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Association of the *FABP2* Ala54Thr polymorphism with type 2 diabetes, obesity, and metabolic syndrome: a population-based case-control study and a systematic meta-analysis

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ABSTRACT. Previous studies have reported associations between the functional *FABP2* Ala54Thr (rs1799883) polymorphism and type 2 diabetes mellitus (T2DM), obesity, and metabolic syndrome in different populations with conflicting results. We investigated the association between the *FABP2* Ala54Thr polymorphism and T2DM (235 cases, 431 controls), obesity (377 cases, 431 controls), and metabolic syndrome (315 cases, 323 controls) by logistic regression analysis in a Chinese study cohort recruited from Yichang, Hubei Province. We then comprehensively reviewed the association of the *FABP2* Ala54Thr polymorphism with T2DM, obesity, and metabolic syndrome via meta-analysis. The strength of association was assessed by odds ratios (ORs) with 95% confidence intervals (CIs). The *FABP2* Ala54Thr polymorphism was significantly associated with obesity (AT *vs* AA:

OR = 2.633, 95%CI = 1.065-6.663, P = 0.036; TT *vs* AA: OR = 4.160, 95%CI = 1.609-10.757, P = 0.003) and metabolic syndrome (TT *vs* AA: OR = 2.273, 95%CI = 1.242-4.156, P = 0.008) by logistic regression with adjustment for covariates. However, no significant association was found between T2DM and the *FABP2* Ala54Thr polymorphism. We identified 24 studies on T2DM (4517 cases, 5224 controls), 9 studies on obesity (949 cases, 2002 controls), and 6 studies on metabolic syndrome (2194 cases, 3282 controls) by literature search. The meta-analyses revealed significant associations for metabolic syndrome (T allele: OR = 1.179, 95%CI = 1.015-1.362, P = 0.031) and T2DM (T allele: OR = 1.160, 95%CI = 1.08-1.24, P < 0.001), but no association for obesity (T allele: OR = 1.069, 95%CI = 0.925-1.235, P = 0.367).

Key words: *FABP2*; Metabolic syndrome; Obesity; Meta-analysis; Type 2 diabetes mellitus

INTRODUCTION

Metabolic syndrome (MetS) is defined by a clustering of abdominal obesity, an increased serum concentration of triglycerides, a decreased serum concentration of high-density lipoprotein (HDL)-cholesterol, high blood pressure, and an increased fasting blood glucose level. MetS has become a global health concern over the past few decades. Individuals with MetS have a two-fold higher risk of mortality and a three-fold higher risk of experiencing a cardiovascular event, compared with those without MetS (Cheung et al., 2007). The etiology of MetS is highly complex; both genetic and environmental factors are thought to play an important role. Many genetic polymorphisms might be involved in the pathogenesis of MetS. The genes responsible for the metabolism and transport of lipids, the regulation of arterial blood pressure, the transport, regulation, and metabolism of glucose, hormonal regulation, and other factors might contribute to the development of MetS.

Type 2 diabetes mellitus (T2DM), characterized by hyperglycemia, insulin resistance, impaired insulin secretion, and increased hepatic glucose production, is caused by both hereditary factors and environmental factors such as physical inactivity, unhealthy dietary habits, and obesity. According to the latest statistics from the International Diabetes Federation (IDF), the number of diabetes patients will rise from 366 million in 2011 to 552 million by 2030 (Sanghera and Blackett, 2012). The prevalence of obesity has increased at an alarming rate worldwide over past decades. The increasing prevalence of T2DM and obesity constitutes a major public health problem of the 21st century. As components of MetS, both T2DM and obesity are under strong genetic control.

Fatty acid-binding proteins (FABPs) are members of the super family of small (14-15 kDa) intracellular lipid-binding proteins. Intestinal FABP (I-FABP or FABP2) is one of nine different FABPs identified in mammals, besides liver, heart, muscle, adipocyte, epidermal, ileal, brain, myelin, and testis FABPs. The *FABP2* gene consists of approximately 3.4 kilobases (kb) located in chromosomal region 4q28-4q31, arranged in four exons containing ~700 bp and three introns containing ~2650 bp. FABP2 consists of 131 amino acid residues and has a high content of the β-strand structure. It contains a high affinity-binding site for both saturated and unsaturated long-chain fatty acids, indicating that it might have a role in the absorption and intracellular transport of dietary long-chain fatty acids.

The most extensively studied polymorphism in the *FABP2* gene is the Ala54Thr (rs1799883) in exon 2 that results from a G to A nucleotide substitution. The Thr54 allelic frequency is 30% in most populations. The Thr-containing protein has a two-fold higher affinity for long-chain fatty acids than the Ala-containing protein (Wanby et al., 2005). The Ala54Thr polymorphism increases free fatty acid transport and triglyceride secretion *in vitro* (Yamauchi et al., 2010), which are associated with high levels of fasting insulin. Moreover, previous studies have found that *FABP2* is a candidate gene possibly implicated in the pathogenesis of T2DM, MetS, and obesity in different ethnic groups (Table 1).

In this study, we further investigated the association of the *FABP2* Ala54Thr polymorphism with T2DM, MetS, and obesity in a Han Chinese cohort recruited from Hubei Province and systematically reviewed the association between *FABP2* Ala54Thr and T2DM, MetS, and obesity through a worldwide meta-analysis.

MATERIAL AND METHODS

Study subjects

All Hubei Han Chinese subjects were recruited by the government-funded physical examination project from Yichang, Hubei Province (Dehwah et al., 2010). A total of 1173 individuals included 377 obese patients (134 males, 243 females, age 47.85 ± 9.23 years) and 431 non-obese people (220 males, 211 females, age 62.15 ± 10.39 years); 315 MetS patients (88 males, 227 females, age 52.15 ± 10.35 years) and 323 controls (171 males, 152 females, age 58.34 ± 10.63 years); and 235 T2DM patients (107 males, 128 females, age 54.09 ± 10.40 years) and 431 controls (220 males, 211 females, age 62.38 ± 10.45 years). The weight, height, and waist and hip circumferences were measured in all individuals. Waist to hip ratio was calculated as waist (cm)/hip (cm). Measured clinical parameters included fasting blood glucose (FBG), 2-h postprandial blood glucose (PBG), systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, triacylglycerol, HDL-cholesterol, LDL-cholesterol, and fasting insulin (Table 2).

Body mass index (BMI) was calculated according to the standard ratio of weight (kg) to height squared (m^2).We set the cutoff point for obesity at a BMI $\geq$ 25 kg/m^2 and control subjects had a BMI < 25 kg/m^2. According to the criteria of the IDF (Alberti et al., 2005), MetS was confirmed when three or more of the following five criteria were satisfied: i) a BMI $\geq$ 25 kg/m^2; ii) a serum triglyceride concentration $\geq$ 1.65 mM (150 mg/dL) or drug treatment for elevated triglycerides; iii) a serum HDL-cholesterol concentration < 1.04 mM (40 mg/dL) for men or < 1.30 mM (50 mg/dL) for women, or drug treatment for reduced HDL-cholesterol; iv) an SBP $\geq$ 130 mmHg, a DBP $\geq$ 85 mmHg, or drug treatment for hypertension; and v) a fasting plasma glucose concentration $\geq$ 5.50 mM (100 mg/dL) or drug treatment for elevated glucose. Control subjects did not meet any IDF criteria for MetS. T2DM was defined according to the 1997 American Diabetes Association (ADA) criteria: FBG $\geq$ 7.0 mM (126 mg/dL) and 2-h PBG $\geq$ 11.1 mM (200 mg/dL). The subjects with a family history of maturity-onset diabetes of the young, maternally inherited diabetes, gestational diabetes, mitochondrial diabetes, type 1 diabetes, and other obvious chronic diseases, such as hypertension, coronary heart disease, cancer, and so on were excluded. Healthy controls all had FBG < 6.1 mM (110 mg/dL) and 2-h PBG < 7.8 mM; no family history of T2DM in first-degree relatives; normal blood pressure; normal liver and kidney function; and no chronic heart or lung disease. The survey and sampling received consent, and informed agreements were signed by the subjects themselves.

Table 1. Characteristics of case-control studies included in the meta-analysis.

Diseases	Study	Population	Group	Diagnostic criteria	Gender (M/F)	Age	BMI (kg/m^2)	Sample size	SNP Ala54Thr AA/AT/TT	T allele frequency (%)	P
	Vimaleswaran et al. (2006)	Indians	Case	ATPIII	-	-	-	600	275/259/66	32.6	**0.010**
			Control		-	-	-	900	476/363/61	26.9	
	Miller et al. (2007)	Indians	Case	ATPIII	84/38	54.5 ± 13.1	29.9 ± 5.5	122	65/48/9	27	0.919
			Control		84/38	54.5 ± 13.3	25.5 ± 4.4	122	69/41/12	26.6	
	Csép et al. (2007)	Romanians	Case	IDF	-	-	31.79 ± 6.75	144	57/71/16	35.8	0.108
			Control		-	-	25.19 ± 4.24	73	35/35/3	28.1	
MetS	Yamada et al. (2008)	Japanese	Case	AHA/NHLBI	210/131	67.0 ± 9.7	24.5 ± 3.5	341	114/140/57	39.7	**0.002**
			Control		473/498	68.2 ± 9.2	25.3 ± 3.2	971	448/405/118	32.9	
	Oguri et al. (2009)	Japanese	Case	AHA/NHLBI	597/176	64.8 ± 10.0	25.3 ± 8.0	773	301/356/116	39.4	**0.001**
			Control		761/353	68.3 ± 8.9	25.4 ± 3.2	1114	515/465/134	32.9	
	Turkovic et al. (2012)	Croatian descent	Case	IDF	95/119	77.6 ± 4.2	29.4 ± 3.44	214	131/70/13	22.4	**0.027**
			Control		45/57	78.8 ± 4.7	26.6 ± 3.7	102	60/36/16	33.3	
	Our study (2014)	Chinese Han	Case	IDF	88/227	52.15 ± 10.35	28.83 ± 2.75	315	160/116/39	30.8	0.677
			Control		171/152	58.34 ± 10.63	21.93 ± 3.33	323	156/142/25	29.7	
	Lei et al. (1999)	African-Americans	Case	WHO	-	53.3 ± 5.7	40.63 ± 4.91	260	159/84/17	22.7	0.946
			Control		-	52.9 ± 5.8	26.99 ± 4.10	992	587/357/48	22.8	
	Ito et al. (1999)	Chile Mapuche	Case	WHO	-	-	-	30	15/12/3	30	0.249
			Control		-	-	-	58	19/33/6	38.8	
	Carlsson et al. (2000)	Swedes	Case	WHO	15/44	40.5 ± 12.0	41.7 ± 5	59	31/23/5	28	0.710
			Control		28/31	58.5 ± 12/2	23.6 ± 2.6	59	30/21/7	30.2	
	He (2002)	Samoans	Case	WHO	13/81	41.17 ± 7.82	44.04 ± 4.85	94	68/16/5	14.6	0.598
			Control		47/40	36.94 ± 8.43	23.73 ± 2.00	87	61/18/5	16.7	
	Duarte et al. (2003)	Tongan population	Case	WHO	-	-	-	100	53/39/8	27.5	0.581
			Control		-	-	-	100	52/36/12	30	
	Albala et al. (2004)	Chileans	Case	WHO	0/33	38.3 ± 8.3	37.2 ± 5.6	33	8/19/6	47	0.08
			Control		0/30	36.4 ± 1.2	22.5 ± 0.28	30	15/11/4	31.7	
Obesity	Takakura et al. (2005)	Japanese	Case	WHO	0/80	58.4 ± 9.6	32.9 ± 5.8	80	33/32/15	38.8	0.21
			Control		0/146	58.2 ± 10.2	21.7 ± 2.3	146	64/68/14	32.9	
	Tavridou et al. (2009)	Caucasians	Case	WHO	80/89	67.6 ± 9.2	33.9 ± 3.5	172	74/78/20	34.3	**0.005**
			Control		157/94	68.7 ± 10.1	26.4 ± 37.2	258	144/97/17	25.4	
	Wang et al. (2011)	Chinese Han	Case	WHO	82/39	55 ± 10	>25	121	62/49/10	28.5	0.921
			Control		142/130	53 ± 11	<25	272	137/113/22	28.9	
	Our study (2014)	Chinese Han	Case	WHO	134/243	47.85 ± 9.23	29.79 ± 1.45	377	183/152/42	31.3	0.848
			Control		220/221	62.15 ± 10.39	21.59 ± 2.99	431	202/192/37	30.9	
	Yamada et al. (1997)	Japanese	Case	WHO	32/0	50.5 ± 8.8	24.4 ± 3.0	32	14/13/5	36	0.912
			Control		237/0	50.5 ± 8.8	24.4 ± 3.0	237	96/115/26	35	
T2DM	Xiang et al. (1998)	Chinese Han	Case	WHO	41/38	55 ± 10	26.7 ± 3.30	79	36/36/7	31.6	0.859
			Control		44/42	54 ± 9	26.4 ± 4.01	86	39/38/9	32.5	
	Huang et al. (1999)	Chinese Han	Case	WHO	-	58 ± 10	-	146	51/72/23	40.4	0.068
			Control		29/31	54 ± 6	-	60	29/25/6	30.8	
	Xiang et al. (1999)	Chinese Han	Case	WHO	33/28	55.8 ± 10.1	26.7 ± 3.1	61	25/30/6	34.4	0.463
			Control		54/62	52.3 ± 11.2	26.5 ± 4.1	116	54/53/9	30.6	

Continued on next page

Table 1. Continued.

Diseases	Study	Population	Group	Diagnostic criteria	Gender (M/F)	Age	BMI (kg/m^2)	Sample size	SNP Ala54Thr AA/AT/TT	T allele frequency (%)	P
	Ito et al. (1999)	Japanese	Case	WHO	111/39	56.7 ± 11.0	-	150	51/76/23	40.7	0.248
			Control		115/32	51.8 ± 7.8	-	147	63/62/22	36.1	
	Hayakawa et al. (1999)	Japanese	Case	WHO	-	51.5 ± 7.1	-	15	6/5/4	43.3	0.336
			Control		-	51.5 ± 7.1	-	205	91/86/28	34.6	
	Boullu-Sanchis et al. (1999)	Guadeloupe Indians	Case	WHO	50/39	53.1 ± 9.8	28.1 ± 4.40	89	34/33/22	43.3	**0.01**
			Control		56/44	48.9 ± 9.6	25.4 ± 4.30	100	53/33/14	30.5	
	Kim et al. (2001)	Koreans	Case	WHO	-	44 ± 6	-	76	30/38/8	35.5	0.67
			Control		-	25 ± 3	-	96	44/40/12	33.3	
	Wang et al. (2001)	Chinese Han	Case	ADA	44/58	54.9 ± 8.3	-	102	53/38/11	29.4	0.829
			Control		58/44	55.6 ± 9.6	-	102	49/44/9	30.4	
	Liu and Lu (2004)	Chinese Han	Case	WHO	-	44.04 ± 0.69	25.26 ± 0.28	258	116/118/24	32.2	0.824
			Control		-	45.18 ± 0.32	23.76 ± 0.16	308	135/144/29	32.8	
	Xiong et al. (2005)	Chinese Han	Case	WHO	37/28	56.8 ± 11.8	-	65	37/24/4	24.6	0.657
			Control		16/14	55.5 ± 10.1	-	30	17/13/0	21.7	
	Vimaleswaran et al. (2006)	South Indians	Case	WHO	-	51 ± 12	25.1 ± 4.0	773	383/317/73	29.9	**0.041**
			Control		-	43 ± 14	23.4 ± 4.6	899	482/353/64	26.75	
	Chang et al. (2007)	Chinese Han	Case	WHO	64/72	56 ± 13	27.39 ± 4.4	136	72/44/20	30.8	0.436
			Control		52/60	51 ± 12	24.72 ± 3.1	112	61/40/11	27.7	
	Li et al. (2010)	Chinese Han	Case	WHO	-	55.7 ± 9.6	-	300	121/133/46	37.5	**0.00**
			Control		55/25	53.8 ± 9.7	-	80	49/26/5	22.5	
	Shi et al. (2012)	Chinese Han	Case	ADA	58/59	61.44 ± 9.69	23.28 ± 1.82	117	32/64/21	45.3	**0.029**
			Control		54/54	61.28 ± 11.49	23.28 ± 1.82	108	46/48/14	35.2	
	Our study (2014)	Chinese Han	Case	WHO	107/128	54.09 ± 10.40	24.70 ± 4.17	235	120/93/22	29.14	0.516
			Control		220/211	62.38 ± 10.45	21.04 ± 2.86	431	202/192/37	30.86	
	Raza et al. (2014)	North Indians	Case	WHO	129/61	41.29 ± 11.39	26.01 ± 4.12	190	35/127/28	48.2	0.671
			Control		60/50	40.03 ± 10.28	23.99 ± 2.36	110	25/68/17	46.4	
	Alharbi et al. (2014)	Saudis	Case	WHO	251/187	53.5 ± 10.78	29.9 ± 5.89	438	225/174/39	28.8	0.064
			Control		242/218	45.99 ± 7.77	29.22 ± 5.58	460	260/171/29	25	
	Lei et al. (1999)	African-Americans	Case	ADA	-	54.6 ± 6.0	30.8 ± 5.29	321	190/119/12	22.3	0.769
			Control		-	52.8 ± 5.8	26.9 ± 4.10	992	587/357/48	22.8	
	Carlsson et al. (2000)	Swedes	Case	WHO	200/199	60.1 ± 12.3	27.8 ± 4.7	399	215/160/24	26.06	0.409
			Control		28/31	58.5 ± 12.2	23.6 ± 2.6	59	31/21/7	29.66	
	Tavridou et al. (2009)	Caucasians	Cases	WHO	119/123	67.9 ± 8.8	30.5 ± 4.9	242	114/104/24	31.4	0.072
			Control		122/66	70.3 ± 13.9	28.1 ± 4.1	188	104/71/13	25.8	
	Bu et al. (2011)	non-Hispanic Whites	Case	WHO	-	61.8 ± 10.9	30.9 ± 5.3	99	62/31/6	21.7	0.620
			Control		-	37.1 ± 15.8	-	99	65/29/5	19.7	
	Bu et al. (2011)	Hispanic Americans	Case	WHO	-	57.5 ± 10.8	30.5 ± 6.5	97	45/42/10	32	**0.03**
			Control		-	30.5 ± 13.2	-	99	61/32/6	22.2	
	Bu et al. (2011)	African-Americans	Case	WHO	-	54.8 ± 11.1	33.0 ± 8.3	97	56/34/7	24.7	0.600
			Control		-	29.2 ± 9.4	-	100	61/33/6	22.5	

BMI = body mass index; SNP = single nucleotide polymorphism; MetS = metabolic syndrome; ADPIII = Adult Treatment Panel III guidelines; IDF = International Diabetes Federation; AHA/NHLBI = American Heart Association/National Heart, Lung, and Blood Institute; WHO = World Health Organization; ADA = American Diabetes Association; T2DM = type 2 diabetes mellitus; P values <0.05 are shown in bold.

Table 2. Clinical characteristic of the study subjects.

Characteristics	Obesity			MetS			T2DM		
	Case	Control	P value	Case	Control	P value	Case	Control	P value
Gender (M/F)	134/243	220/211	<0.001	88/227	171/152	<0.001	107/128	220/211	0.149
Age (years)	47.85 ± 9.23	62.15 ± 10.39	<0.001	52.15 ± 10.35	58.34 ± 10.63	<0.001	54.09 ± 10.40	62.38 ± 10.45	<0.001
Height (cm)	156.32 ± 8.59	154.87 ± 8.01	0.011	155.96 ± 7.99	155.79 ± 7.88	0.778	156.48 ± 8.13	154.78 ± 8.101	0.010
Weight (kg)	74.35 ± 7.75	51.87 ± 8.55	<0.001	71.96 ± 11.79	53.31 ± 10.44	<0.001	60.70 ± 12.30	51.58 ± 8.524	<0.001
Waist circumference (cm)	90.46 ± 8.15	71.56 ± 8.19	<0.001	91.77 ± 6.54	71.03 ± 7.74	<0.001	80.99 ± 10.25	71.54 ± 7.841	<0.001
Hip circumference (cm)	101.54 ± 6.12	87.38 ± 6.23	<0.001	101.39 ± 5.79	87.33 ± 6.17	<0.001	92.99 ± 7.54	87.27 ± 5.956	<0.001
SBP (mmHg)	133.55 ± 21.58	116.95 ± 14.41	<0.001	145.69 ± 24.44	113.24 ± 10.80	<0.001	137.44 ± 24.89	117.10 ± 15.34	<0.001
DBP (mmHg)	86.15 ± 12.02	74.01 ± 8.95	<0.001	92.94 ± 13.12	74.49 ± 7.74	<0.001	85.78 ± 12.96	73.83 ± 9.39	<0.001
BMI (kg/m^2)	29.79 ± 1.45	21.59 ± 2.99	<0.001	28.83 ± 2.75	21.93 ± 3.33	<0.001	24.70 ± 4.17	21.54 ± 2.86	<0.001
Total cholesterol (mM)	5.31 ± 1.01	4.99 ± 0.92	<0.001	5.01 ± 1.76	4.96 ± 0.92	0.845	5.55 ± 1.24	5.84 ± 1.74	0.29
Triacylglycerol (mM)	1.93 ± 1.25	1.10 ± 0.53	<0.001	2.92 ± 1.96	1.01 ± 0.31	<0.001	2.33 ± 2.15	1.08 ± 0.51	<0.001
HDL-cholesterol (mM)	1.49 ± 0.54	1.71 ± 0.42	<0.001	1.44 ± 0.45	1.74 ± 0.41	<0.001	1.57 ± 0.51	1.73 ± 0.42	<0.001
LDL-cholesterol (mM)	2.37 ± 0.59	2.04 ± 0.62	<0.001	2.50 ± 0.61	2.07 ± 0.67	<0.001	2.71 ± 2.73	2.13 ± 2.17	0.003
Fasting insulin (mU/mL)	11.80 ± 7.49	6.64 ± 4.91	<0.001	13.29 ± 10.49	7.02 ± 6.42	<0.001	11.56 ± 11.13	7.57 ± 15.59	<0.001

MetS = metabolic syndrome; T2DM = type 2 diabetes mellitus; SBP = systolic blood pressure; DBP = diastolic blood pressure; BMI = body mass index; HDL = high-density lipoprotein; LDL = low density lipoprotein.

Genotyping

Genomic DNA was obtained from whole blood leukocytes using the standard phenol/chloroform method. Detection of the *FABP2* Ala54Thr polymorphism was carried out using the polymerase chain reaction (PCR)-restriction fragment length polymorphism technique with forward primers: 5'-CTACCGAGTTTTCTTCCCACC-3'; and reverse primers: 5'-AATT AAACCATCCAATGAAATAGAGC-3'. The PCR reaction mixture consisted of 0.5 µL of each primer (10 µM) in a total volume of 25 µL containing 100 ng DNA template (50 ng/µL), 0.5 µL *Taq* DNA polymerase (2 U/µL), 2.5 µL 10X PCR buffer (Mg^{2+} Plus), and 0.5 µL dNTP mixture. The PCR conditions were as follows. Initial denaturation at 95°C for 5 min was followed by 40 cycles of PCR under the following conditions: denaturation at 95°C for 1 min, annealing at 54°C for 1 min, and extension at 72°C for 30 s. A final extension step at 72°C for 10 min followed the last PCR cycle. The PCR product (6 µL) was digested by 12 U *Hha*I restriction enzyme at 37°C overnight. The AA genotype is cleaved by *Hha*I into 207 bp and 169-bp DNA fragments. The TT genotype lacks a *Hha*I restriction site and migrates as one 376-bp DNA fragment. All digestion products were resolved on 3% agarose gel and visualized using ethidium bromide.

Association analysis

We used χ^2 analysis with exact probability to test departure from the Hardy-Weinberg equilibrium (HWE) for the genotype distribution in the cases and controls before association analysis. All continuous variables are reported as means ± standard deviation. The Student *t*-test was used to compare the difference in continuous variables. The genotype-disease association analyses were performed by logistic regression analysis with or without the adjustment for covariates. A P value less than 0.05 was considered to be statistically significant. Statistical analyses were performed using the SPSS software (version 11.5) for Windows.

Literature and search strategy

A computerized literature search was conducted to identify the relevant available studies published in English or Chinese from four databases: PubMed, the China National Knowledge Infrastructure, the Database of Chinese Scientific and Technical Periodicals (VIP), and the Wanfang database. All possible studies were identified using the following key words: “FABP2” or “I-FABP”; “obesity”; “gene polymorphism”; “metabolic syndrome” or “MetS”; and “type 2 diabetes”, or “type 2 diabetes mellitus,” or “T2DM”, or “T2D”. The references of all publications identified were searched for additional studies. The PubMed option ‘‘Related Articles’’ was used to search for potentially relevant papers. Reference lists in retrieved articles were also screened. Without any language restriction, we only selected published manuscripts (including their online supporting materials). Studies included in the meta-analysis were required to meet all the following criteria: first, the association of the *FABP2* Ala54Thr polymorphism with MetS, T2DM, or obesity was assessed; second, each study had case-control groups and had been published as an original study; third, odds ratios (ORs) with 95% confidence intervals (CIs), or genotype frequency among case and control groups, were provided; fourth, if more than one article was published using the same case series, only the study with the largest sample size or the most recent study was selected. The following information was extracted:

name of the first author, year of publication, ethnicity of the study population, sample size, numbers of cases and controls, gender and age of enrolled subjects, genotype distribution and minor allele frequency in cases and controls, and P values for allele frequency (Figure 1). The literature search was updated on June 1, 2013.

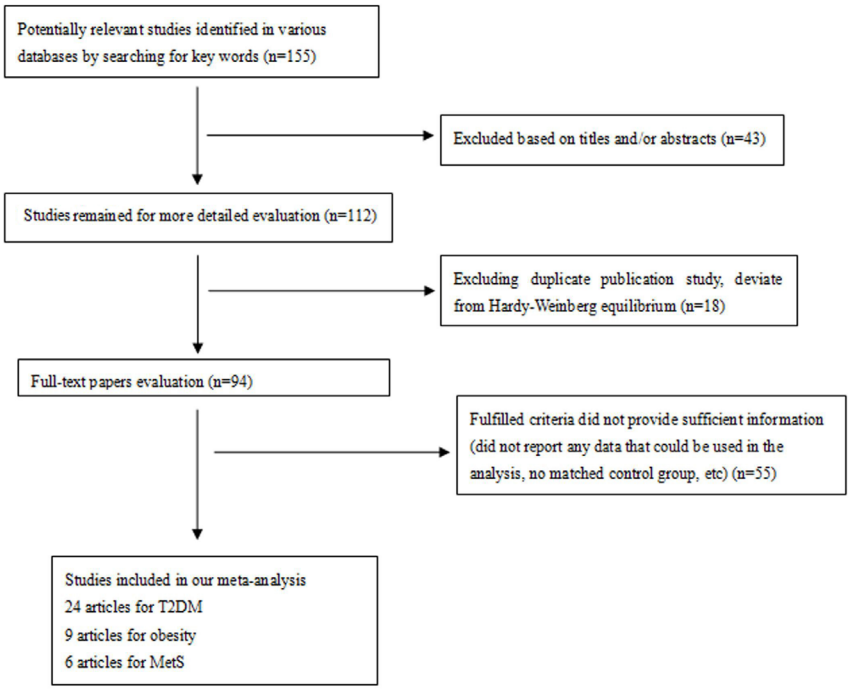

Figure 1. Search strategy for the publications included in our study.

Meta-analysis

The associations of the *FABP2* Ala54Thr polymorphism with MetS, T2DM, and obesity were estimated by calculating pooled ORs and 95%CIs using the Stata 10.0 software. The ORs were calculated using 2 x 2 contingency tables for each study. Heterogeneity among studies was assessed using the χ^2-based Q-test as well as the inconsistency index (I^2) statistic. Probabilities less than 0.05 were judged significant except for the I^2 statistic. Sensitivity analysis was conducted by removing one study at a time and calculating the pooled ORs for the remaining studies. The Z-test was used to calculate the P value of the overall effect for the meta-analysis. Pooled ORs were computed by the fixed-effects method of Mantel-Haenszel (Peto method) for data combined under no heterogeneity between studies ($P > 0.1$). If significant heterogeneity exists between studies ($P \leq 0.1$), then the random-effects model of DerSimonian and Laird is appropriate for combined data.

Publication bias was checked by funnel plots and Egger regression analysis. Funnel plots are asymmetric when there is publication bias. The Egger test was performed to measure the funnel plot asymmetry. A significance level of 0.05 was regarded as an indication of potential publication bias.

RESULTS

Clinical characteristics of the enrolled subjects

The clinical characteristics of the subjects enrolled are presented in Table 2. Independent *t*-test analysis showed that the weight, waist circumference, hip circumference, SBP, DBP, BMI, triacylglycerol, and fasting insulin were consistently higher in obesity, T2DM, and MetS patients than in the control group ($P < 0.01$). The height was significantly higher in T2DM and obesity patients than in the control group, and total cholesterol in obesity patients was higher than in the controls.

Association of the *FABP2* Ala54Thr polymorphism with T2DM, obesity, and MetS in Hubei Han Chinese

Genotypic distributions of the *FABP2* Ala54Thr polymorphism were in HWE for obesity, MetS, and T2DM patients and controls. The logistic regression revealed significant associations between the *FABP2* Ala54Thr polymorphism and MetS with adjustment for gender and age (TT *vs* AA: OR = 2.273, 95%CI = 1.242-4.159, P = 0.008) and without adjustment (TT *vs* AA: OR = 1.910, 95%CI = 1.092-3.339, P = 0.023) (Table 3)

Table 3. Logistic regression analysis of *FABP2* Ala54Thr polymorphism and metabolic syndrome (MetS), obesity, and type 2 diabetes mellitus (T2DM).

Diseases	Genotype	Group		Unadjusted			Adjusted		
		Case	Control	OR	95%CI	P	OR	95%CI	P
MetS	AA	160	156	1.00	-	-	1.00	-	-
	AT	116	142	1.521	0.879-2.632	0.134	1.647	0.908-2.988	0.100
	TT	39	25	1.910	1.092-3.339	**0.023**	2.273	1.242-4.159	**0.008**
Obesity	AA	183	202	1.00	-	-	1.00	-	-
	AT	152	192	1.253	0.771-2.035	0.362	2.663	1.065-6.663	**0.036**
	TT	42	37	1.434	0.878-2.342	0.150	4.160	1.609-10.757	**0.003**
T2DM	AA	120	202	1.00	-	-	1.00	-	-
	AT	93	192	1.001	0.564-1.777	0.998	0.920	0.426-1.984	0.831
	TT	22	37	1.228	0.685-2.199	0.491	1.211	0.553-2.652	0.631

OR = odds ratio; CI = confidence interval; P values <0.05 are shown in bold.

Although no significant association was found between obesity and *FABP2* Ala54Thr polymorphism by logistic regression without the adjustment for covariates, logistic regression with the adjustment for gender, age, blood pressure, and fasting insulin revealed significant associations (AT *vs* AA: OR = 2.663, 95%CI = 1.065-6.663, P = 0.036; TT *vs* AA: OR = 4.160, 95%CI = 1.609-10.757, P = 0.003) (Table 3). For T2DM, the *FABP2* Ala54Thr polymorphism was not associated with T2DM by logistic regression with or without adjustment for gender, age, blood pressure, weight, and BMI.

Meta-analysis

For T2DM, 24 studies (Table 1) with complete allele and genotype frequency information were used in our final meta-analysis. Figure 2A shows the forest plot of risk allele OR

of individual studies and meta-analysis for association between the Ala54Thr polymorphism and T2DM in a total of 4517 T2DM patients and 5224 healthy controls in global populations. Eighteen studies presented a trend of elevated OR for the allele T. Six studies showed a trend in the opposite direction. Because there was no heterogeneity between studies (P = 0.134, I^2 = 24.7%), a fixed effect model was performed and generated a pooled OR of 1.17 (95%CI = 1.07-1.27, P < 0.001) for the T allele (Figure 2A).

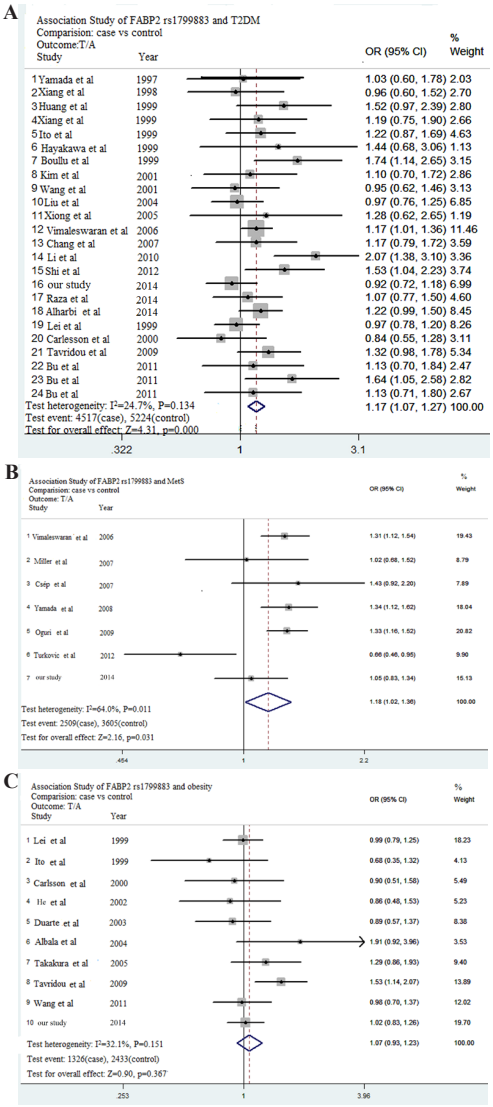

Figure 2. Forest plots of meta-analysis of the association of the *FABP2* rs1799883 polymorphism with type 2 diabetes (**A**), metabolic syndrome (**B**), and obesity (**C**) in the global population. Estimation of odds ratios (ORs) and 95% confidence intervals (CIs) in each study are displayed as closed squares and horizontal lines, respectively. The size of the black squares reflects the weight of the study in the meta-analysis. The diamonds represent the combined OR, calculated using a random or fixed-effect model, with its 95%CI.

Besides our case-control study, we identified 6 association studies with 5476 individuals between the *FABP2* Ala54Thr polymorphism and MetS (Table 1). Five studies showed a trend of elevated OR for the allele T (Vimaleswaran et al., 2006; Miller et al., 2007; Csép et al., 2007; Yamada et al., 2008; Oguri et al., 2009). Only one study showed a trend in the opposite direction (Turkovic et al., 2012). A significant association was found for the T allele (OR = 1.18, 95%CI = 1.02-1.36, P = 0.031, heterogeneity, P = 0.011, I^2 = 64.0%) (Figure 2B).

We identified 9 studies (2951 individuals) that considered the association between the *FABP2* Ala54Thr polymorphism and obesity. As shown in Figure 2C, four studies had a trend of elevated OR for the allele T (Albala et al., 2004; Takakura et al., 2005; Tavridou et al., 2009), and six studies showed a trend in the opposite direction (Lei et al., 1999; Ito et al., 1999; Carlsson et al., 2000; He, 2002; Duarte et al., 2003; Wang et al., 2011). No significant association was found between the *FABP2* Ala54Thr polymorphism and obesity (Figure 2C).

Sensitivity analysis

A sensitivity analysis was conducted by removing one study at a time and calculating the pooled ORs for the remaining studies. This analysis showed that none of the individual studies influenced the pooled ORs, which ranged from 1.29 (95%CI = 1.08-1.55) to 1.41 (95%CI = 1.19-1.69) for T2DM and from 1.009 (95%CI = 0.897-1.135) to 1.089 (95%CI = 0.945-1.256) for obesity, indicating that the results of the meta-analysis were reliable and stable. However, the results of the meta-analysis for MetS were not stable, being more significant (P < 0.001, OR = 1.281, 95%CI = 1.182-1.389) after removing Turkovic's study, and non-significant after excluding studies by Vimaleswaran et al. (2006), Csép et al. (2007), Yamada et al. (2008), or the one by Mitsutoshi et al. (2007).

Heterogeneity analysis

A significant heterogeneity was observed for MetS (P = 0.011, I^2 = 64.0%). Meta-regression analysis showed that the age in case groups and control groups contributed to the heterogeneity. The inconsistency index I^2 decreased from 64.0% to 0.0% after removing Turkovic's study that had the highest age in case groups and control groups, and the lowest T allele frequency of 0.224 in control groups, indicating that Turkovic's study was responsible for the heterogeneity in the mixed populations.

Publication bias

Begg's funnel plots were generated to assess publication bias. The Egger test was performed to statistically evaluate funnel plot symmetry. Neither the Begg test nor the Egger test results suggested publication bias for the association of the *FABP2* A45T polymorphism and the risk of obesity, MetS, and T2DM (data not shown).

DISCUSSION

The *FABP2* Ala54Thr polymorphism has previously been associated with T2DM, obesity, and MetS with conflicting results (Table 1). Reasons for the lack of consistency across studies included small sample sizes, ethnic differences, and research methodologies. Meta-

analysis can provide more reliable results than a single study by combining the results from different studies and producing a single estimate of the major effect with enhanced statistical power. In the current study, we examined the association of the functional Ala54Thr polymorphism in the *FABP2* gene with T2DM, obesity, and MetS risk in Hubei Han Chinese, and performed a systematical review across different populations by meta-analysis.

For T2DM, no association was found in our Hubei Han Chinese. However, meta-analyses suggested a strong association between the *FABP2* Ala54Thr polymorphism and risk of T2DM in the global populations (OR = 1.16, 95%CI = 1.08-1.24, P < 0.001). Unlike our meta-analysis on risk of T2DM, Zhao et al. (2010) previously performed a meta-analysis of the *FABP2* Ala54Thr polymorphism with insulin resistance and blood glucose in 31 studies with 13,451 subjects. The Thr54 allele is weakly associated with a higher degree of insulin resistance, a higher level of fasting insulin, and a higher level of 2-h blood glucose. Therefore, both meta-analyses with different methods supported the association between the *FABP2* Ala54Thr polymorphism and T2DM. Because the Thr54 variant contributes to the excessive absorption of fatty acids, skeletal muscles preferentially use fatty acids for energy rather than glucose, leading to increased glucose levels (Chiu et al., 2001).

Our meta-analyses showed no evidence that the *FABP2* Ala54Thr polymorphism is associated with obesity in overall populations. Previously, Zhao et al. (2011) performed meta-analyses of 27 studies with 10,974 subjects on the association between the *FABP2* Ala54Thr polymorphism and BMI; their analyses did not support the association. It is worth noting that although no significant association was found between obesity and the *FABP2* Ala54Thr polymorphism by logistic regression without the adjustment for covariates, logistic regression with the adjustment for the gender, age, blood pressure, and fasting insulin revealed significant associations (AT *vs* AA: OR = 2.633, 95%CI = 1.065-6.663, P = 0.036; TT *vs* AA: OR = 4.160, 95%CI = 1.609-10.757, P = 0.003) in our Han Chinese study cohort. Therefore, the interactions between the *FABP2* Ala54Thr polymorphism and environmental factors/different polymorphic loci might modulate BMI.

For MetS, we conducted the first association study between the *FABP2* Ala54Thr polymorphism and MetS in the Chinese Han population, and a significant association was observed for TT *vs* AA with adjustment for gender and age (OR = 2.273, 95%CI = 1.242-4.159, P = 0.008). Six small studies previously conducted in different populations examined the Ala54Thr polymorphism in relation to MetS with inconsistent results. Our meta-analysis supports the association between the *FABP2* Ala54Thr polymorphism and MetS. The Thr54 allele may increase the risk of MetS (OR = 1.176, 95%CI = 1.015-1.362, P = 0.031). To the best of our knowledge, this study represents the first meta-analysis between polymorphisms in the *FABP2* gene and MetS. Therefore, both our results and the meta-analyses across different populations throughout the world support the association of the *FABP2* Ala54Thr polymorphism with MetS risk.

Our meta-analysis revealed significant between-study heterogeneity only for MetS. The between-study heterogeneity may have arisen for one of the following reasons. First, different diagnostic criteria for MetS: IDF (Csép et al., 2007; Turkovic et al., 2012), American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) (Yamada et al., 2008; Oguri et al., 2009); and Adult Treatment Panel III guidelines (ATPIII) (Vimaleswaran et al., 2006; Miller et al., 2007). Second, ethnicity differences; the T allele frequencies of control-subject Croatians, Indians, Romanians, Han Chinese, and Japanese were 0.224, 0.269, 0.281, 0.297, and 0.329, respectively. Third, selection bias; the differences in age and gender distributions among the studies included and the difference in sample content might also contribute

to the heterogeneity. The age of the control subjects ranged from our 52.1 to 78.8 (Turkovic et al., 2012), and sample sizes ranged from 73 (Yamada et al., 2008) to 1114 (Oguri et al., 2009).

Our study has some limitations. First, the sample size was comparatively small and had insufficient statistical power to detect the association. Second, the most common publication bias was caused by a preference for publishing positive, rather than negative, results. Third, since we were not able to obtain the original data, further evaluation of potential interactions, such as the effects of gene-gene and gene-environment interactions were not considered in our current study. Fourth, the present meta-analysis was based primarily on unadjusted effect estimates and the confounding factors (age, gender, etc.) were not controlled for, all of which could have influenced the relationship between the *FABP2* Ala54Thr polymorphism and the risk of T2DM, obesity and MetS.

To conclude, the results from our meta-analyses demonstrate the associations between the *FABP2* Ala54Thr polymorphism and T2DM and MetS in global populations.

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