic variants in vitamin D pathway genes, namely in the vitamin D nuclear receptor (*VDR*) gene, have been associated with obesity in some,^{10–13} but not all studies.^{14,15} Studies of other genes in the vitamin D pathway, including vitamin D binding protein (*DBP*) or group-specific component (*GC*) or *CYP27B1* and BMI, have also produced inconsistent results.^{16,17} No epidemiologic study to date has comprehensively investigated associations of the multiple genes directly involved in the vitamin D metabolism and signaling pathways with obesity-related traits. The present study aimed to evaluate the role of genetic variants in these genes with BMI and body weight using genome-wide association (GWA) scan data for approximately 7,000 Chinese women.

Materials and Methods

Study population

A total of 6,922 women (aged 25–70 years) with both anthropometrics and genomic DNA samples who participated in three ongoing, GWA studies: 1) the Shanghai Breast Cancer Genetics Study (SBCGS),¹⁸ 2) the Shanghai Endometrial Cancer Genetics Study (SECGS),¹⁹ and 3) the Shanghai Diabetes Genetics Study (SDGS).²⁰ Detailed methods for the GWA study^{21,22} and its contributing studies have been described previously.^{19,23,24} Briefly, the SBCGS included 2,889 breast cancer cases; the SECGS included 839 women with endometrial cancer; and the SDGS included 913 women with type 2 diabetes (T2D). Both the SECGS and SDGS used shared controls (n=2,318) from the SBCGS who were randomly selected from the general population and were free of cancer or diabetes (for the SDGS). All these studies used population-based designs and applied similar study protocols to collect blood or buccal samples and relevant exposure information. Interviews were conducted in-person by trained, retired medical personnel, and anthropometric parameters including height, weight, and waist-to-hip ratio were measured according to a standard protocol. All studies were approved by all participating institutions, and participants provided written, informed consent.

SNP genotyping, selection, and imputation

Genotyping was performed by using the Affymetrix 6.0 array, which includes 906,602 SNPs, as described in detail previously.²² The six genes (*CYP27A1*, *CYP27B1*, *CYP24A1*, *CYP2R1*, *GC*, and *VDR*) evaluated in this study were selected based on their potential role in the vitamin D metabolism and signaling pathways using literature review and the informatics tool, STRING 8.3 (<http://string-db.org>). A total of 198 SNPs (74 directly observed; 124 imputed) in these genes with a MAF $\geq 5\%$ were included. Of the 198 SNPs, 13 SNPs in the *CYP24A1*, *GC*, and *CYP2R1* genes were associated with 25(OH)D level in the Insulin Resistance Atherosclerosis Family Study (IRAS)⁸ and in a recent GWAS^{7,9} (Supplementary Table S1).

Statistical analysis

Descriptive statistics and genome-wide analyses were conducted within each sample set and in aggregate using SAS Version 9.1 and *PLINK*, respectively, as described previously.²¹ Linear regression was used to estimate the effect of genotypes on BMI (weight, kg/height, m²) or weight under an additive genetic model controlling for age, square of age, menopausal status, and sample set or disease status. For body weight associations, we also

adjusted for height. *P*-values were not corrected for multiple comparison tests. Linkage disequilibrium was assessed by Haploview.

Results

In general, subjects were comparable with a few exceptions (Table 1). The mean age of participants across the four sample sets ranged from 49.6 to 54.8 years. The mean BMI was 24.9 (range: 23.4–26.7, kg/m² across sample sets). Cases with endometrial cancer were older and postmenopausal as a result of the late age of the disease onset. As compared with healthy controls and cases with breast cancer, cases with endometrial cancer were more likely to have lower educational attainment, followed by cases with T2D. Cases with T2D and endometrial cancer were more likely to be heavier or overweight/obese at study enrollment than healthy controls and breast cancer cases (*P* < 0.05 for all). There were no differences in weight at age 20, caloric intake, or regular exercise among the sample groups. Of the 198 SNPs examined, only two (rs2248359 *CYP24A1* and rs10832313 *CYP2R1*) had a nominal association with BMI or weight in the combined sample set (*P* = 0.02 for both, Table 2), but did not remain significant after accounting for multiple testing. A similar association was seen across each of the four sample sets. Further, in analyses stratified by menopausal status, physical activity, or dietary energy intake, none of the polymorphisms were associated with BMI or weight (*P* interaction > 0.05 for all, data not shown). Neither single markers nor haplotypes in the *CYP27B1*, *CYP27A1*, *GC*, or *VDR* genes were associated with obesity. Previously identified genetic variants associated with circulating 25(OH)D level had no effect on BMI and weight in our population (Table S1).

Discussion

Association studies of genetic variants in vitamin D pathway genes and BMI or obesity-related traits are limited and inconsistent.¹⁵ Xu *et al* observed a significant association between the *VDR* Apal (rs7975232) polymorphism and BMI among 260 healthy postmenopausal Chinese women.²⁵ Jiang *et al* found a significant association of the *DBP* rs17467825 polymorphism and its corresponding haplotype *GAA* with fat mass and percentage of fat mass among 1,873 European-ancestry individuals aged 19–88 years, mainly among females. In another study, *VDR* (BsmI, rs1544410) was not associated with BMI in healthy postmenopausal Polish women (n = 351) aged 50–60 years.¹⁴ In a recent study of 1,773 healthy women aged 35–80 years from western New York state, USA, the *VDR* rs3782905 polymorphism was positively associated with adiposity markers.¹² However, in our study this association was not significant. All of the above studies had a relatively small sample size and investigated only a single gene or a few SNPs. In our large scale study, we comprehensively examined associations of multiple genes involved in the vitamin D metabolism pathway in relation to BMI or weight. In general, we found no strong evidence among Chinese women of altered risk of obesity for the 198 SNPs in the six genes we studied. The association of two SNPs (rs2248359 *CYP24A1* and rs10832313 *CYP2R1*) with BMI or weight did not stand up after an adjustment for multiple comparisons and thus could be due to chance. There is a need to replicate this finding in other populations.

The strengths of this study include a large sample size, population-based design, high participation rates in the parent studies, racial homogeneity, standardized measurement of anthropometrics, comprehensive analysis of common genetic variants in the vitamin D metabolism and signaling pathway and relevance to current topics of interest in obesity and nutrition-related research.

Obesity and adiposity have been linked to vitamin D deficiency,^{5,6} but the direction of the association is unknown. The advantage of studying the genetic determinants of vitamin D

level and obesity is that genetic factors precede obesity and do not change with obesity status. To our knowledge this approach has not been previously applied in research on associations of obesity and vitamin D. Having no direct measurement for 25(OH)D level is a limitation of our study. This prevented us from evaluating whether the SNPs under study are indeed associated with circulating vitamin D level in our study population. Another limitation of the study is that we did not measure circulating calcium or parathyroid hormone (PTH) levels or other factors, such as kidney function, that influence vitamin D metabolism. PTH up-regulates enzyme *CYP27B1*, which converts 25(OH)D to its active form 1,25-dihydroxy vitamin D [1,25(OH)₂D] in the kidney, and 1,25(OH)₂D regulates calcium homeostasis.¹ The general health of our study participants should also be considered in interpreting our results. About 66.7% of our study participants were diagnosed with cancer or diabetes, diseases that are related to obesity. We carried out additional analyses among healthy controls and each of the 3 subgroups (breast cancer, endometrial cancer, and type 2 diabetes) and found similar null results (data not shown). Finally, our analysis was conducted in a Chinese population, and the results may not be directly generalizable to other ethnic populations. In conclusion, this large GWA study shows no strong evidence for the effect of genetic variants in vitamin D metabolism and pathway genes on BMI or the risk of obesity in Chinese women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Holick MF. Vitamin D: its role in cancer prevention and treatment. *Prog Biophys Mol Biol*. 2006; 92:49–59. [PubMed: 16566961]
2. Renzaho AM, Halliday JA, Nowson C. Vitamin D, obesity, and obesity-related chronic disease among ethnic minorities: A systematic review. *Nutrition*. 2011
3. Arunabh S, Pollack S, Yeh J, Aloia JF. Body fat content and 25-hydroxyvitamin D levels in healthy women. *J Clin Endocrinol Metab*. 2003; 88:157–161. [PubMed: 12519845]
4. Lagunova Z, Porojnicu AC, Grant WB, Bruland O, Moan JE. Obesity and increased risk of cancer: does decrease of serum 25-hydroxyvitamin D level with increasing body mass index explain some of the association? *Mol Nutr Food Res*. 2010; 54:1127–1133. [PubMed: 20512788]
5. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr*. 2000; 72:690–693. [PubMed: 10966885]
6. Caron-Jobin M, Morisset AS, Tremblay A, Huot C, Legare D, Tchernof A. Elevated Serum 25(OH)D Concentrations, Vitamin D, Calcium Intakes Are Associated With Reduced Adipocyte Size in Women. *Obesity (Silver Spring)*. 2011; 19:1335–1341. [PubMed: 21527900]
7. Ahn J, Yu K, Stolzenberg-Solomon R, Simon KC, McCullough ML, Gallicchio L, et al. Genome-wide association study of circulating vitamin D levels. *Hum Mol Genet*. 2010; 19:2739–2745. [PubMed: 20418485]
8. Engelman CD, Fingerlin TE, Langefeld CD, Hicks PJ, Rich SS, Wagenknecht LE, et al. Genetic and environmental determinants of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels in

- Hispanic and African Americans. *J Clin Endocrinol Metab.* 2008; 93:3381–3388. [PubMed: 18593774]
9. Wang TJ, Zhang F, Richards JB, Kestenbaum B, van Meurs JB, Berry D, et al. Common genetic determinants of vitamin D insufficiency: a genome-wide association study. *Lancet.* 2010; 376:180–188. [PubMed: 20541252]
 10. Filus A, Trzmiel A, Kuliczowska-Plaksej J, Tworowska U, Jedrzejuk D, Milewicz A, et al. Relationship between vitamin D receptor BsmI and FokI polymorphisms and anthropometric and biochemical parameters describing metabolic syndrome. *Aging Male.* 2008; 11:134–139. [PubMed: 18821289]
 11. Grundberg E, Brandstrom H, Ribom EL, Ljunggren O, Mallmin H, Kindmark A. Genetic variation in the human vitamin D receptor is associated with muscle strength, fat mass and body weight in Swedish women. *Eur J Endocrinol.* 2004; 150:323–328. [PubMed: 15012617]
 12. Ochs-Balcom HM, Chennamaneni R, Millen AE, Shields PG, Marian C, Trevisan M, et al. Vitamin D receptor gene polymorphisms are associated with adiposity phenotypes. *Am J Clin Nutr.* 2011; 93:5–10. [PubMed: 21048058]
 13. Funakoshi Y, Omori H, Katoh T. Relation of bone mineral density to vitamin D receptor gene polymorphism and lifestyle factors in Japanese female workers aged 22–44 years: a cross-sectional study. *J Nutr Sci Vitaminol (Tokyo).* 2010; 56:27–33. [PubMed: 20354343]
 14. Tworowska-Bardzinska U, Lwow F, Kubicka E, Laczmanski L, Jedrzejuk D, Dunajska K, et al. The vitamin D receptor gene BsmI polymorphism is not associated with anthropometric and biochemical parameters describing metabolic syndrome in postmenopausal women. *Gynecol Endocrinol.* 2008; 24:514–518. [PubMed: 18958772]
 15. Reis AF, Hauache OM, Velho G. Vitamin D endocrine system and the genetic susceptibility to diabetes, obesity and vascular disease. A review of evidence. *Diabetes Metab.* 2005; 31:318–325. [PubMed: 16369193]
 16. Hirai M, Suzuki S, Hinokio Y, Hirai A, Chiba M, Akai H, et al. Variations in vitamin-D binding protein (group-specific component protein) are associated with fasting plasma insulin levels in Japanese with normal glucose tolerance. *J Clin Endocrinol Metab.* 2000; 85:1951–1953. [PubMed: 10843180]
 17. Malecki MT, Klupa T, Wolkow P, Bochenski J, Wanic K, Sieradzki J. Association study of the vitamin D: 1alpha-hydroxylase (CYP1alpha) gene and type 2 diabetes mellitus in a Polish population. *Diabetes Metab.* 2003; 29:119–124. [PubMed: 12746631]
 18. Zheng W, Long J, Gao YT, Li C, Zheng Y, Xiang YB, et al. Genome-wide association study identifies a novel breast cancer susceptibility locus at 6q25. 1. *Nature genetics.* 2009; 41:324. [PubMed: 19219042]
 19. Delahanty RJ, Beeghly-Fadiel A, Xiang YB, Long J, Cai Q, Wen W, et al. Association of Obesity-related Genetic Variants With Endometrial Cancer Risk: A Report From the Shanghai Endometrial Cancer Genetics Study. *Am J Epidemiol.* 2011
 20. Shu XO, Long J, Cai Q, Qi L, Xiang YB, Cho YS, et al. Identification of new genetic risk variants for type 2 diabetes. *PLoS Genetics.* 2010; 6:e1001127. [PubMed: 20862305]
 21. Shi J, Long J, Gao YT, Lu W, Cai Q, Wen W, et al. Evaluation of genetic susceptibility loci for obesity in Chinese women. *Am J Epidemiol.* 2010; 172:244–254. [PubMed: 20616199]
 22. Zheng W, Long J, Gao YT, Li C, Zheng Y, Xiang YB, et al. Genome-wide association study identifies a new breast cancer susceptibility locus at 6q25.1. *Nat Genet.* 2009; 41:324–328. [PubMed: 19219042]
 23. Dorjgochoo T, Shrubsole MJ, Shu XO, Lu W, Ruan Z, Zheng Y, et al. Vitamin supplement use and risk for breast cancer: the Shanghai Breast Cancer Study. *Breast Cancer Res Treat.* 2008; 111:269–278. [PubMed: 17917808]
 24. Zheng W, Chow WH, Yang G, Jin F, Rothman N, Blair A, et al. The Shanghai Women's Health Study: rationale, study design, and baseline characteristics. *Am J Epidemiol.* 2005; 162:1123–1131. [PubMed: 16236996]
 25. Xu H, Xiong DH, Xu FH, Zhang YY, Lei SF, Deng HW. Association between VDR ApaI polymorphism and hip bone mineral density can be modified by body mass index: a study on

postmenopausal Chinese women. *Acta Biochim Biophys Sin (Shanghai)*. 2005; 37:61–67.
[PubMed: 15645083]

Novelty & Impact

The direction of correlation between vitamin D and obesity is unclear. This comprehensive evaluation of genetic polymorphisms in vitamin D metabolism-related genes and obesity-related traits did not provide strong evidence to support low vitamin D levels as a cause of obesity.

Table 1

Characteristics of participants (n=6,922) included in the study

Characteristics	Healthy controls (n=2,305)	Breast cancer cases (n=2,903)	Type 2 diabetes cases (n=885)	Endometrial cancer cases (n=829)
Age, year (mean, SD)	49.6 (8.5)	50.7 (9.1)	51.3 (6.3)	54.8 (8.7)
Education, <less than middle school (%)	13.9	12.2	18.1	24.3
Calorie intake, kcal/day (mean, SD)	1,778 (444)	1,801 (451)	1,757 (425)	1,791 (458)
Did not exercise regularly (%)	69.1	67.8	67.1	70.9
Postmenopausal (%)	41.4	42.7	51.1	56.8
Weight at study enrollment, kg (mean, SD)	58.6 (8.6)	60.0 (8.8)	66.2 (9.7)	64.1 (10.4)
Height at study enrollment, cm (mean, SD)	158.4 (5.4)	158.7 (5.2)	157.3 (5.5)	160.0 (39.8)
BMI at age 20, kg/m ² (mean, SD)	19.6 (2.5)	19.6 (2.3)	19.6 (2.4)	N/A
BMI at study enrollment, kg/m ² (mean, SD)	23.4 (3.3)	23.9 (3.4)	26.7 (3.6)	25.7 (4.1)
Waist circumference, cm (mean, SD)	77.3 (8.9)	79.5 (8.9)	84.5 (8.5)	84.6 (10.1)
Hip circumference, cm (mean, SD)	95.4 (7.5)	96.7 (7.6)	100.5 (8.3)	100.5 (9.2)
Waist-hip ratio (mean, SD)	0.81 (0.06)	0.82 (0.06)	0.84 (0.05)	0.84 (0.05)
Obesity at study enrollment (%) ^a	11.5	13.5	38.1	29.4

^aObesity was defined as BMI ≥ 27.5 (kg/m²) as categorized by the World Health Organization for Asian populations

Table 2

Two of 198 SNPs were associated with body mass index and body weight among Chinese women (n=6,922)

Gene/chromosome SNP	Participants by sample set	No. of subjects	BMI (kg/m ²)		Weight (kg)	
			Per-Allele ^a effect (-estimate)	P value	Per-Allele ^b effect (-estimate)	P value
<i>CYP24A1/chr20</i> rs2248359 (position: 52224925)	All women	6,921	-0.13	0.02	-0.30	0.02
	Healthy controls	2,305	-0.10	0.33	-0.22	0.37
	Breast cancer	2,903	-0.18	0.03	-0.44	0.04
	Endometrial cancer	829	-0.06	0.75	-0.13	0.79
	Type 2 diabetes	885	-0.14	0.39	-0.39	0.33
<i>CYP2R1/chr11</i> rs10832313 (position: 14878939)	All women	6,921	-0.31	0.02	-0.79	0.01
	Healthy controls	2,305	-0.01	0.96	-0.07	0.89
	Breast cancer	2,903	-0.42	0.04	-1.10	0.02
	Endometrial cancer	829	-0.47	0.29	-1.04	0.35
	Type 2 diabetes	885	-0.49	0.18	-1.20	0.18

^aChange (-estimate) in BMI or body weight for each copy of effective allele, -estimate was adjusted for age, square of age, menopausal status, and sample set or diseases status

^b Additionally adjusted for height

Note: P values were not corrected for multiple comparison tests