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Meta-analyses between 18 candidate genetic markers and overweight/obesity

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Abstract

Aims: The goal of our study is to investigate the associations between 18 candidate genetic markers and overweight/obesity.

Methods: A total of 72 eligible articles were retrieved from literature databases including PubMed, Embase, SpringerLink, Web of Science, Chinese National Knowledge Infrastructure (CNKI), and Wanfang. Meta-analyses of 18 genetic markers among 56,738 controls and 48,148 overweight/obese persons were done by Review Manager 5.0.

Results: Our results showed that *SH2B1* rs7498665 polymorphism was significantly associated with the risk of overweight/obesity (overall odds ratio (OR) = 1.21, 95% confidence interval (CI) = 1.09-1.34, P = 0.0004). Increased risk of overweight/obesity was also observed in *FAIM2* rs7138803 polymorphism (overall OR = 1.11, 95% CI = 1.01-1.22, P = 0.04).

Conclusion: Our meta-analyses have shown the important role of 2 polymorphisms (*SH2B1* rs7498665 and *FAIM2* rs7138803) in the development of overweight/obesity. This study highlighted the importance of above two candidate genes (*SH2B1* and *FAIM2*) in the risk of overweight/obesity.

Virtual slides: The virtual slide(s) for this article can be found here: <http://www.diagnosticpathology.diagnomx.eu/vs/2785487401176182>.

Keywords: *SH2B1*, *FAIM2*, Polymorphism, Overweight, Obesity, Meta-analysis

Introduction

Overweight/obesity as a metabolic disorder is closely associated with diabetes mellitus and cardiovascular disease, which are chronic diseases influencing the average life expectancy [1,2]. In 2008, world health organization (WHO) has reported that a large portion of adults (>20 yr) were overweight (35%) and obese (12%) [3]. The overweight/obesity will become an epidemic [4] and cause a huge economic burden of society [4] in the near future.

The occurrence and the development of obesity are influenced by both environmental and genetic factors [5,6]. Environmental factors, such as poor nutritional state and a lack of physical exercise, have an impact on the development of overweight/obesity [7,8] through the epigenetic modifications such as gene methylation [9]. Genetic polymorphisms can confer the susceptibility of overweight/obesity and obesity-related morbidities [10]. Recent genome-wide association studies (GWAS) have identified a handful of candidate genetic markers to the risk of overweight/obesity [11].

In the present study, we performed a systematic search for eligible studies in the meta-analyses. Our results identified 18 polymorphisms among 16 genes that were all the candidate genes of obesity. Among these genes, *GNB3* encodes $\beta 3$ -subunit protein which is involved in the process of hypertension and obesity [12]. *MTHFR* gene encodes methylenetetrahydrofolate reductase that

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Table 1 Characteristics of 17 single nucleotide polymorphisms

Gene	SNP	Year	Author	Race	Cases/ Controls (n)	Allele 1 (Case/Controls, n)	Allele 2 (Case/Controls, n)	Model selected	Heterogeneity (I ²)%	P value	Odds ratio (95% confidence interval)
<i>GNB3</i>	rs5443 (C/T)	1999	Siffert W	Caucasian	92/207	108/392	76/122	Fixed	42	0.47	1.04 (0.93-1.16)
		1999	Siffert W	Asian Chinese	186/832	166/886	206/778				
		1999	Siffert W	African	127/607	34/219	220/995				
		2000	Siffert W	Caucasian	207/92	292/108	122/76				
		2001	Hinney A	Caucasian	491/330	695/442	287/218				
		2001	Benjafield AV	Caucasian	92/188	133/284	51/92				
		2001	Ohshiro Y	Asian Japanese	208/150	215/148	201/152				
		2004	Suwazono Y	Asian Japanese	505/2120	517/2177	493/2063				
		2008	Wang X	Asian Chinese	129/270	442/285	376/255				
<i>MTHFR</i>	rs1801133 (C/T)	2007	Terruzzi I	Caucasian	84/52	90/61	78/43	Fixed	0	0.59	1.05 (0.87-1.27)
		2010	Tavakkoly Bazzaz J	Asian Iranian	74/207	109/306	39/108				
		2012	Yin RX	Asian Chinese	751/978	1049/1383	453/573				
<i>CNR1</i>	rs806381 (A/G)	2008	Benzinou M	Caucasian	839/1726	1163/2362	515/1090	Fixed	0	0.5	1.04 (0.93-1.17)
		2008	Jaeger JP	Caucasian	430/317	613/464	247/170				
		2012	Zhuang M	Asian Chinese	1662/1070	2345/1550	979/590				
<i>BDNF</i>	rs6265 (G/A)	2005	Friedel S	Caucasian	183/283	342/448	81/118	Fixed	46	0.8	1.01 (0.92-1.11)
		2009	Hotta K	Asian Japanese	1127/1733	1367/2013	887/1453				
		2009	Marti A	Caucasian	155/147	242/226	68/68				
		2011	Xi B	Asian Chinese	1229/1619	1095/1554	1363/1684				
		2011	Rouskas K	Caucasian	510/469	826/732	194/206				
		2012	Skledar M	Caucasian	74/226	111/374	37/78				
<i>FAAH</i>	rs324420 (C/A)	2005	Sipe JC	Caucasian	1094/1594	1777/984	411/204	Random	79	0.54	0.94 (0.76-1.16)
		2005	Sipe JC	African	507/107	687/161	327/53				
		2005	Sipe JC	Asian	271/94	471/148	71/40				
		2007	Jensen DP	Caucasian	4190/2507	6817/3991	1563/1023				
		2008	Durand E	Caucasian	1517/1320	2473/2104	561/536				
		2008	Papazoglou D	Caucasian	158/121	265/209	51/33				
		2008	Moneletone P	Caucasian	378/110	614/194	142/26				
		2010	Muller TD	Caucasian	2818/2818	3027/4607	689/1029				

Table 1 Characteristics of 17 single nucleotide polymorphisms (Continued)

<i>ADRB1</i>	rs1801253 (C/G)	2001	Rydén M	Caucasian	141/157	206/214	76/100	Fixed	0	0.5	1.03 (0.94-1.14)
		2004	Tafel J	Caucasian	296/134	403/180	189/88				
		2007	Gjesing AP	Caucasian	4575/3073	6781/4609	2369/1537				
		2008	Ohshiro Y	Asian Japanese	180/132	284/215	76/49				
<i>SH2B1</i>	rs7498665 (A/G)	2009	Hotta K	Asian Japanese	1129/1735	1943/3003	315/467	Fixed	0	0.0004	1.21 (1.09-1.34)
		2010	Shi J	Asian Chinese	829/1859	1427/3317	231/401				
		2011	Beckers S	Caucasian	1045/317	1223/401	867/223				
		2011	Rouskas K	Caucasian	510/469	673/675	347/263				
<i>PCSK1</i>	rs6232 (A/G)	2009	Happé F	Caucasian	3570/7933	6735/15028	405/838	Fixed	34	0.08	1.14 (0.97-1.12)
		2012	Villalobos-Comparán M	South American Mexican	1018/1364	2005/2709	31/19				
		2013	Choquet H	European American	263/547	485/1041	41/53				
		2013	Dušátková L	Asian Czech	668/770	1255/1469	81/71				
		2013	Happé F	Caucasian	3559/7793	5164/11432	1954/4154				
<i>PCSK1</i>	rs6235 (G/C)	2009	Happé F	Caucasian	3559/7793	5164/11432	1954/4154	Fixed	0	0.26	1.04 (0.97-1.12)
		2012	Villalobos-Comparán M	South America Mexican	994/1336	1575/2156	413/516				
		2013	Choquet H	European - American	263/547	368/793	158/301				
		2013	Choquet H	African - American	453/251	740/432	166/70				
		2013	Dušátková L	Asian Czech	670/772	996/1130	344/414				
<i>NPY2R</i>	rs1047214 (T/C)	2006	Torekov SS	Caucasian	939/4767	1026/5295	852/4239	Fixed	0	0.54	0.97 (0.88-1.07)
		2007	Siddiq A	Caucasian	953/1042	1048/1132	858/952				
		2007	Wang HJ	Caucasian	184/183	189/169	179/197				
		2009	Zhang J	Asian Chinese	705/1325	1171/2133	239/517				
<i>FAIM2</i>	rs7138803 (G/A)	2009	Hotta K	Asian Japanese	1125/1726	1408/2251	842/1201	Fixed	0	0.04	1.11 (1.01-1.22)
		2011	Xi B	Asian Chinese	1229/1619	1711/2332	747/906				
		2011	Rouskas K	Caucasian	510/469	643/610	377/328				
		2013	Li C	Asian Chinese	242/469	331/663	153/275				
<i>SERPINE1</i>	rs1799768 (4G/5G)	2001	Sartori MT	Caucasian	93/79	95/84	91/74	Fixed	39	0.07	0.83 (0.67-1.02)
		2002	Hoffstedt J	Caucasian	317/188	305/141	329/235				
		2006	Berberoğlu M	Asian Turk	126/133	151/133	101/133				

Table 1 Characteristics of 17 single nucleotide polymorphisms (Continued)

		2008	Solá E	Caucasian	67/67	70/65	64/69				
		2008	Kinik ST	Asian Turk	39/38	52/36	26/40				
		2011	Espino A	South American Chilean	50/71	32/51	44/52				
		2012	Wingeyer SD	South American Argentine	110/111	92/109	128/113				
<i>PON1</i>	rs854560	2011	Veiga L	Caucasian	81/74	101/90	61/58	Fixed	31	0.4	0.87 (0.62-1.21)
	(A/T)	2011	Martínez-Salazar MF	South American Mexican	63/64	114/101	12/27				
		2013	Rupérez AI	Caucasian	177/81	210/219	137/143				
<i>PON1</i>	rs662	2011	Veiga L	Caucasian	81/74	68/44	94/104	Fixed	18	0.6	1.09 (0.79-1.51)
	(G/A)	2011	Martínez-Salazar MF	South American Mexican	63/64	66/65	60/63				
		2013	Rupérez AI	Caucasian	177/81	252/249	102/111				
<i>CETP</i>	TaqIB	2006	Huang ZY	Asian Chinese	199/141	243/162	155/120	Fixed	0	0.23	0.91 (0.79-1.06)
	(B1/B2)	2008	Srivastava N	Asian Indian	159/278	153/263	165/293				
		2010	Ruan X	Asian Chinese	934/924	1104/1028	764/820				
		2011	Huang Y	Asian Chinese	206/132	250/155	162/109				
<i>UCP1</i>	rs1800592	1998	Gagnon J	Caucasian	674/311	1013/473	335/149	Random	60	0.23	1.19 (0.90-1.57)
	(A/G)	2000	Proenza AM	Asian Turk	136/94	189/131	83/57				
		2002	Kieć-Wilk B	Caucasian	12/106	18/146	6/66				
		2002	Nieters A	Caucasian	154/153	232/231	76/75				
		2003	Forga LI	Caucasian	159/154	258/244	60/64				
		2004	Ramis JM	Caucasian	82/170	259/433	49/81				
		2008	Mottagui-Tabar S	Caucasian	91/479	433/736	149/222				
		2009	Shen ZN	Asian Chinese	127/257	129/240	125/274				
<i>ABCA1</i>	rs2230806	2006	Porchay I	Caucasian	2097/2947	2992/4238	1202/1656	Fixed	0	0.87	1.01 (0.90-1.13)
	(G/A)	2007	Kitjaroentham A	Asian Thai	112/117	143/143	81/91				
		2011	Huang Y	Asian Chinese	206/132	233/141	179/123				

Table 2 Characteristics of APOE ε2/ε3/ε4 polymorphism

Year	Author	Race	Case/Controls (n)	Genotypes (case/controls, n)						Alleles (case/controls, n)		
				ε2/ε2	ε2/ε3	ε2/ε4	ε3/ε3	ε3/ε4	ε4/ε4	ε2	ε3	ε4
2003	Guerra A	Caucasian	31/81	0/0	6/4	0/0	63/20	13/7	0/0	6/4	145/51	13/7
2008	Srivastava N	Asian Indian	159/278	0/1	17/18	2/6	90/198	41/55	9/0	19/30	238/469	61/61
2010	Ergun MA	Asian Chinese	38/42	0/2	2/0	12/4	8/9	16/26	0/1	14/8	34/44	28/32
2012	Zhang J	Asian Chinese	282/172	1/3	46/16	7/2	186/123	40/27	2/1	55/24	458/289	51/31
2012	Zarkesh M	Asian Iran	463/370	1/1	48/38	6/7	348/268	63/53	3/3	56/47	807/627	75/66
Module	Case/Controls (n)	Model selected	Heterogeneity (I2)%	P value	OR (95% CI)							
ε2/ε2/ε3/ε3	954/813	Fixed	0	0.12	0.35 (0.09-1.32)							
ε2/ε3ε3/ε3	814/694	Fixed	48	0.07	1.33 (0.98-1.82)							
ε2/ε4/ε3/ε3	695/618	Fixed	0	0.92	0.96 (0.45-2.05)							
ε3/ε4/ε3/ε3	868/786	Fixed	28	0.7	1.05 (0.82-1.35)							
ε4/ε4/ε3/ε3	695/618	Random	63	0.54	1.89 (0.25-14.46)							
ε2/ε3	1832/1593	Fixed	23	0.26	1.16 (0.90-1.51)							
ε4/ε3	1910/1681	Random	65	0.54	1.13 (0.77-1.66)							

is shown to be associated with increased fasting homocysteine [13]. *MTHFR* polymorphism is shown to be associated with lipid metabolism in the elderly women [14]. *CNR1* is shown to regulate the endocannabinoid system that might stimulate the metabolism of lipogenesis through central and peripheral mechanisms [15,16]. *CNR1* is associated with low HDL dyslipidemia and a common haplotype of *CNR1* could be a protective factor of obesity-related dyslipidemia [17]. *BDNF* is shown to play an important role in the development of several neuronal systems [18]. As an effector on energy homeostasis through MC4R signaling pathway, *BDNF* has an effect on the glucose and lipid metabolism in obese diabetic animals [19,20]. *FAAH* gene encodes fatty acid amide hydrolase [21] and plays an important role in the development of obesity [22]. *ADRB1* is shown to mediate in lipolysis and thus is important for obesity [23]. Rat study identifies that *ADRB1* mediates the sympathetic nervous system (SNS) stimulation of thermogenesis in brown adipose tissue [24]. *SH2B1* is able to bind leptin to its receptor, and thus increases the JAK2 activation which is involved in the insulin and leptin signaling [25,26]. *PCSK1* encodes prohormone convertase 1/3 that is a vital enzyme in the regulation of a majority of neuroendocrine body weight control [27]. A novel homozygous missense mutation in *PCSK1* leads to early-onset obesity [28]. *NPY2R* is a presynaptic receptor [29] playing an inhibitory role in the control of appetite regulation [30], and thus influences the development of obesity [31]. *FAIM2* (Fas apoptotic inhibitory molecule 2) is an anti-apoptotic gene [32]. Mutations of *FAIM2* which interferes with Fas-mediated cell death confer risk for obesity [33]. *SERPINE1* encodes a member of serine proteinase inhibitor which influences plasma PAI-1 activity with relation to obesity [34]. Serum paraoxonase-1 (PON1) encoded by *PON1* as an enzyme associated with HDL-C could be a protector against oxidative damage in obesity [35]. *CETP* protein product transfers cholesterylesters from HDL to pro-atherogenic apoB-lipoproteins and thus has an impact on the lipid and HDL metabolism [36,37]. *UCP1* encodes uncoupling protein 1 that is mediated by long-chain fatty acids (LCFAs) from brown adipose tissue [38]. *UCP1* expression in adipose tissue has an impact on regulating the thermogenesis and lipolysis [39,40]. Mitochondrial uncoupling by UCP1 has demonstrated to be a target in antiobesity therapies [41]. *ABCA1* gene product mediates the transport of cholesterol, phospholipids, and other metabolites [42]. Exercise has an impact on *ABCA1* expression along with increased HDL levels in obese boys [43]. *APOE* plays a fundamental role with ligand-receptor in uptaking lipoproteins, and thus participates in the lipid metabolism [44]. In addition, *APOE* correlates with inflammation in adipose tissue in high-fat diet-induced obesity [45].

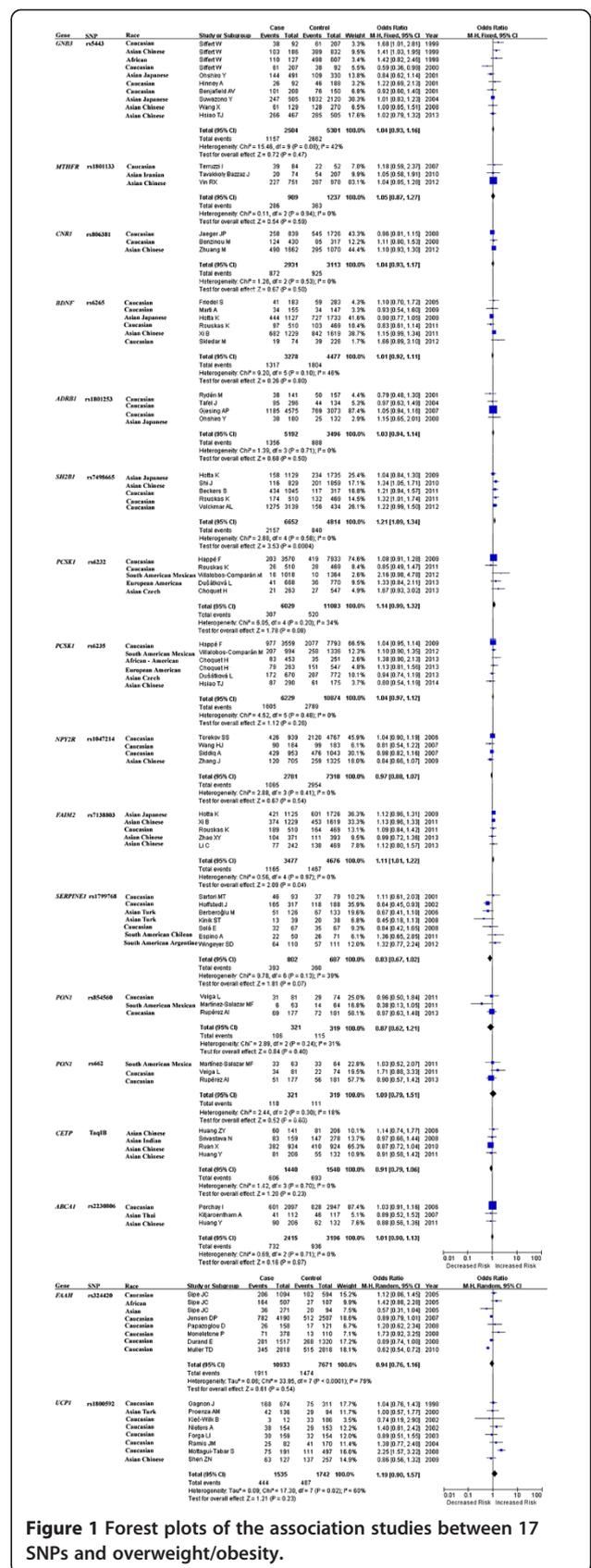


Figure 1 Forest plots of the association studies between 17 SNPs and overweight/obesity.

Meta-analysis is a systematic evaluation by combining the results from collected studies [46,47]. The major advantages of meta-analysis are to improve the precision and accuracy by pooling up the data from multiple sources, and to analyze and quantify the inconsistency of results and the publish bias [48]. In the present study, we conducted comprehensive meta-analyses to identify the contribution of 18 polymorphisms to overweight/obesity.

Materials and methods

Literature search and data extraction

We performed the literature research using related databases such as PubMed, Embase, SpingerLink, Web of Science, Chinese National Knowledge Infrastructure (CNKI), and Wanfang. The combination of keywords in the literature search was obesity or overweight together with polymorphism or mutation or variant or single

nucleotide polymorphism (SNP). The studies excluded in the meta-analysis met the following criteria: (1) the study had been included in the previous meta-analysis; (2) the study was not involved with genetic testing; (3) the study was not a case-control study. The criteria for overweight or obesity in adolescents and children were defined by WHO [49,50]. Finally, we harvested 18 polymorphisms of 16 genes in the current meta-analysis. These included *GNB3* rs5443, *MTHFR* rs1801133, *CNR1* rs806381, *BDNF* rs6265, *FAAH* rs324420, *ADRB1* rs1801253, *SH2B1* rs7498665, *PCSK1* rs6232 and rs6235, *NPY2R* rs1047214, *FAIM2* rs7138803, *SERPINE1*rs1799768, *PON1* rs854560 and rs662, *CETP* TaqIB, *UCP1* rs1800592, *ABCA1* rs2230806 and *APOE* ϵ 2/ ϵ 3/ ϵ 4.

Statistical analysis

Meta-analysis was performed by using Statistical software Review Manager 5.0 [51]. Forest plots included the

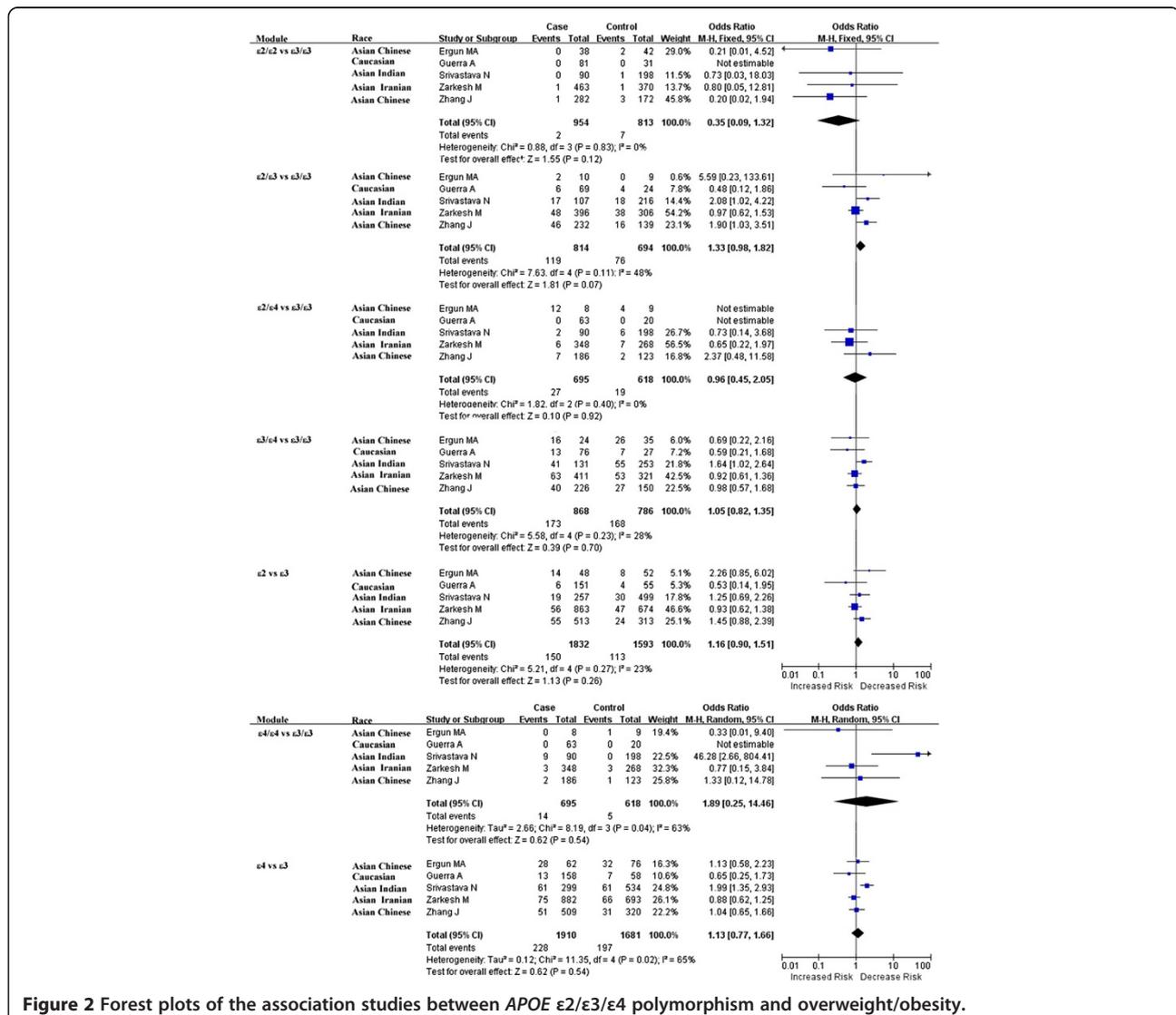


Figure 2 Forest plots of the association studies between *APOE* ϵ 2/ ϵ 3/ ϵ 4 polymorphism and overweight/obesity.

ORs with the corresponding 95% CIs, cochrans' Q and the inconsistency index (I^2). If there were no significant heterogeneity ($I^2 < 50\%$, $P > 0.05$) of the studies in the meta-analysis, we used a fixed-effect model for the analysis. Otherwise, a random-effect model was used for the meta-analysis with large heterogeneity ($I^2 > 50\%$, $P < 0.05$). The weight of each involved study was calculated whatever in fixed-effect or random-effect model in forest plots by Review Manager 5.0. Two tailed P value < 0.05 was treated as significant. Power analyses were calculated by Power and Sample Size Calculation software (v3.0.43) [52].

Results

An initial search returned a total of 7,750 literatures from databases including PubMed, Embase, SpingerLink, Web of Science, Chinese National Knowledge Infrastructure (CNKI), and Wanfang. After a systematic filtration, 72 eligible articles, including 64 English, 6 Chinese, 1 German and 1 Spanish articles, were left for the meta-analyses (Additional file 1: Table S1). The detailed information for the retrieved studies was shown in Tables 1 and 2.

Heterogeneity is an important indicator to identify if there is difference in the collected studies. According to the extent of heterogeneity, we categorized the

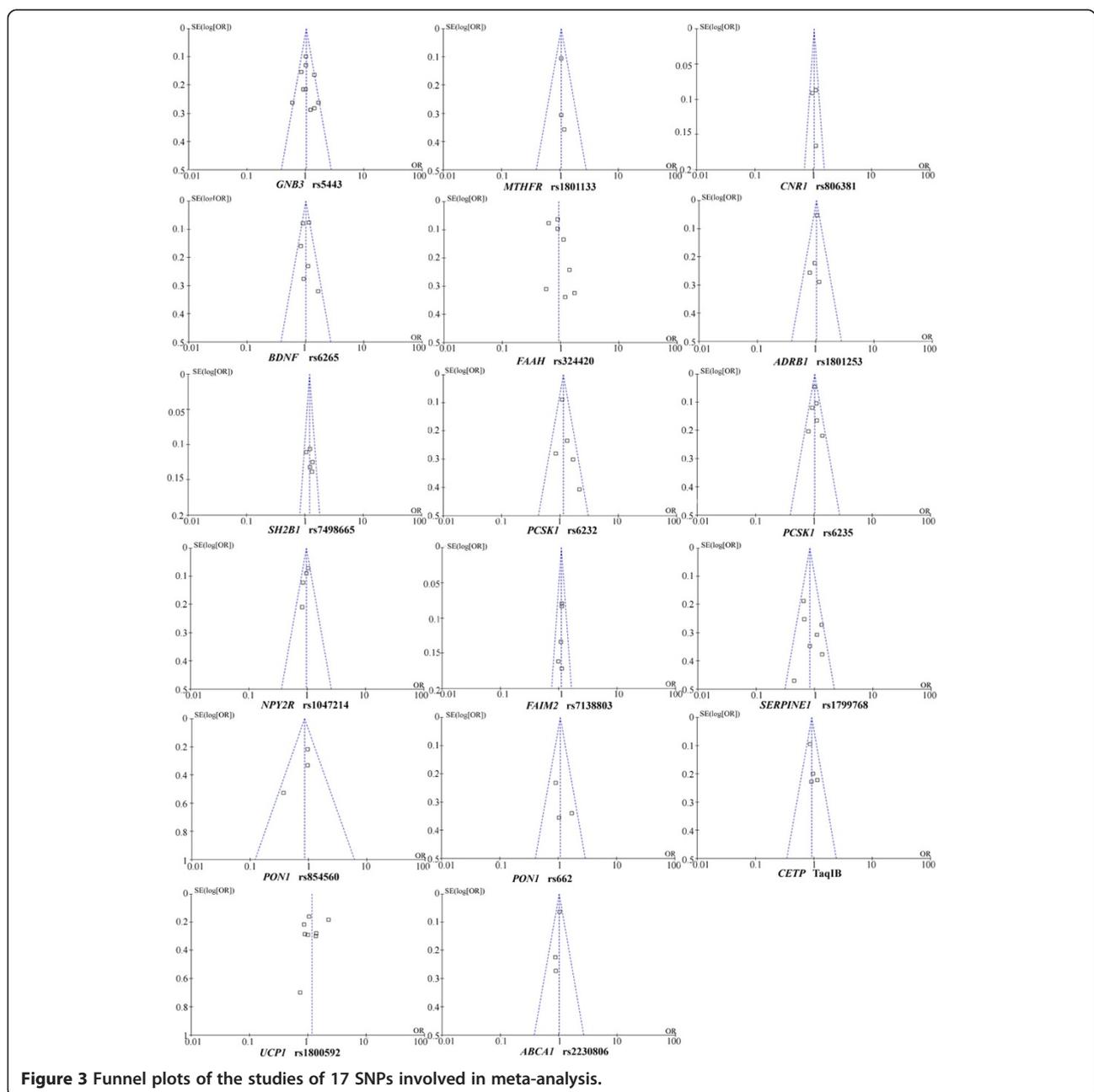


Figure 3 Funnel plots of the studies of 17 SNPs involved in meta-analysis.

meta-analyses into three groups that have minimal ($I^2 = 0$), moderate ($I^2 < 50\%$), and significant heterogeneity ($I^2 \geq 50\%$), respectively. As shown in Figure 1, minimal heterogeneity ($I^2 = 0$) was found for the meta-analyses of 10 polymorphisms that included *MTHFR* rs1801133, *CNR1* rs806381, *ADRB1* rs1801253, *SH2B1* rs7498665, *PCSK1* rs6235, *NPY2R* rs1047214, *FAIM2* rs7138803, *CETP* TaqIB and *ABCA1* rs2230806. Moderate heterogeneity was found for 5 polymorphisms, including *BDNF* rs6265 ($I^2 = 46\%$), *PCSK1* rs6232 ($I^2 = 34\%$), *GNB3* rs5443 ($I^2 = 42\%$), *PON1* rs854560 ($I^2 = 31\%$), *PON1* rs662 ($I^2 = 18\%$), and *SERPINE1* rs1799768 ($I^2 = 39\%$). Significant heterogeneity was found for *UCP1* rs1800592 ($I^2 = 60\%$) and *FAAH* rs324420 ($I^2 = 79\%$). Moreover, As shown in Figure 2, various heterogeneities were shown in the meta-analyses of *APOE* $\epsilon 2/\epsilon 3/\epsilon 4$ polymorphism under the seven genetic models ($\epsilon 2/\epsilon 3$ versus $\epsilon 3/\epsilon 3$: $I^2 = 48\%$; $\epsilon 2/\epsilon 4$ versus $\epsilon 3/\epsilon 3$: $I^2 = 0\%$; $\epsilon 3/\epsilon 4$ versus $\epsilon 3/\epsilon 3$: $I^2 = 28\%$; $\epsilon 4/\epsilon 4$ versus $\epsilon 3/\epsilon 3$: $I^2 = 63\%$; $\epsilon 2/\epsilon 3$ versus $\epsilon 3/\epsilon 3$: $I^2 = 0\%$; $\epsilon 2$ versus $\epsilon 3$: $I^2 = 23\%$; $\epsilon 4$ versus $\epsilon 3$: $I^2 = 65\%$). No obvious publication bias was observed based on their funnel plots (Figures 3 and 4).

Our results showed that *SH2B1* rs7498665 was significantly associated with the risk of overweight/obesity among 6,142 cases and 4,345 controls from four studies (overall OR = 1.21, 95% CI = 1.09-1.34, $P = 0.0004$, Figure 1). Increased risk of overweight/obesity was also observed in rs7138803 of *FAIM2* among 3,477 cases and 4,676 controls from five studies (overall OR = 1.11, 95% CI = 1.01-1.22, $P = 0.04$, Figure 1). No evidence of association was observed for the meta-analyses of the rest 16

variants (Figures 1 and 3). For the meta-analyses with large heterogeneity, we further performed subgroup meta-analyses by ethnicity. No significant association of *UCP1* rs1800592 with overweight/obesity was observed in Caucasian ($P = 0.13$, $I^2 = 62\%$), and Asian ($P = 0.59$, $I^2 = 0\%$, Additional file 2: Figure S1). And the subgroup meta-analysis of *APOE* $\epsilon 2/\epsilon 3/\epsilon 4$ polymorphism by excluding the study of Srivastava et al. [53] didn't produce any significant association of *APOE* $\epsilon 2/\epsilon 3/\epsilon 4$ with overweight/obesity (Additional file 3: Figure S2). There was no visual publication bias in all the above meta-analyses (Additional file 4: Figure S3).

Discussion

Current meta-analyses were performed among 48,148 cases and 56,738 controls from 72 studies, covering a total of 6 populations, including Caucasian, Asian, Japanese-American, European-American, African-American, South American, and African. Among the tested 18 polymorphisms, there were two (*SH2B1* rs7498665 and *FAIM2* rs7138803) with significant association results ($P < 0.05$). Power analysis also showed large power existed in our meta-analyses of two significant polymorphisms including *SH2B1* rs7498665 (100%) and *FAIM2* rs7138803 (100%).

SH2B1 encodes an adaptor protein associated with leptin and insulin signaling in the lipid metabolism [54]. *SH2B1* is an enhancer that may influence the phenotype of obesity through JAK-STAT pathway [55], which is important in the development and function of adipocytes [56]. *SH2B1* acts as a mediator through PI3-kinase pathway which is correlated with the biological actions of

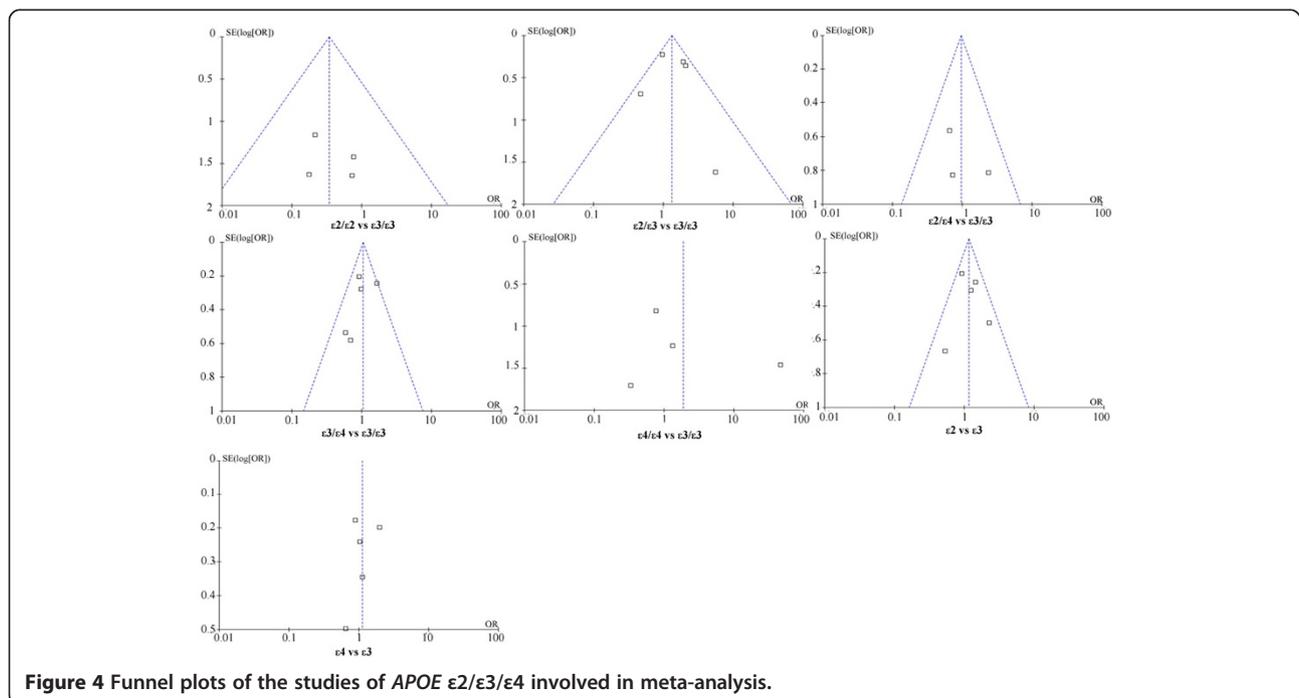


Figure 4 Funnel plots of the studies of *APOE* $\epsilon 2/\epsilon 3/\epsilon 4$ involved in meta-analysis.

leptin [26]. Many animal studies have shown that *SH2B1* is involved in the development of obesity. *SH2B1* through its participation in the regulation of leptin sensitivity, energy metabolism and body weight [57]. *SH2B1* has been identified to be related to obesity through genome-wide association studies (GWAS) [55]. Our meta-analysis of *SH2B1* rs7498665 was performed among 6,652 cases and 4,814 controls with four studies. Among the tested populations, no heterogeneity was observed ($I^2 = 0$). Our results confirmed the relationship between *SH2B1* and the risk of overweight/obesity (overall OR = 1.21, 95% CI = 1.09-1.34, P = 0.0004, Figure 1).

FAIM2 is an anti-apoptotic gene that provides protection from Fas-mediated cell death [32] that is associated with extreme overweight by GWAS [58]. *FAIM2* rs7138803 polymorphism is associated with increased risk of obesity in Japanese [59]. But there is no relationship between *FAIM2* rs7138803 and obesity in Chinese [60]. Minor allele frequency of rs7138803 in Chinese populations ranges from 0.28 to 0.29, while *FAIM2* rs7138803 is monomorphic in Japanese and Caucasian populations. Our meta-analysis among 3477 cases and 4676 controls demonstrated that *FAIM2* rs7138803 was associated with the risk of overweight/obesity (overall OR = 1.11, 95% CI = 1.01-1.22, P = 0.04, Figure 1).

Although meta-analysis is an important method to improve the precision and accuracy, to analyze and quantify the published results [61-63], some disadvantages exist in the meta-analysis. For the current meta-analyses, several limitations need to be taken with cautions. Firstly, obesity is always accompanied by other complications such as coronary artery diseases and hypertension. These confounding factors needed to be adjusted in the original case-control studies. We were unable to obtain the related information. Therefore we can't exclude a chance of the positive findings confounded by these obesity-related factors. Secondly, the significant result of *FAIM2* rs7138803 needs to be validated in the future. However, after Bonferroni's correction by the number of testing, the association of *FAIM2* rs7138803 was unable to retain significant. Thirdly, power analysis suggested moderate power in the meta-analyses of *MTHFR* rs1801133 (power = 78.2%) and *SERPINE1* rs1799768 (power = 69.4%). The negative results of them might be caused by a lack of power in our meta-analyses. Future studies with larger samples may help clarify the contribution of these biomarkers to the risk of overweight/obesity.

Our results identified significant associations between 2 polymorphisms (*SH2B1* rs7498665 and *FAIM2* rs7138803) and overweight/obesity. Moreover, overweight/obesity is a complicated disease influenced by both genetic and environmental factors. The potential mechanism of interaction between gene and environment could be taken into consideration in the future study. Well-designed studies with

large samples could help elucidate the contribution of above polymorphisms to overweight/obesity.

Additional files

Additional file 1: Table S1. Flow diagram of selecting studies for meta-analysis.

Additional file 2: Figure S1. Forest plots of the association studies of *UCP1* rs1800592 in our subgroup meta-analysis.

Additional file 3: Figure S2. Forest plots of the association studies of *APOE* $\epsilon 2/\epsilon 3/\epsilon 4$.

Additional file 4: Figure S3. Funnel plots of the studies related to *UCP1* rs1800592 by subgroup meta-analysis and *APOE* $\epsilon 2/\epsilon 3/\epsilon 4$.

Competing interests

The authors declare that they have no competing interests.

Authors' contribution

QH, LX and SB conceived the study idea and designed the study. FC, QL and QH reviewed the literature and performed statistical analyses. LT and HY extracted data and drafted the manuscript. SD, YM DW and MY reviewed and edited the manuscript. All authors read and approved the final manuscript.

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References

1. Ogunbode AM, Ladipo M, Ajayi IO, Fatiregun AA: **Obesity: an emerging disease.** *Niger J Clin Pract* 2011, **14**(4):390-394.
2. Haslam DW, James WP: **Obesity.** *Lancet* 2005, **366**(9492):1197-1209.
3. **The situation and trends of obesity and overweight.** http://www.who.int/gho/ncd/risk_factors/overweight/en/index.html.
4. Keaver L, Webber L, Dee A, Shiely F, Marsh T, Balanda K, Perry I: **Application of the UK foresight obesity model in ireland: the health and economic consequences of projected obesity trends in ireland.** *PLoS One* 2013, **8**(11):e79827.
5. Schwenk RW, Vogel H, Schurmann A: **Genetic and epigenetic control of metabolic health.** *Mol Metab* 2013, **2**(4):337-347.
6. Latham KE, Sapienza C, Engel N: **The epigenetic lorax: gene-environment interactions in human health.** *Epigenomics* 2012, **4**(4):383-402.
7. Wei D, Zhang X, Zou H, Wang L, Fu B, Wu X, Luo Z, Li X, Ge J, Li Y, Zhu H, Wang K, Wang T, Yang P, Hou Z, Wang W: **WW domain containing oxidoreductase induces apoptosis in gallbladder-derived malignant cell by upregulating expression of P73 and PUMA.** *Tumour Biol* 2013, **35**(2):1539-1550.
8. Fukuoka H, Mukai S, Taniguchi T: **[Nutritional environment in utero and development of obesity].** *Nihon Rinsho* 2013, **71**(2):237-243.
9. Jiang D, Zheng D, Wang L, Huang Y, Liu H, Xu L, Liao Q, Liu P, Shi X, Wang Z, Sun L, Zhou Q, Li N, Le Y, Ye M, Shao G, Duan S: **Elevated PLA2G7 gene**

- promoter methylation as a gender-specific marker of aging increases the risk of coronary heart disease in females. *PLoS One* 2013, **8**(3):e59752.
10. Tisherman SA: **Salvage techniques in traumatic cardiac arrest: thoracotomy, extracorporeal life support, and therapeutic hypothermia.** *Curr Opin Crit Care* 2013, **19**(6):594–598.
 11. Monda KL, Chen GK, Taylor KC, Palmer C, Edwards TL, Lange LA, Ng MC, Adeyemo AA, Allison MA, Bielak LF, Chen G, Graff M, Irvin MR, Rhie SK, Li G, Liu Y, Lu Y, Nalls MA, Sun YV, Wojczynski MK, Yanek LR, Aldrich MC, Ademola A, Amos CI, Bandera EV, Bock CH, Britton A, Broecker U, Cai Q, Caporaso NE, et al: **A meta-analysis identifies new loci associated with body mass index in individuals of African ancestry.** *Nat Genet* 2013, **45**(6):690–696.
 12. Klenke S, Kussmann M, Siffert W: **The GNB3 C825T polymorphism as a pharmacogenetic marker in the treatment of hypertension, obesity, and depression.** *Pharmacogenet Genomics* 2011, **21**(9):594–606.
 13. Piedade MC, Galhardo MS, Battlehner CN, Ferreira MA, Caldini EG, de Toledo OM: **Effect of ultrasound therapy on the repair of gastrocnemius muscle injury in rats.** *Ultrasonics* 2008, **48**(5):403–411.
 14. Chmurzynska A, Malinowska AM, Twardowska-Rajewska J, Gawecki J: **Elderly women: homocysteine reduction by short-term folic acid supplementation resulting in increased folic acid concentrations and affecting lipid metabolism (C677T MTHFR polymorphism).** *Nutrition* 2013, **29**(6):841–844.
 15. Engeli S, Bohnke J, Feldpausch M, Gorzelniak K, Janke J, Batkai S, Pacher P, Harvey-White J, Luft FC, Sharma AM, Jordan J: **Activation of the peripheral endocannabinoid system in human obesity.** *Diabetes* 2005, **54**(10):2838–2843.
 16. Di Marzo V, Matias I: **Endocannabinoid control of food intake and energy balance.** *Nat Neurosci* 2005, **8**(5):585–589.
 17. Feng Q, Jiang L, Berg RL, Antonik M, MacKinney E, Gunnell-Santoro J, McCarty CA, Wilke RA: **A common CNR1 (cannabinoid receptor 1) haplotype attenuates the decrease in HDL cholesterol that typically accompanies weight gain.** *PLoS One* 2010, **5**(12):e15779.
 18. Kernie SG, Liebl DJ, Parada LF: **BDNF regulates eating behavior and locomotor activity in mice.** *EMBO J* 2000, **19**(6):1290–1300.
 19. Xu B, Goulding EH, Zang K, Cepoi D, Cone RD, Jones KR, Techt LH, Reichardt LF: **Brain-derived neurotrophic factor regulates energy balance downstream of melanocortin-4 receptor.** *Nat Neurosci* 2003, **6**(7):736–742.
 20. Tsuchida A, Nonomura T, Nakagawa T, Itakura Y, Ono-Kishino M, Yamanaka M, Sugaru E, Tajiri M, Noguchi H: **Brain-derived neurotrophic factor ameliorates lipid metabolism in diabetic mice.** *Diabetes Obes Metab* 2002, **4**(4):262–269.
 21. Cravatt BF, Giang DK, Mayfield SP, Boger DL, Lerner RA, Gilula NB: **Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides.** *Nature* 1996, **384**(6604):83–87.
 22. Lieb W, Manning AK, Florez JC, Dupuis J, Cupples LA, McAteer JB, Vasan RS, Hoffmann U, O'Donnell CJ, Meigs JB, Fox CS: **Variants in the CNR1 and the FAAH genes and adiposity traits in the community.** *Obesity (Silver Spring)* 2009, **17**(4):755–760.
 23. Louis SN, Jackman GP, Nero TL, Iakovidis D, Louis WJ: **Role of beta-adrenergic receptor subtypes in lipolysis.** *Cardiovasc Drugs Ther* 2000, **14**(6):565–577.
 24. Ueta CB, Fernandes GW, Capelo LP, Fonseca TL, Maculan FD, Gouveia CH, Brum PC, Christoffolete MA, Aoki MS, Lancellotti CL, Kim B, Bianco AC, Ribeiro MO: **beta(1) Adrenergic receptor is key to cold- and diet-induced thermogenesis in mice.** *J Endocrinol* 2012, **214**(3):359–365.
 25. Penas-Steinhardt A, Tellechea ML, Gomez-Rosso L, Brites F, Frechtel GD, Poskus E: **Association of common variants in JAK2 gene with reduced risk of metabolic syndrome and related disorders.** *BMC Med Genet* 2011, **12**:166.
 26. Duan C, Li M, Rui L: **SH2-B promotes insulin receptor substrate 1 (IRS1)- and IRS2-mediated activation of the phosphatidylinositol 3-kinase pathway in response to leptin.** *J Biol Chem* 2004, **279**(42):43684–43691.
 27. Helwig M, Khoroshii RM, Tups A, Barrett P, Archer ZA, Exner C, Rozman J, Braulke LJ, Mercer JG, Klingenspor M: **PC1/3 and PC2 gene expression and post-translational endoproteolytic pro-opiomelanocortin processing is regulated by photoperiod in the seasonal Siberian hamster (Phodopus sungorus).** *J Neuroendocrinol* 2006, **18**(6):413–425.
 28. Farooqi IS, Volders K, Stanhope R, Heuschkel R, White A, Lank E, Keogh J, O'Rahilly S, Creemers JW: **Hyperphagia and early-onset obesity due to a novel homozygous missense mutation in prohormone convertase 1/3.** *J Clin Endocrinol Metab* 2007, **92**(9):3369–3373.
 29. Dionne JJ, Garant MJ, Nolan AA, Pollin TI, Lewis DG, Shuldiner AR, Poehlman ET: **Association between obesity and a polymorphism in the beta(1)-adrenoceptor gene (Gly389Arg ADRB1) in Caucasian women.** *Int J Obes Relat Metab Disord* 2002, **26**(5):633–639.
 30. Naveilhan P, Hassani H, Canals JM, Ekstrand AJ, Larefalk A, Chhajlani V, Arenas E, Gedda K, Svensson L, Thoren P, Ernfors P: **Normal feeding behavior, body weight and leptin response require the neuropeptide Y Y2 receptor.** *Nat Med* 1999, **5**(10):1188–1193.
 31. Siddiq A, Gueorguiev M, Samson C, Hercberg S, Heude B, Levy-Marchal C, Jouret B, Weill J, Meyre D, Walley A, Froguel P: **Single nucleotide polymorphisms in the neuropeptide Y2 receptor (NPY2R) gene and association with severe obesity in French white subjects.** *Diabetologia* 2007, **50**(3):574–584.
 32. Somia NV, Schmitt MJ, Vetter DE, Van Antwerp D, Heinemann SF, Verma IM: **LFG: an anti-apoptotic gene that provides protection from Fas-mediated cell death.** *Proc Natl Acad Sci U S A* 1999, **96**(22):12667–12672.
 33. Leon-Mimila P, Villamil-Ramirez H, Villalobos-Comparan M, Villarreal-Molina T, Romero-Hidalgo S, Lopez-Contreras B, Gutierrez-Vidal R, Vega-Badillo J, Jacobo-Alavera L, Posadas-Romeros C, Canizalez-Roman A, Rio-Navarro BD, Campos-Perez F, Acuna-Alonzo V, Aguilar-Salinas C, Canizales-Quinteros S: **Contribution of common genetic variants to obesity and obesity-related traits in Mexican children and adults.** *PLoS One* 2013, **8**(8):e70640.
 34. Eriksson P, Reynisdottir S, Lonngqvist F, Stemme V, Hamsten A, Arner P: **Adipose tissue secretion of plasminogen activator inhibitor-1 in non-obese and obese individuals.** *Diabetologia* 1998, **41**(1):65–71.
 35. Ferretti G, Bacchetti T, Masciangelo S, Bicchiaga V: **HDL-para-oxonase and membrane lipid peroxidation: a comparison between healthy and obese subjects.** *Obesity (Silver Spring)* 2010, **18**(6):1079–1084.
 36. Pachocka LM, Wlodarczyk M, Nowicka G, Klosiewicz-Latoszek L, Wolanska D, Stolarska I: **[CETP gene TaqIB polymorphism and plasma lipids in patients with overweight and obesity].** *Rocz Panstw Zaki Hig* 2012, **63**(2):149–154.
 37. Chapman MJ, Le Goff W, Guerin M, Kontush A: **Cholesteryl ester transfer protein: at the heart of the action of lipid-modulating therapy with statins, fibrates, niacin, and cholesteryl ester transfer protein inhibitors.** *Eur Heart J* 2010, **31**(2):149–164.
 38. Cannon B, Nedergaard J: **Brown adipose tissue: function and physiological significance.** *Physiol Rev* 2004, **84**(1):277–359.
 39. Miyaki K, Sutani S, Kikuchi H, Takei I, Murata M, Watanabe K, Omae K: **Increased risk of obesity resulting from the interaction between high energy intake and the Trp64Arg polymorphism of the beta3-adrenergic receptor gene in healthy Japanese men.** *J Epidemiol* 2005, **15**(6):203–210.
 40. Dalgaard LT, Pedersen O: **Uncoupling proteins: functional characteristics and role in the pathogenesis of obesity and Type II diabetes.** *Diabetologia* 2001, **44**(8):946–965.
 41. Costford S, Gowing A, Harper ME: **Mitochondrial uncoupling as a target in the treatment of obesity.** *Curr Opin Clin Nutr Metab Care* 2007, **10**(6):671–678.
 42. Oram JF, Heinecke JW: **ATP-binding cassette transporter A1: a cell cholesterol exporter that protects against cardiovascular disease.** *Physiol Rev* 2005, **85**(4):1343–1372.
 43. Ghorbanian B, Ravassi A, Kordi MR, Hedayati M: **The Effects of Rope Training on Lymphocyte ABCA1 Expression, Plasma ApoA-I and HDL-c in Boy Adolescents.** *Int J Endocrinol Metab* 2013, **11**(2):76–81.
 44. Mahley RW: **Apolipoprotein E: cholesterol transport protein with expanding role in cell biology.** *Science* 1988, **240**(4852):622–630.
 45. Wang J, Perrard XD, Perrard JL, Mukherjee A, Rosales C, Chen Y, Smith CW, Pownall HJ, Ballantyne CM, Wu H: **ApoE and the role of very low density lipoproteins in adipose tissue inflammation.** *Atherosclerosis* 2012, **223**(2):342–349.
 46. Xu Z, Yu L, Zhang X: **Association between the hOGG1 Ser326Cys polymorphism and lung cancer susceptibility: a meta-analysis based on 22,475 subjects.** *Diagn Pathol* 2013, **8**:144.
 47. de Matos LL, Del Giglio AB, Matsubayashi CO, de Lima Farah M, Del Giglio A, da Silva Pinhal MA: **Expression of CK-19, galectin-3 and HBME-1 in the differentiation of thyroid lesions: systematic review and diagnostic meta-analysis.** *Diagn Pathol* 2012, **7**:97.
 48. **Meta-analysis.** <http://en.wikipedia.org/wiki/Meta-analysis>.
 49. **The criteria for overweight or obesity in children and adolescents.** http://www.who.int/dietphysicalactivity/childhood_what/en/index.html.
 50. **The criteria for overweight or obesity in children.** http://www.who.int/growthref/who2007_bmi_for_age/en/index.html.
 51. Jiang H, Sun MW, Hefright B, Chen W, Lu CD, Zeng J: **Efficacy of hypocaloric parenteral nutrition for surgical patients: a systematic review and meta-analysis.** *Clin Nutr* 2011, **30**(6):730–737.

52. Dupont WD, Plummer WD Jr: **Power and sample size calculations. A review and computer program.** *Control Clin Trials* 1990, **11**(2):116–128.
53. Srivastava N, Achyut BR, Prakash J, Agarwal CG, Pant DC, Mittal B: **Association of cholesteryl ester transfer protein (TaqlB) and apolipoprotein E (HhaI) gene variants with obesity.** *Mol Cell Biochem* 2008, **314**(1–2):171–177.
54. Maures TJ, Kurzer JH, Carter-Su C: **SH2B1 (SH2-B) and JAK2: a multifunctional adaptor protein and kinase made for each other.** *Trends Endocrinol Metab* 2007, **18**(1):38–45.
55. Speakman JR: **Functional analysis of seven genes linked to body mass index and adiposity by genome-wide association studies: a review.** *Hum Hered* 2013, **75**(2–4):57–79.
56. Richard AJ, Stephens JM: **Emerging roles of JAK-STAT signaling pathways in adipocytes.** *Trends Endocrinol Metab* 2011, **22**(8):325–332.
57. Ren D, Li M, Rui L: **Identification of SH2-B as a key regulator of leptin sensitivity, energy balance, and body weight in mice.** *Cell Metab* 2005, **2**(2):95–104.
58. Paternoster L, Evans DM, Nohr EA, Holst C, Gaborieau V, Brennan P, Gjesing AP, Grarup N, Witte DR, Jorgensen T, Linneberg A, Lauritzen T, Sandbaek A, Hansen T, Pedersen O, Elliott KS, Kemp JP, St Pourcain B, McMahon G, Zelenika D, Hager J, Lathrop M, Timpson NJ, Smith GD, Sorensen TI: **Genome-wide population-based association study of extremely overweight young adults—the GOYA study.** *PLoS One* 2011, **6**(9):e24303.
59. Hotta K, Nakamura M, Nakamura T, Matsuo T, Nakata Y, Kamohara S, Miyatake N, Kotani K, Komatsu R, Itoh N, Mineo I, Wada J, Masuzaki H, Yoneda M, Nakajima A, Funahashi T, Miyazaki S, Tokunaga K, Kawamoto M, Ueno T, Hamaguchi K, Tanaka K, Yamada K, Hanafusa T, Oikawa S, Yoshimatsu H, Nakao K, Sakata T, Matsuzawa Y, Kamatani N, et al: **Association between obesity and polymorphisms in SEC16B, TMEM18, GNPDA2, BDNF, FAIM2 and MC4R in a Japanese population.** *J Hum Genet* 2009, **54**(12):727–731.
60. Li C, Qiu X, Yang N, Gao J, Rong Y, Xiong C, Zheng F: **Common rs7138803 variant of FAIM2 and obesity in Han Chinese.** *BMC Cardiovasc Disord* 2013, **13**:56.
61. Liu Y, Tang W, Wang J, Xie L, Li T, He Y, Qin X, Li S: **Clinicopathological and prognostic significance of S100A4 overexpression in colorectal cancer: a meta-analysis.** *Diagn Pathol* 2013, **8**(1):181.
62. Wang Z, Zhang Y, Kong X, Li S, Hu Y, Wang R, Li Y, Lu C, Lin N, Chen W: **Association of a polymorphism in PON-1 gene with steroid-induced osteonecrosis of femoral head in Chinese Han population.** *Diagn Pathol* 2013, **8**(1):186.
63. Zhang Y, Wang R, Li S, Kong X, Wang Z, Chen W, Lin N: **Genetic polymorphisms in plasminogen activator inhibitor-1 predict susceptibility to steroid-induced osteonecrosis of the femoral head in Chinese population.** *Diagn Pathol* 2013, **8**(1):169.

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