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, SpingerLink, 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.

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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 β3-subunit protein which is involved in the process of hypertension and obesity [12]. MTHFR gene encodes methenyltetrahydrofolate reductase that
| Gene   | SNP     | Year | Author          | Race            | Cases/Controls (n) | Allele 1 (Case/Controls, n) | Allele 2 (Case/Controls, n) | Model selected | Heterogeneity I2% | P value | Odds ratio (95% confidence interval) |
|--------|---------|------|-----------------|-----------------|-------------------|-----------------------------|-----------------------------|----------------|----------------|---------|-----------------------------------|
| GNB3   | rs5443  | 1999 | Siffert W       | Caucasian       | 92/207            | 108/392                    | 76/122                      | Fixed          | 42              | 0.47    | 1.04 (0.93-1.16)                  |
|        | (C/T)  |      |                 |                 |                   |                             |                             |                |                 |         |                                   |
|        |         |      |                 |                 |                   |                             |                             |                |                 |         |                                   |
|        |         | 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 | Benajfield 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                     |                |                 |         |                                   |
|        |         | 2013 | Hsiao TJ        | Asian Chinese   | 467/505           | 402/441                    | 532/569                     |                |                 |         |                                   |
|        |         | 2007 | Terruzzi I      | Caucasian       | 84/52             | 90/61                      | 78/43                       | Fixed          | 0               | 0.59    | 1.05 (0.87-1.27)                  |
| MTHFR  | rs1801133| 2007 | Terruzzi I      | Caucasian       | 84/52             | 90/61                      | 78/43                       | Fixed          | 0               | 0.59    | 1.05 (0.87-1.27)                  |
|        | (C/T)  |      |                 |                 |                   |                             |                             |                |                 |         |                                   |
|        |         | 2010 | Tavakkoly Bazzaz J | Asian Iranian | 74/207            | 109/306                    | 39/108                      |                |                 |         |                                   |
|        |         | 2012 | Yin RX          | Asian Chinese   | 751/978           | 1049/1383                  | 453/573                     |                |                 |         |                                   |
| CNR1   | rs806381| 2008 | Benzinou M      | Caucasian       | 839/1726          | 1163/2362                  | 515/1090                    | Fixed          | 0               | 0.5     | 1.04 (0.93-1.17)                  |
|        | (A/G)  |      |                 |                 |                   |                             |                             |                |                 |         |                                   |
|        |         | 2008 | Jaeger JP       | Caucasian       | 430/317           | 613/464                    | 247/170                     |                |                 |         |                                   |
|        |         | 2012 | Zhuang M        | Asian Chinese   | 1662/1070         | 2345/1550                  | 979/590                     |                |                 |         |                                   |
| BDNF   | rs6265  | 2005 | Friedel S       | Caucasian       | 183/283           | 342/448                    | 81/118                      | Fixed          | 46              | 0.8     | 1.01 (0.92-1.11)                  |
|        | (G/A)  |      |                 |                 |                   |                             |                             |                |                 |         |                                   |
|        |         | 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                       |                |                 |         |                                   |
| FAAH   | rs324420| 2005 | Sipe JC         | Caucasian       | 1094/1594         | 1777/984                   | 411/204                     | Random         | 79              | 0.54    | 0.94 (0.76-1.16)                  |
|        | (C/A)  |      |                 |                 |                   |                             |                             |                |                 |         |                                   |
|        |         | 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 | Monelton P      | Caucasian       | 378/110           | 614/194                    | 142/26                      |                |                 |         |                                   |
|        |         | 2010 | Muller TD       | Caucasian       | 2818/2818         | 3027/4607                  | 689/1029                    |                |                 |         |                                   |
| rsID   | Year | Author(s)      | Region                      | Minor Allele | Y/N   | OR    | 95% CI    |
|--------|------|----------------|-----------------------------|-------------|------|-------|-----------|
| ADRB1  | 2001 | Rydén et al.   | Caucasian                   |             |      | 1.03  | (0.94-1.14) |
|        | 2004 | Tafel et al.   | Caucasian                   |             |      | 1.03  | (0.94-1.14) |
|        | 2007 | Gjesing et al. | Caucasian                   |             |      | 1.09  | (1.04-1.15) |
|        | 2008 | Ohshiro et al. | Asian Japanese              |             |      | 1.11  | (1.04-1.18) |
| SH2B1  | 2009 | Hotta et al.   | Asian Japanese              |             |      | 1.21  | (1.09-1.34) |
|        | 2010 | Shi et al.     | Asian Chinese               |             |      | 1.08  | (0.97-1.20) |
|        | 2011 | Beckers et al. | Caucasian                   |             |      | 1.14  | (1.07-1.21) |
|        | 2011 | Rouskas et al. | Caucasian                   |             |      | 1.10  | (1.04-1.18) |
|        | 2012 | Volckmar et al.| Caucasian                   |             |      | 1.11  | (1.04-1.20) |
| PCSK1  | 2009 | Happel et al.  | Caucasian                   |             |      | 1.14  | (0.97-1.17) |
|        | 2011 | Rouskas et al. | Caucasian                   |             |      | 1.11  | (1.04-1.19) |
|        | 2012 | Villalobos et al.| South American Mexican      |             |      | 1.11  | (1.04-1.18) |
|        | 2013 | Choquet et al. | European American           |             |      | 1.10  | (1.03-1.17) |
|        | 2013 | Dušátková et al.| Asian Czech                |             |      | 1.10  | (1.04-1.16) |
| PCSK1  | 2009 | Happel et al.  | Caucasian                   |             |      | 1.15  | (1.08-1.18) |
|        | 2012 | Villalobos et al.| South American Mexican      |             |      | 1.19  | (1.12-1.27) |
|        | 2013 | Choquet et al. | European - American         |             |      | 1.12  | (1.05-1.19) |
|        | 2013 | Choquet et al. | African - American          |             |      | 1.12  | (1.05-1.19) |
|        | 2013 | Dušátková et al.| Asian Czech                |             |      | 1.12  | (1.05-1.19) |
|        | 2014 | Hsiao et al.   | Asian Chinese               |             |      | 1.12  | (1.05-1.19) |
| NPY2R  | 2006 | Torekov et al. | Caucasian                   |             |      | 0.97  | (0.88-1.07) |
|        | 2007 | Siddiq et al.  | Caucasian                   |             |      | 0.98  | (0.91-1.06) |
|        | 2007 | Wang et al.    | Caucasian                   |             |      | 1.00  | (0.97-1.04) |
|        | 2009 | Zhang et al.   | Asian Chinese               |             |      | 1.00  | (0.94-1.06) |
| FAIM2  | 2009 | Hotta et al.   | Asian Japanese              |             |      | 1.11  | (1.01-1.22) |
|        | 2011 | Xi et al.      | Asian Chinese               |             |      | 0.87  | (0.78-0.97) |
|        | 2011 | Rouskas et al. | Caucasian                   |             |      | 0.86  | (0.75-0.98) |
|        | 2013 | Li et al.      | Asian Chinese               |             |      | 0.83  | (0.74-0.93) |
|        | 2013 | Zhao et al.    | Asian Chinese               |             |      | 0.85  | (0.75-0.95) |
| SERPIN1| 2001 | Sartori et al. | Caucasian                   |             |      | 1.07  | (0.87-1.31) |
|        | 2002 | Hoffstedt et al.| Caucasian                  |             |      | 1.03  | (0.87-1.21) |
|        | 2006 | Berberoğlu et al.| Asian Turk                |             |      | 1.01  | (0.87-1.17) |
| Year | Study | Population | Phenotype | PON1 rs854560 | CETP TaqIB | UCP1 rs1800592 | ABCA1 rs230806 |
|------|-------|------------|-----------|---------------|-----------|---------------|---------------|
| 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 | Wingeeyer SD | South American Argentine | 110/111 | 92/109 | 128/113 |
| 2011 | Veiga L | Caucasian | 81/74 | 101/90 | 61/58 | Fixed | 31 | 0.4 | 0.87 (0.62-1.21) |
| 2011 | Martínez-Salazar MF | South American Mexican | 63/64 | 114/101 | 12/27 | 2013 | Rupérez Al | Caucasian | 177/81 | 210/219 | 137/143 |
| 2011 | Veiga L | Caucasian | 81/74 | 68/44 | 94/104 | Fixed | 18 | 0.6 | 1.09 (0.79-1.51) |
| 2011 | Martínez-Salazar MF | South American Mexican | 63/64 | 66/65 | 60/63 | 2013 | Rupérez Al | Caucasian | 177/81 | 252/249 | 102/111 |
| 2006 | Huang ZY | Asian Chinese | 199/141 | 243/162 | 155/120 | Fixed | 0 | 0.23 | 0.91 (0.79-1.06) |
| 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 | 2000 | Proenza AM | Asian Turk | 136/94 | 189/131 | 83/57 |
| 2002 | Kieć-Wilk B | Caucasian | 12/106 | 18/146 | 6/66 | 2002 | Niehrs A | Caucasian | 154/153 | 232/231 | 76/75 |
| 2003 | Forga L | 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 |
| 2006 | Porchay I | Caucasian | 2097/2947 | 2992/4238 | 1202/1656 | Fixed | 0 | 0.87 | 1.01 (0.90-1.13) |
| 2007 | Kitjaroentharn A | Asian Thai | 112/117 | 143/143 | 81/91 | 2011 | Huang Y | Asian Chinese | 206/132 | 233/141 | 179/123 |
| 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/ε3/ε3/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].
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, CETP TaqIB, UCPI rs1800592, ABCA1 rs2230806 and APOE e2/e3/e4.

**Statistical analysis**

Meta-analysis was performed by using Statistical software Review Manager 5.0 [51]. Forest plots included the
ORs with the corresponding 95% CIs, Cochran’s 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, SpringerLink, 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

![Funnel plots of the studies of 17 SNPs involved in meta-analysis.](image)
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 ε2/ε3/ε4 polymorphism under the seven genetic models (ε2/ε3 versus ε3/ε3: $I^2 = 48\%$; ε2/ε4 versus ε3/ε3: $I^2 = 0\%$; ε3/ε4 versus ε3/ε3: $I^2 = 28\%$; ε4/ε4 versus ε3/ε3: $I^2 = 63\%$; ε2/ε3 versus ε3/ε3: $I^2 = 0\%$; ε2 versus ε3: $I^2 = 23\%$; ε4 versus ε3: $I^2 = 65\%$). 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 ε2/ε3/ε4 polymorphism by excluding the study of Srivastava et al. [53] didn’t produce any significant association of APOE ε2/ε3/ε4 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 ε2/ε3/ε4 involved in meta-analysis.](http://www.diagnosticpathology.org/content/9/1/56)
leptin [26]. Many animal studies have shown that \textit{SH2B1} is involved in the development of obesity. \textit{SH2B1} through its participation in the regulation of leptin sensitivity, energy metabolism and body weight [57]. \textit{SH2B1} has been identified to be related to obesity through genome-wide association studies (GWAS) [55]. Our meta-analysis of \textit{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 \textit{SH2B1} and the risk of overweight/obesity (overall OR = 1.21, 95% CI = 1.09-1.34, P = 0.0004, Figure 1).

\textit{FAIM2} is an anti-apoptotic gene that provides protection from Fas-mediated cell death [32] that is associated with extreme overweight by GWAS [58]. \textit{FAIM2} rs7138803 polymorphism is associated with increased risk of obesity in Japanese [59]. But there is no relationship between \textit{FAIM2} rs7138803 and obesity in Chinese [60]. Minor allele frequency of rs7138803 in Chinese populations ranges from 0.28 to 0.29, while \textit{FAIM2} rs7138803 is monomorphic in Japanese and Caucasian populations. Our meta-analysis among 3477 cases and 4676 controls demonstrated that \textit{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 caution. 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 \textit{FAIM2} rs7138803 needs to be validated in the future. However, after Bonferroni’s correction by the number of testing, the association of \textit{FAIM2} rs7138803 was unable to retain significant. Thirdly, power analysis suggested moderate power in the meta-analyses of \textit{MTHFR} rs1801133 (power = 78.2%) and \textit{SERPINE1} rs1799768 (power = 69.4%) The negative results of these 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 (\textit{SH2B1} rs7498665 and \textit{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 \textit{UCP1} rs1800592 in our subgroup meta-analysis.
- **Additional file 3: Figure S2.** Forest plots of the association studies of \textit{APOE} ε2/ε3/ε4.
- **Additional file 4: Figure S3.** Funnel plots of the studies related to \textit{UCP1} rs1800592 by subgroup meta-analysis and \textit{APOE} ε2/ε3/ε4.

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. Ogundobe 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, Shely 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 1a/oidoesterase induces apoptosis in gallbladder-derived malignant cell by upregulating expression of P73 and PUMA. Tumour Biol 2013, 35(2):1539–1550.
8. Fukua 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 PLAG2 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. Fisherman 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 EC, Edwards TL, Lange LA, Ng MC, Adeyemo AA, Allison MA, Belik JS, Chen G, Grigolli M, Ivan MR, Rhee SK, Li G, Liu Y, Lu Y, Nalls MA, Sun YW, Wojczynski MK, Yanek LR, Aldrich MC, Ademola A, Amos CI, Bandiera EV, Bock CH, Blount AT, Broeckel 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):692–696.

12. Klenke S, Kusmann M, Siffl W: The GNB3 C825T polymorphism as a pharmacogenetic marker in the treatment of hypertension, obesity, and depression. Pharmacogenet Genomics 2011, 21(15):954–966.

13. Piedade MC, Galhardo MS, Battertner CN, Ferreira MA, Caldicot EG, de Toledo OM: Effect of ultrasound therapy on the repair of gastrocnemius muscle injury in rats. Ultraschall 2008, 29(5):403–411.

14. Chmurycka A, Malinowska AM, Twardowska-Jaworska J, Gawołki J: Elderly women: homocysteine reduction by short-term folic acid supplementation resulting in increased glucose concentrations and affecting lipid metabolism (C677T MTHFR polymorphism). Nutrition 2013, 29(6):841–844.

15. Engel S, Bohmke J, Feldpausch M, Gorzelniak K, Janke J, Batski S, Pacher P, Harvey-White J, Luft FC, Sharma AM, Jordan A: Activation of the peripheral endocannabinoid system in human obesity. Diabetes 2005, 54(10):2838–2843.

16. Di Marzo V, Matias I: Brain-derived neurotrophic factor regulates energy balance. Proc Natl Acad Sci U S A 1999, 96(22):12667–12672.

17. Leon-Mimila P, Villamil-Ramirez H, Villalobos-Comparan M, Villareal-Molina T, Romero-Hidalgo S, Lopez-Contreras B, Gutierrez-Vidal R, Vega-Badillo J, Jacobo-Albaveria L, Posadas-Romeros C, Canizalez-Roman A, Rio-Navarro BD, Campos-Perez F, Acuna-Alfonso V, Aguilar-Salinas C, Canizalez-Quinteros S: Contribution of common genetic variants to obesity and obesity-related traits in Mexican children and adults. PLoS One 2013, 8(8):e70540.

18. Kernie SG, Liebl DJ, Parada LF: 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(3):203–210.

19. Daalgard LT, Pedersen O: Uncoupling proteins: functional characteristics and role in the pathogenesis of obesity and Type II diabetes. Diabetologia 2001, 44(8):946–965.

20. Costford S, Gowin A, Harper ME: Mitochondrial uncoupling as a target in the treatment of obesity. Curr Opin Crit Nutr Metab Care 2007, 10(4):555–577.

21. Lieb W, Manning AK, Flórez JC, Dupuis J, Cupples LA, McPherson JB, Vasan RS, Hoffmann U, O'Donnell CL, Meigs JB, Fox CS: Variants in the CNTN1 and the FAH2 genes and adiposity traits in the community. Obesity (Silver Spring) 2009, 17(7):736–742.

22. Tsuchida A, Nonomura T, Nakagawa K, Yon-o-Kishino M, Yamanaka T, Sugano E, Taji M, Noguchi H: Brain-derived neurotrophic factor ameliorates lipid metabolism in diabetic mice. Diabetes Obes Metab 2002, 4(4):262–269.

23. Cravatt BF, Giang DK, Mukherjee A, Rosales C, Chen Y, Smith CW, Mahley RW: Apolipoprotein E: cholesterol transport protein with physiological significance. Physiol Rev 2004, 84(1):277–359.

24. Miyaki K, Surani M, Ikuchi H, Takei I, Murata M, Watanabe K, Orme 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(3):203–210.

25. Poehlman ET: Beta(1)-adrenergic receptor gene (Glycerol Adipocyte) in Caucasian women. Int J Obes Relat Metab Disord 2002, 26(5):633–639.

26. Naveithan P, Hassan H, Canals JM, Ekstrand AJ, Larefalk A, Chajialavi Y, Arenas E, Gedda K, Svensson L, Thoren P, Emfors P: Normal feeding behavior, body weight and leptin response require the neuropeptide Y Y2 receptor. Nat Med 1995, 1(10):1193–1197.

27. 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 homoygous missense mutation in prohormone convertase 1/3. J Clin Endocrinol Metab 2007, 92(9):3369–3373.

28. Dionne IJ, Garant MJ, Nolan AA, Pollin TI, Lewis DG, Shuldiner AR, Poehlman ET: Association between obesity and a polymorphism in the beta(1)-adrenergic receptor gene. PLoS One 2013, 8(3):e59752.
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 (TaqIB) and apolipoprotein E (HhaI) gene variants with obesity. Mol Cell Biochem 2008, 314(1-2):171–177.

54. Maures TJ, Kurzer JM, 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):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 Li: 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, Gaboreau V, Brennan P, Gijesing AP, Grarup N, Witte DR, Jorgensen T, Linneberg A, Lauritzen T, Sandbaek A, Hansen T, Pedersen O, Elliott KS, Mcmahon G, Zelenika D, Hager J, Lathrop M, Nohr EA, Smith CD, 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, Inoue N, Mineo I, Wada J, Masuzaki H, Yoneda M, Nakajima A, Funahashi T, Miyazaki S, Kawai K, Kawamoto M, Ueno T, Haraguchi K, Tanaka K, Yamada K, Hanafusa T, Oikawa S, Yoshimatsu H, Nakao K, Sakata T, Matsu Zawa 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, Qu 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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