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Review

Uncoupling protein 2 gene polymorphisms in association with overweight and obesity susceptibility: A meta-analysis ☆

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ABSTRACT

A meta-analysis was performed to evaluate the associations of uncoupling protein 2 (*UCP2*) gene polymorphisms (Ala55Val, 45-bp insertion/deletion, and -866G/A) with overweight and obesity. A total of 42 studies were included in our analysis. Pooled effect estimates and 95% confidential intervals of each polymorphism were calculated under different inherited models. Fixed or random effect model was selected based on the between-study heterogeneity evaluated with I^2. Source of heterogeneity was explored by subgroup analysis and meta-regression analysis. Potential publication bias was assessed using funnel plot and Peters test. After excluding studies that deviated from the Hardy–Weinberg equilibrium, T allele of Ala55Val polymorphism was associated with an increased risk of overweight and obesity under recessive model in the overall (OR = 1.24, 95%CI = 1.06–1.45) and Asian (OR = 1.28, 95%CI = 1.06–1.55) populations; and A allele of -866G/A polymorphism had a protective effect on overweight and obesity, especially for European populations (dominant model: OR = 0.88, 95%CI = 0.81–0.96, co-dominant 1 model: OR = 0.89, 95%CI = 0.81–0.98, co-dominant 2 model: OR = 0.85, 95%CI = 0.74–0.94, additive model: OR = 0.88, 95%CI = 0.80–0.95, and allelic model: OR = 0.91, 95%CI =0.86–0.97). No evidence was observed in the association of 45-bp insertion/deletion polymorphism with overweight and obesity

Abbreviations: UCP, uncoupling protein; OR, odds ratio; CI, confidence interval; REM, random effect model; FEM, fixed effect model; HWE, Hardy–Weinberg equilibrium

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susceptibility. We failed to fully explore the between-study heterogeneity regarding the association of Ala55Val polymorphism with overweight and obesity. Further studies are required to provide more convincing evidence.

Contents

Introduction

Uncoupling proteins (UCP), a member of mitochondrial membrane transporters, were considered to be associated with energy homeostasis (Dalgaard and Pedersen, 2001). The UCP2, which is widely expressed in human tissues and serves as an uncoupler of oxidative phosphorylation, is involved in the regulation of lipid metabolism and ATP production (Diano and Horvath, 2012; Zhang et al., 2001). It has been reported that impaired expression of UCP2 mRNA in adipose tissue may be responsible for the pathophysiology of obesity (Oberkofler et al., 1998). Ala55Val (rs660339) in Exon 4, 45-bp insertion/deletion in Exon 8, and -866G/A (rs659366) in the promoter region, have been considered as the most interesting polymorphisms in *UCP2* gene. The -866G/A and 45-bp insertion/deletion polymorphisms were found to be functional on mRNA expression (Esterbauer et al., 2001; Krempler et al., 2002). A variant allele of the Ala55Val polymorphism was reported to be associated with lower 24-h energy expenditure (Astrup et al., 1999). Associations of the three polymorphisms with the risk of overweight and obesity have been widely evaluated, but the conclusions remain controversial. In the present study, we performed a meta-analysis to assess the effect of *UCP2* Ala55Val, 45-bp insertion/deletion, and -866G/A polymorphisms on the risk of overweight and obesity.

Methods

Search strategy

Relevant articles published in English and Chinese were searched from five databases: (1) PubMed (1990–2013); (2) Web of Science (ISI) (1990–2013); (3) China National Knowledge Infrastructure (CNKI) (1990–2013); (4) Database of Chinese Scientific and Technical Periodicals (VIP) (1990–2013); and (5) China Biology Medical literature database (CBM) (1990–2013). The search strategy involved the following keywords: 'uncoupling protein 2', 'UCP2', 'polymorphism', 'obesity', 'adiposity', 'obese', and

'overweight'. References of the retrieved articles were checked for additional studies. The literature search was updated on February 22, 2013.

Eligibility criteria

A study that met the following criteria was included in the meta-analysis: (1) case–control, cohort study, or cross-sectional studies which evaluated the association of *UCP2* gene polymorphisms with overweight and obesity; (2) provided sufficient data of genotypes in case (exposed) and control (unexposed) groups; (3) subjects were recruited from the same ethnicity during the same period; (4) if data were repetitively reported, the most complete one was included; (5) the genotype distribution of the controls obey Hardy–Weinberg equilibrium (HWE). The articles were independently assessed by two authors. Disagreements were resolved by consensus with a third reviewer.

Data extraction

Information of the studies was extracted by two independent authors, including first author, publication year, location, ethnicity of subjects, sample size, frequencies of genotype and allele, percentage of male subjects and mean age of subjects in case (exposed) and control (unexposed) groups.

Statistical analysis

HWE for *UCP2* Ala55Val, 45-bp insertion/deletion, and -866G/A genotype distributions in controls was tested using Pearson χ^2 test. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the associations of the *UCP2* Ala55Val, 45-bp insertion/deletion, and -866G/A polymorphisms with risk of overweight and obesity under dominant (CT+TT vs. CC for Ala55Val, ID+II vs. DD for 45-bp insertion/deletion, and GA+AA vs. GG for -866G/A), recessive (TT vs. CT+CC for Ala55Val, II vs. ID+DD for 45-bp insertion/deletion, and AA vs. GA+GG for -866G/A), co-dominant 1 (CT vs. CC for Ala55Val, ID vs. DD for 45-bp insertion/deletion, and GA vs. GG for -866G/A), co-dominant 2 (TT vs. CC for Ala55Val, II vs. DD for 45-bp insertion/deletion, and AA vs. GG for -866G/A), additive (2TT+CT vs. CC for Ala55Val, 2II+ID vs. DD for 45-bp insertion/deletion, and 2AA+ vs. GG for -866G/A), over-dominant (CT vs. CC+TT for Ala55Val, ID vs. II+DD for 45-bp insertion/deletion, and GA vs. AA+GG for -866G/A) and allelic (T vs. C for Ala55Val, I vs. D for 45-bp insertion/deletion, and A vs. G for -866G/A) models, respectively. Pooled ORs in subgroups stratified by ethnicity were also calculated. In addition, cumulative analyses were performed to track the evidence over sample size. *Z* test was used to determine the significance of pooled OR. The I^2 was used to assess heterogeneity among studies (Higgins and Thompson, 2002). Heterogeneity was considered significant if $I^2 > 50\%$, when random-effect model (REM) was adopted as the pooling method; otherwise, fix-effect model (FEM) was used. Meta-analysis regression was performed to identify potential covariates, including ethnicity, publication year, sex, age and sample size, which may contribute to between-study heterogeneity. Sensitive analysis was performed to identify 'outlying' studies and decrease statistical heterogeneity if $I^2 > 50\%$ using *hetred* module (Patsopoulos et al., 2008). Influence of each individual study on the pooled estimate was investigated with influence analysis. A study was suspected of excessive influence if the point estimate of its omitted meta-analysis was beyond the 95%CI of the full analysis. Publication bias was evaluated by funnel plot and Peters test (Peters et al., 2006). All statistical analyses were performed with STATA version 11.0 (Stata Corporation, College Station, TX, USA). P value < 0.05 was considered statistically significant (two-tailed).

Results

Characteristics of studies

A total of 37 published articles with 42 studies (Andersen et al., 2013; Dalgaard et al., 1999, 2003; Esterbauer et al., 2001; Evans et al., 2000; Feng et al., 2004; Gu, 2005; Heidari et al., 2010; Hong et al., 2005; Kosuge et al., 2008; Kring et al., 2008; Kubota et al., 1998; Li, 2007; Li et al., 2007; Lin et al., 2009; Liu

et al., 2012; Maestrini et al., 2003; Mancini et al., 2003; Marti et al., 2004; Mottagui-Tabar et al., 2008; Nieters et al., 2002; Ochoa et al., 2007; Oktavianthi et al., 2012; Papazoglou et al., 2012; Schauble et al., 2003; Shen, 2004; Shen, 2007; Srivastava et al., 2010; Sui et al., 2004; Urhammer et al., 1997; Wang et al., 2007; 2009; Xu, 2005; Yang, 2012; Yang et al., 2004; Yiew et al., 2010; Zou et al., 2011) were eligible for this meta-analysis, including 12 studies on Ala55Val (2011 cases and 2752 controls), 12 studies on 45-bp insertion/deletion (3416 cases and 3260 controls), and 18 studies on -886G/A (5780 cases and 10,196 controls). General characteristics and genotype distributions of the three polymorphisms were summarized in Tables 1–3. In the Asian population, the average frequency of T allele in Ala55Val polymorphism was 38.5% in cases and 41.5% in controls, that of I allele in 45-bp insertion/deletion polymorphism was 12.3% in cases and 11.9% in controls, and that of A allele in -866G/A polymorphism was 41.0% in cases and 44.7% in controls. In the European population, the average frequency of T allele in Ala55Val polymorphism was 53.1% in cases and 51.7% in controls, that of I allele in 45-bp insertion/deletion polymorphism was 27.8% in cases and 27.0% in controls, and that of A allele in -866G/A polymorphism was 37.3% in cases and 39.3% in controls.

Quantitative synthesis

The results of pooled analyses were summarized in Table 4.

UCP2 Ala55Val polymorphism

In the overall population, T allele was found to be significantly associated with an increased risk of overweight and obesity in the recessive (FEM: OR = 1.24, 95%CI = 1.06–1.45), co-dominant 2 (REM: OR = 1.38, 95%CI = 1.03–1.84), additive (REM: OR = 1.34, 95%CI = 1.04–1.72), and allelic (REM: OR = 1.25, 95%CI = 1.07–1.48) models.

Subgroup analysis stratified by ethnicity revealed a significant association in recessive (FEM: OR = 1.28, 95%CI = 1.06–1.55), co-dominant 2 (REM: OR = 1.50, 95%CI = 1.01–2.20), additive (REM: OR = 1.41, 95%CI = 1.04–1.93) and allelic (REM: OR = 1.32, 95%CI = 1.07–1.63) models for Asians. No significant association between Ala55Val polymorphism and risk of overweight and obesity was found in any of the models for Europeans. The pooled ORs for the association of Ala55Val polymorphism with overweight and obesity under recessive model in the main and cumulative meta-analysis were presented in Fig. 1.

UCP2 45-bp insertion/deletion polymorphism

The meta-analysis showed no significant association between the 45-bp insertion/deletion polymorphism and the risk of overweight and obesity in dominant (FEM: OR = 1.02, 95%CI = 0.92–1.13), recessive (FEM: OR = 1.19, 95%CI = 0.95–1.49), co-dominant 1 (FEM: OR = 1.00, 95%CI = 0.89–1.12), co-dominant 2 (FEM: OR = 1.16, 95%CI = 0.92–1.46), additive (REM: OR = 1.04, 95%CI = 0.93–1.15), over-dominant (FEM: OR = 0.98, 95%CI = 0.88–1.09) and allelic (REM: OR = 1.02, 95%CI = 0.89–1.17) models. The results remained non-significant after stratification by ethnicity. The pooled ORs for the association of 45-bp insertion/deletion polymorphism with overweight and obesity under dominant model in the main and cumulative meta-analysis were presented in Fig. 2.

UCP2 -866G/A polymorphism

In the overall population, no significant association between -866G/A polymorphism and risk of overweight and obesity was found in any of the models. Subgroup analysis stratified by ethnicity revealed significant associations in dominant (FEM: OR = 0.88, 95%CI = 0.81–0.96), co-dominant 1 (FEM: OR = 0.89, 95%CI = 0.81–0.98), co-dominant 2 (FEM: OR = 0.85, 95%CI = 0.74–0.94), additive (FEM: OR = 0.88, 95%CI = 0.80–0.95), and allelic (FEM: OR = 0.91, 95%CI = 0.86–0.97) models for Europeans. However, no significant association was found in any inherited models in the population of Asian descent. The pooled ORs for the association of -866G/A polymorphism with overweight and obesity under dominant model in the main and cumulative meta-analysis were presented in Fig. 3.

Table 1
Characteristics of UCP2 gene Ala55Val (rs660339) polymorphism genotype distributions in studies included in this meta-analysis.

First author	Year	Location	Ethnicity	Genotypes (CC/CT/TT)		T allele frequency (%)		% of male (case/control)	Mean age (case/control)	*P* for HWE
				Case	Control	Case	Control			
Urhammer SA	1997	Denmark	European	41/67/36	56/86/40	48.3	45.6	100/100	Na/Na	0.5209
Kubota T	1998	Japan	Asian	15/13/14	64/97/57	48.8	48.4	28.6/56.0	47.1/58.2	0.1070
Yang M	2004	China	Asian	36/45/18	19/29/9	40.9	41.2	Na/Na	Na/Na	0.7066
Sui Y	2004	China	Asian	41/52/26	82/81/14	43.7	30.8	31.1/38.4	54.2/56.0	0.3266
Shen LQ	2004	China	Asian	96/34/14	37/9/2	21.5	13.5	50.0/50.0	Na/Na	0.1674
Xu R	2005	China	Asian	102/193/89	185/356/159	48.3	48.1	42.5/33.9	64.1/62.9	0.6236
Mottagui-Tabar S	2006	Sweden	European	57/136/88	90/227/127	55.5	54.2	0/0	Na/Na	0.5318
Wang TN	2007	Taiwan	Asian	211/104/9	90/24/0	18.8	10.5	38.0/51.9	55.86/58.95	0.2091
Li Q	2007	China	Asian	44/87/38	77/72/24	48.2	34.7	57.4/58.4	7.7/7.6	0.2842
Kosuge K	2008	Japan	Asian	56/80/46	91/199/79	47.3	48.4	70.9/64.2	50.1/50.7	0.1256
Wang W	2009	China	Asian	15/23/5	32/13/3	38.4	19.8	67.4/58.1	Na/Na	0.3086
Yang RR	2012	China	Asian	23/45/12	70/114/38	43.1	42.8	Na/Na	Na/Na	0.4670

Na: not available.

Table 2
Characteristics of *UCP2* gene 45-bp insertion/deletion polymorphism genotype distributions in studies included in this meta-analysis.

First author	Year	Location	Ethnicity	Genotypes (DD/ID/II)		I allele frequency (%)		% of male (case/control)	Mean age (case/control)	*P* for HWE
				Case	Control	Case	Control			
Dalgaard LT	1999	Denmark	European	371/293/80	177/149/28	30.4	29.0	100/100	19–20/19–20	0.6645
Evans D	2000	Germany	European	145/130/30	286/198/24	31.1	24.2	Na/Na	Na/Na	0.1621
Esterbauer H	2001	Australia	European	179/132/29	117/115/24	27.9	31.8	20/25	41.4/40.1	0.5751
Nieters A	2002	Germany	European	88/58/8	78/57/16	24.0	29.5	37.7/37.7	51.2/51.3	0.2585
Maestrini S	2003	Italy	European	211/124/25	51/42/10	24.2	30.1	29.2/Na	45.0/Na	0.7537
Marti A	2004	Spain	European	83/63/11	92/52/6	27.1	21.3	Na/Na	20–60/20–60	0.6875
Feng QW	2004	China	Asian	75/27/1	138/31/2	14.1	10.2	Na/Na	Na/Na	0.8618
Hong QR	2005	China	Asian	165/35/1	190/36/4	9.2	9.6	12.7/13.0	63.2/61.3	0.1485
Ochoa MC	2007	Spain	European	103/71/18	79/76/11	27.9	29.5	51.3/49.3	11.5/11.8	0.1963
Yiew Sk	2010	Malaysia	Asian	71/14/1	130/37/3	9.3	12.6	Na/Na	Na/Na	0.8454
Papazoglou D	2012	Greece	European	96/55/7	60/27/4	21.8	19.2	41.1/40.6	50.0/Na	0.6684
Liu XQ	2012	China	Asian	463/141/12	696/199/15	13.4	12.6	51.8/49.8	45.4/44.6	0.8581

Na: not available.

Table 3
Characteristics of UCP2 gene -866G/A (rs659366) polymorphism genotype distributions in studies included in this meta-analysis.

First author	Year	Location	Ethnicity	Genotypes (GG/GA/AA)		A allele frequency (%)		% of male (case/control)	Mean age (case/control)	*P* for HWE
				Case	Control	Case	Control			
Esterbauer H	2001	Australia	European	54/42/13	221/286/82	31.2	38.2	53.2/56.2	53.5/52.8	0.4905
Esterbauer H	2001	Australia	European	156/140/44	85/127/44	33.5	42.0	20.0/25.0	41.4/40.1	0.0642
Dalgaard LT	2003	Denmark	European	292/322/135	299/369/148	39.5	40.7	100/100	20.0/20.0	0.0696
Schauble N	2003	Germany	European	108/135/34	72/89/27	36.6	38.0	41.5/54.8	14.7/25.5	0.9524
Mancini FP	2003	Italy	European	96/82/20	183/165/26	30.8	29.0	66.7/69.0	36.8/45.0	0.1691
Xu R	2005	China	Asian	105/197/82	179/357/164	47.0	48.9	42.5/33.9	64.1/62.9	0.5881
Gu GY	2005	China	Asian	5/5/3	32/73/44	42.3	54.0	69.2/51.7	59.8/52.8	0.8668
Ochoa MC	2007	Spain	European	79/80/34	59/92/19	38.3	38.2	51.3/49.3	11.5/11.8	0.0573
Wang TN	2007	Taiwan	Asian	193/115/16	81/28/5	22.7	16.7	38.0/51.9	55.9/59.0	0.2163
Li JN	2007	China	Asian	10/16/13	21/28/13	53.8	43.5	Na/Na	Na/Na	0.5211
Shen XJ	2007	China	Asian	32/36/10	45/55/18	35.9	38.6	Na/Na	Na/Na	0.8595
Kring SI	2008	Denmark	European	88/96/41	114/131/49	39.6	38.9	100/100	Na/Na	0.2797
Lin E	2009	Taiwan	Asian	92/101/29	92/146/47	35.8	42.1	48.6/46.3	57.0/57.5	0.3915
Srivastava N	2010	India	Asian	73/86/41	106/113/21	42.0	32.3	Na/Na	Na/Na	0.2346
Heidari J	2010	Iran	Asian	16/48/11	27/41/7	46.7	36.7	24.0/45.3	44.3/35.9	0.1252
Zou HY	2011	China	Asian	176/281/133	623/1115/489	46.4	47.0	23.7/40.8	55.7/55.8	0.8140
Oktavianthi S	2012	Indonesia	Asian	60/120/37	127/195/64	44.7	41.8	64.5/51.8	47.3/50.1	0.4552
Andersen G	2012	Denmark	European	583/754/210	1133/1499/521	37.9	40.3	Na/Na	Na/Na	0.5028

Na: not available.

Table 4
Pooled measures for the associations of the UCP2 Ala55Val, 45-bp insertion/deletion, and -866G/A polymorphisms with overweight and obesity.

Population	Inherited model	Before sensitive analysis			
		Numbers of cases/controls	Pooled OR (95% CI)		I^2 (%)
			FEM	REM	
Ala55Val					
Overall	Dominant	2011/2752	1.19 (1.04–1.36)*	1.27 (0.99–1.62)	65.4
	Recessive	1687/2638	1.24 (1.06–1.45)*	1.29 (1.06–1.56)*	24.7
	Co-dominant 1	2011/2752	1.12 (0.97–1.29)	1.17 (0.91–1.50)	62.0
	Co-dominant 2	1687/2638	1.26 (1.05–1.52)*	1.38 (1.03–1.84)*	51.3
	Additive	2011/2752	1.24 (1.09–1.41)*	1.34 (1.04–1.72)*	69.5
	Over-dominant	2011/2752	1.00 (0.89–1.13)	1.04 (0.85–1.27)	54.6
	Allelic	2011/2752	1.17 (1.07–1.27)*	1.25 (1.07–1.48)*	64.6
Asian	Dominant	1586/2126	1.24 (1.06–1.44)*	1.34 (0.99–1.81)	70.7
	Recessive	1262/2012	1.28 (1.06–1.55)*	1.39 (1.06–1.82)*	37.8
	Co-dominant 1	1586/2126	1.15 (0.98–1.36)	1.22 (0.90–1.67)	68.0
	Co-dominant 2	1262/2012	1.31 (1.06–1.63)*	1.50 (1.01–2.20)*	59.9
	Additive	1586/2126	1.29 (1.11–1.50)*	1.41 (1.04–1.93)*	74.0
	Over-dominant	1586/2126	1.03 (0.89–1.19)	1.09 (0.84–1.40)	61.8
	Allelic	1586/2126	1.20 (1.08–1.33)*	1.32 (1.07–1.63)*	64.6
European	Dominant	425/626	1.04 (0.78–1.40)	1.04 (0.78–1.40)	0.0
	Recessive	425/626	1.15 (0.87–1.52)	1.15 (0.87–1.52)	0.0
	Co-dominant 1	425/626	0.99 (0.72–1.35)	0.99 (0.72–1.35)	0.0
	Co-dominant 2	425/626	1.14 (0.80–1.61)	1.14 (0.80–1.61)	0.0
	Additive	425/626	1.07 (0.80–1.42)	1.07 (0.80–1.42)	0.0
	Over-dominant	425/626	0.92 (0.72–1.18)	0.92 (0.72–1.18)	0.0
	Allelic	425/626	1.07 (0.90–1.28)	1.07 (0.90–1.28)	0.0
45-bp insertion/deletion					
Overall	Dominant	3416/3260	1.02 (0.92–1.13)	1.01 (0.86–1.17)	45.7
	Recessive	3416/3260	1.19 (0.95–1.49)	1.13 (0.85–1.51)	28.6
	Co-dominant 1	3416/3260	1.00 (0.89–1.12)	0.99 (0.86–1.15)	33.4
	Co-dominant 2	3416/3260	1.16 (0.92–1.46)	1.08 (0.78–1.51)	41.4
	Additive	3416/3260	1.04 (0.93–1.15)	1.01 (0.86–1.19)	56.2
	Over-dominant	3416/3260	0.98 (0.88–1.09)	0.98 (0.86–1.11)	20.4
	Allelic	3416/3260	1.04 (0.95–1.13)	1.02 (0.89–1.17)	53.0
Asian	Dominant	1006/1481	1.07 (0.88–1.30)	1.07 (0.86–1.34)	11.8
	Recessive	1006/1481	0.96 (0.50–1.87)	0.96 (0.50–1.87)	0.0
	Co-dominant 1	1006/1481	1.08 (0.89–1.32)	1.09 (0.87–1.36)	11.8
	Co-dominant 2	1006/1481	0.98 (0.50–1.90)	0.98 (0.50–1.90)	0.0
	Additive	1006/1481	1.06 (0.88–1.28)	1.06 (0.84–1.32)	15.8
	Over-dominant	1006/1481	1.08 (0.89–1.32)	1.09 (0.87–1.36)	11.4
	Allelic	1006/1481	1.05 (0.89–1.26)	1.05 (0.87–1.27)	5.8
European	Dominant	2410/1779	1.00 (0.88–1.13)	0.98 (0.80–1.20)	57.5
	Recessive	2410/1779	1.22 (0.96–1.55)	1.16 (0.82–1.65)	47.6
	Co-dominant 1	2410/1779	0.96 (0.84–1.10)	0.96 (0.80–1.15)	42.5
	Co-dominant 2	2410/1779	1.18 (0.92–1.51)	1.12 (0.74–1.68)	58.5
	Additive	2410/1779	1.02 (0.91–1.16)	1.00 (0.80–1.25)	67.3
	Over-dominant	2410/1779	0.94 (0.82–1.07)	0.94 (0.81–1.09)	22.3
	Allelic	2410/1779	1.03 (0.94–1.14)	1.01 (0.85–1.21)	65.3
-866G/A					
Overall	Dominant	5780/10,196	0.93 (0.86–0.99)*	0.94 (0.83–1.06)	52.7
	Recessive	5780/10,196	0.96 (0.88–1.05)	1.02 (0.88–1.18)	44.9
	Co-dominant 1	5780/10,196	0.93 (0.86–1.00)	0.92 (0.82–1.03)	44.3
	Co-dominant 2	5780/10,196	0.91 (0.83–1.01)	0.98 (0.82–1.17)	52.9
	Additive	5780/10,196	0.93 (0.86–0.99)*	0.95 (0.84–1.08)	60.7
	Over-dominant	5780/10,196	0.95 (0.89–1.02)	0.93 (0.85–1.03)	32.6
	Allelic	5780/10,196	0.95 (0.91–1.00)	0.98 (0.90–1.07)	57.6
Asian	Dominant	2142/4356	1.01 (0.90–1.14)	1.07 (0.87–1.32)	58.1
	Recessive	2142/4356	1.05 (0.91–1.21)	1.11 (0.88–1.40)	45.8
	Co-dominant 1	2142/4356	1.00 (0.88–1.13)	1.04 (0.86–1.26)	45.7

After sensitive analysis				Excluded studies in sensitive analysis
Numbers of cases/controls	Pooled OR (95% CI)		I^2 (%)	
	FEM	REM		
1799/2531	1.08 (0.94–1.25)	1.11 (0.91–1.36)	42.6	Li (2007), Wang et al. (2009)
–	–	–	–	–
1799/2531	1.01 (0.87–1.18)	1.02 (0.84–1.25)	35.1	Li (2007), Wang et al. (2009)
1568/2461	1.18 (0.97–1.42)	1.22 (0.96–1.54)	25.4	Sui et al. (2004)
1475/2417	1.07 (0.92–1.23)	1.09 (0.90–1.31)	33.9	Li (2007), Wang et al. (2007, 2009)
1968/2704	0.98 (0.86–1.11)	0.99 (0.83–1.19)	43.5	Wang et al. (2009)
1723/2402	1.08 (0.98–1.19)	1.14 (0.98–1.32)	46.2	Li (2007), Sui et al. (2004)
1050/1791	1.02 (0.85–1.21)	1.03 (0.82–1.31)	35.0	Li (2007), Wang et al. (2007, 2009)
–	–	–	–	–
1192/1536	1.12 (0.92–1.36)	1.13 (0.88–1.45)	29.9	Kosuge et al. (2008), Li (2007), Wang et al. (2009)
1143/1835	1.19 (0.95–1.50)	1.28 (0.92–1.80)	41.2	Sui et al. (2004)
1050/1791	1.07 (0.90–1.26)	1.10 (0.85–1.43)	49.9	Li (2007), Wang et al. (2007, 2009)
1361/1709	1.08 (0.92–1.27)	1.10 (0.88–1.37)	39.2	Kosuge et al. (2008), Wang et al. (2009)
974/1662	1.04 (0.93–1.18)	1.09 (0.91–1.30)	39.7	Li (2007), Sui et al. (2004), Wang et al. (2007)
–	–	–	–	–
–	–	–	–	–
–	–	–	–	–
–	–	–	–	–
–	–	–	–	–
–	–	–	–	–
–	–	–	–	–
–	–	–	–	–
–	–	–	–	–
3111/2752	0.97 (0.87–1.09)	0.96 (0.83–1.12)	38.7	Evans et al. (2000)
				–
3111/2752	0.98 (0.90–1.08)	0.98 (0.87–1.10)	32.2	Evans et al. (2000)
–	–	–	–	–
–	–	–	–	–
–	–	–	–	–
–	–	–	–	–
–	–	–	–	–
–	–	–	–	–
–	–	–	–	–
2105/1271	0.91 (0.79–1.05)	0.91 (0.76–1.09)	33.7	Evans et al. (2000)
–	–	–	–	–
–	–	–	–	–
2105/1271	1.00 (0.76–1.32)	0.97 (0.68–1.39)	34.1	Evans et al. (2000)
2105/1271	0.93 (0.81–1.06)	0.92 (0.76–1.12)	47.4	Evans et al. (2000)
–	–	–	–	
2105/1271	0.96 (0.86–1.07)	0.95 (0.81–1.11)	44.1	Evans et al. (2000)
5440/9940	0.95 (0.88–1.02)	0.97 (0.86–1.02)	43.9	Esterbauer et al. (2001)
–	–	–		–
–	–	–		–
5580/9956	0.88 (0.80–0.98)*	0.91 (0.79–1.05)	28.2	Srivastava et al. (2010)
5240/9700	0.93 (0.86–1.00)	0.95 (0.85–1.06)	44.7	Esterbauer et al. (2001), Srivastava et al. (2010)
–	–	–	–	–
5580/9956	0.94 (0.89–0.99)*	0.95 (0.88–1.03)	44.4	Srivastava et al. (2010)
1596/3957	1.03 (0.90–1.17)	1.08 (0.88–1.32)	42.4	Lin et al. (2009), Wang et al. (2007)
–	–	–	–	–
–	–	–	–	–

Table 4 (*continued*)

Population	Inherited model	Before sensitive analysis			
		Numbers of cases/controls	Pooled OR (95% CI)		I^2 (%)
			FEM	REM	
	Co-dominant 2	2142/4356	1.03 (0.88–1.22)	1.13 (0.83–1.54)	59.4
	Additive	2142/4356	1.03 (0.91–1.15)	1.10 (0.87–1.37)	66.1
	Over-dominant	2142/4356	0.98 (0.88–1.10)	1.00 (0.87–1.14)	19.8
	Allelic	2142/4356	1.02 (0.95–1.11)	1.08 (0.92–1.26)	63.6
European	Dominant	3638/5840	0.88 (0.81–0.96)*	0.86 (0.75–0.97)*	36.8
	Recessive	3638/5840	0.90 (0.80–1.01)	0.95 (0.79–1.14)	39.1
	Co-dominant 1	3638/5840	0.89 (0.81–0.98)*	0.85 (0.73–0.98)*	42.2
	Co-dominant 2	3638/5840	0.85 (0.74–0.94)*	0.87 (0.72–1.05)	33.3
	Additive	3638/5840	0.88 (0.80–0.95)*	0.86 (0.76–0.98)*	41.5
	Over-dominant	3638/5840	0.94 (0.86–1.02)	0.88 (0.76–1.01)	48.5
	Allelic	3638/5840	0.91 (0.86–0.97)*	0.91 (0.84–0.99)*	31.5

Dominant model: CT+TT vs. CC for Ala55Val, ID+II vs. DD for 45-bp insertion/deletion, and GA+AA vs. GG for -866G/A.
Recessive model: TT vs. CT+CC for Ala55Val, II vs. ID+DD for 45-bp insertion/deletion, and AA vs. GA+GG for -866G/A.
Co-dominant 1 model: CT vs. CC for Ala55Val, ID vs. DD for 45-bp insertion/deletion, and GA vs. GG for -866G/A.
Co-dominant 2 model: TT vs. CC for Ala55Val, II vs. DD for 45-bp insertion/deletion, and AA vs. GG for -866G/A.
Additive model: 2TT+CT vs. CC for Ala55Val, 2II+ID vs. DD for 45-bp insertion/deletion, and 2AA+GA vs. GG for -866G/A.
Over-dominant model: CT vs. CC+TT for Ala55Val, ID vs. II+DD for 45-bp insertion/deletion, and GA vs. AA+GG for -866G/A.
Allelic model: T vs. C for Ala55Val, I vs. D for 45-bp insertion/deletion, and A vs. G for -866G/A.
DHWE: deviating from Hardy–Weinberg equilibrium.
FEM: fixed effect model; REM: random effect model.
* $P < 0.05$.

Source of heterogeneity and sensitive analysis

As shown in Table 4, significant heterogeneity ($I^2 > 50\%$) was observed among studies of the Ala55Val, 45-bp insertion/deletion, and -866G/A polymorphisms in some inherited models. Univariate meta-regression with the covariates of ethnicity, publication year, sex (ratio of male in case group to that in control group) and age (ratio of mean age in case group to that in control group) revealed that no covariates had excessive influence on between-study heterogeneity regarding the association of each polymorphism with overweight and obesity.

Significant heterogeneity was observed among studies of the Ala55Val polymorphism under all the inherited models except for the recessive one in the overall population. When stratified by ethnicity, the heterogeneity still existed in participants of Asian descent. Studies that were key contributors to between-study heterogeneity were indicated in Table 4. After sensitive analysis, the associations between T allele and risk of overweight and obesity were no longer significant in the co-dominant 2, additive, and allelic inherited models among the overall population.

Significant heterogeneity was observed among studies regarding the associations of the 45-bp insertion/deletion polymorphism with overweight and obesity in additive and allelic models among the overall population. When stratified by ethnicity, the heterogeneity was significantly decreased in the population of Asian descent, but still existed in that of European descent. Results of sensitive analysis indicated that one study (Evans et al., 2000) was mainly responsible for the between-study heterogeneity in additive and allelic models for the overall population, and that in dominant, co-dominant 2, additive and allelic models for the population of European descent, considering the association of the 45-bp insertion/deletion polymorphism with overweight and obesity. After exclusion of the study, the associations still remained non-significant in all the inherited models.

Significant heterogeneity was observed among studies regarding the associations of the -866G/A polymorphism with overweight and obesity in dominant, co-dominant 2, additive, and allelic models among the overall population. When stratified by ethnicity, the heterogeneity was significantly decreased in the population of European descent, but still existed in that of Asian descent. After sensitive analysis, the associations between A allele and risk of overweight and obesity were significant in the co-dominant 2 (FEM: OR = 0.99, 95%CI = 0.80–0.98) and allelic (FEM: OR = 0.94, 95%CI = 0.89–0.99) models in the

After sensitive analysis				Excluded studies in sensitive analysis
Numbers of cases/controls	Pooled OR (95% CI)		I^2 (%)	
	FEM	REM		
1942/4116	0.95 (0.80–1.13)	0.97 (0.77–1.21)	24.6	Srivastava et al. (2010)
1396/3717	0.99 (0.87–1.13)	1.04 (0.83–1.30)	45.4	Lin et al. (2009), Srivastava et al. (2010), Wang et al. (2007)
–	–	–	–	–
1720/3831	1.02 (0.93–1.11)	1.06 (0.92–1.22)	41.5	Lin et al. (2009), Srivastava et al. (2010)
–	–	–	–	–
–	–	–	–	–
–	–	–	–	–
–	–	–	–	–
–	–	–	–	–
–	–	–	–	–
–	–	–	–	–

overall population. However, the associations remained non-significant in all the aforementioned inherited models among the population of Asian descent.

Influence analysis

With articles that were key contributors to heterogeneity being excluded, no individual study was found to have excessive influence on the pooled effect under all the mentioned inherited models for any of the polymorphisms (data not shown).

Publication bias evaluation

After exclusion of studies that were key contributors to between-study heterogeneity, no publication bias was detected in all the aforementioned inherited models using funnel plot and Peters test regarding the associations between the three polymorphisms with overweight and obesity (data not shown).

Discussion

UCP2 gene was first identified as a candidate gene for obesity by Fleury et al. (1997). Since then, the associations of *UCP2* gene polymorphisms (Aal55Val, 45-bp insertion/deletion, and -866G/A) with overweight and obesity have been widely studied; however, the results were conflicting. Considering the small effect of a genetic variant, a large sample size is certainly required in the primary genetic association study with adequate power. In order to obtain a robust conclusion regarding the role of *UCP2* gene polymorphisms in the risk of overweight and obesity based on a larger scale of population, we performed the meta-analyses consisting 42 studies to evaluate the associations. The pooled ORs from our meta-analyses revealed a risk effect of T allele in Ala55Val polymorphism in populations of Asian descent, a protective effect of A allele in -866G/A polymorphism in populations of European descent and no effect of 45-bp insertion/deletion polymorphism on overweight and obesity. Cumulative meta-analyses showed an increased accuracy in the estimate of effects with larger samples aggregated for the three polymorphisms in *UCP2* gene.

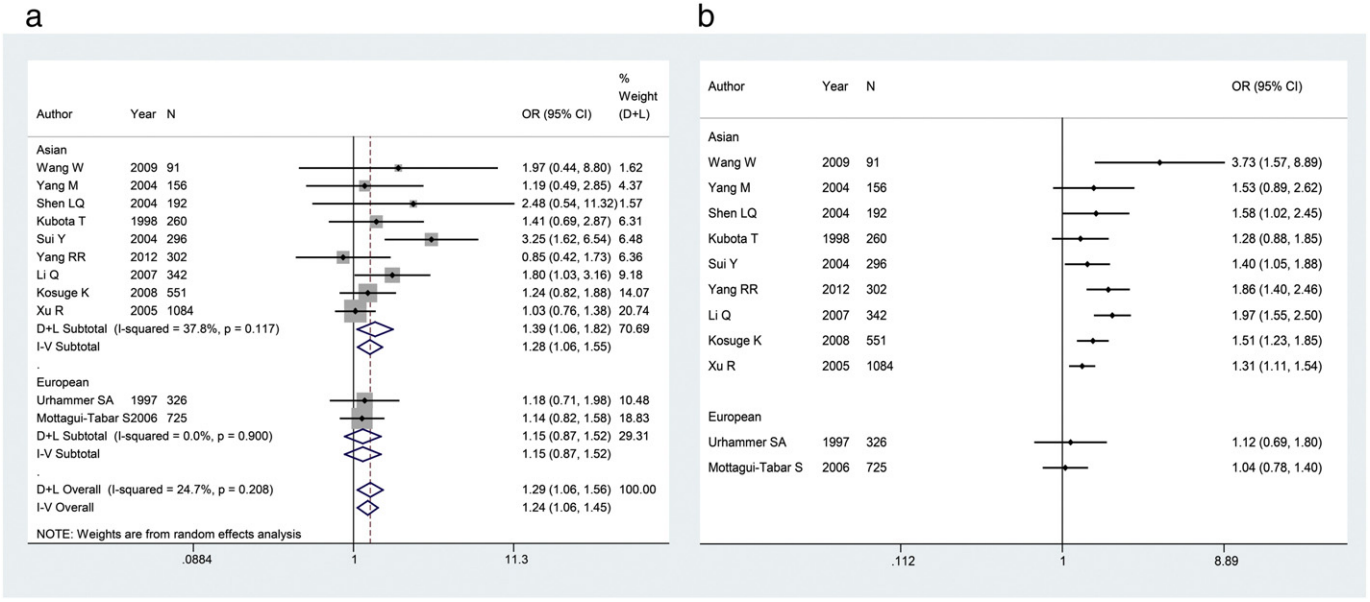

Fig. 1. Stratified analysis of the association of Ala55Val polymorphism with overweight and obesity by ethnicity. (a) Meta-analysis for the association of the Ala55Val polymorphism with overweight and obesity under recessive model (TT vs. CT+CC). (b) Cumulative meta-analysis for the association of Ala55Val polymorphism with overweight and obesity under recessive model.

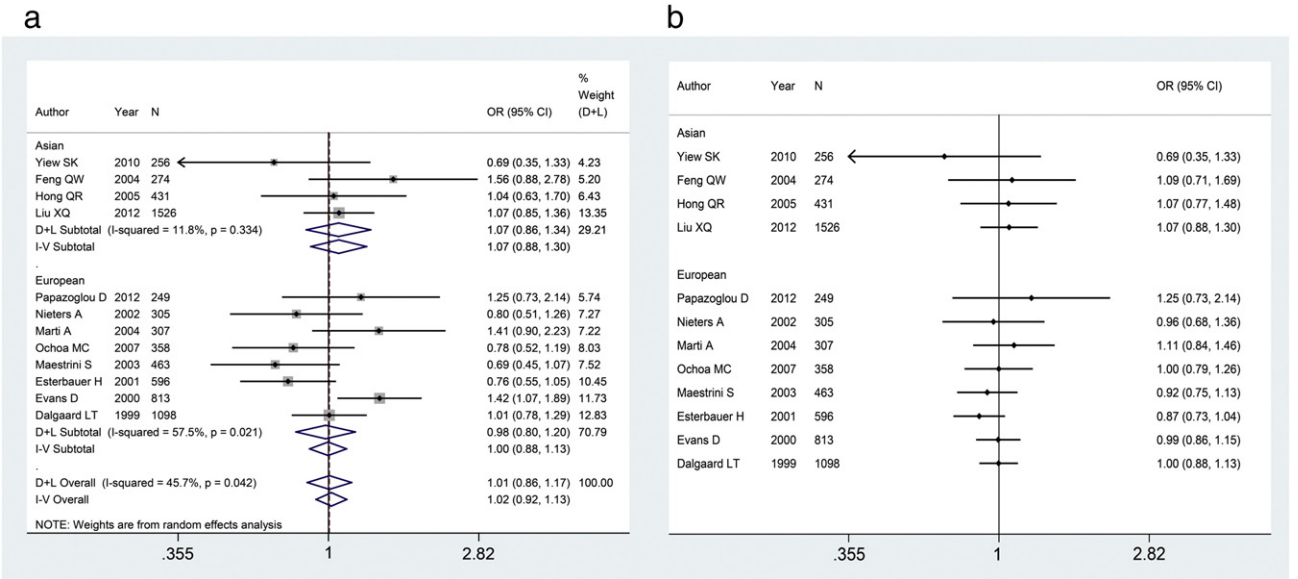

Fig. 2. Stratified analysis of the association of 45-bp insertion/deletion polymorphism with overweight and obesity by ethnicity. (a) Meta-analysis for the association of the 45-bp insertion/deletion polymorphism with overweight and obesity under dominant model (ID+II vs. DD). (b) Cumulative meta-analysis for the association of 45-bp insertion/deletion polymorphism with overweight and obesity under dominant model.

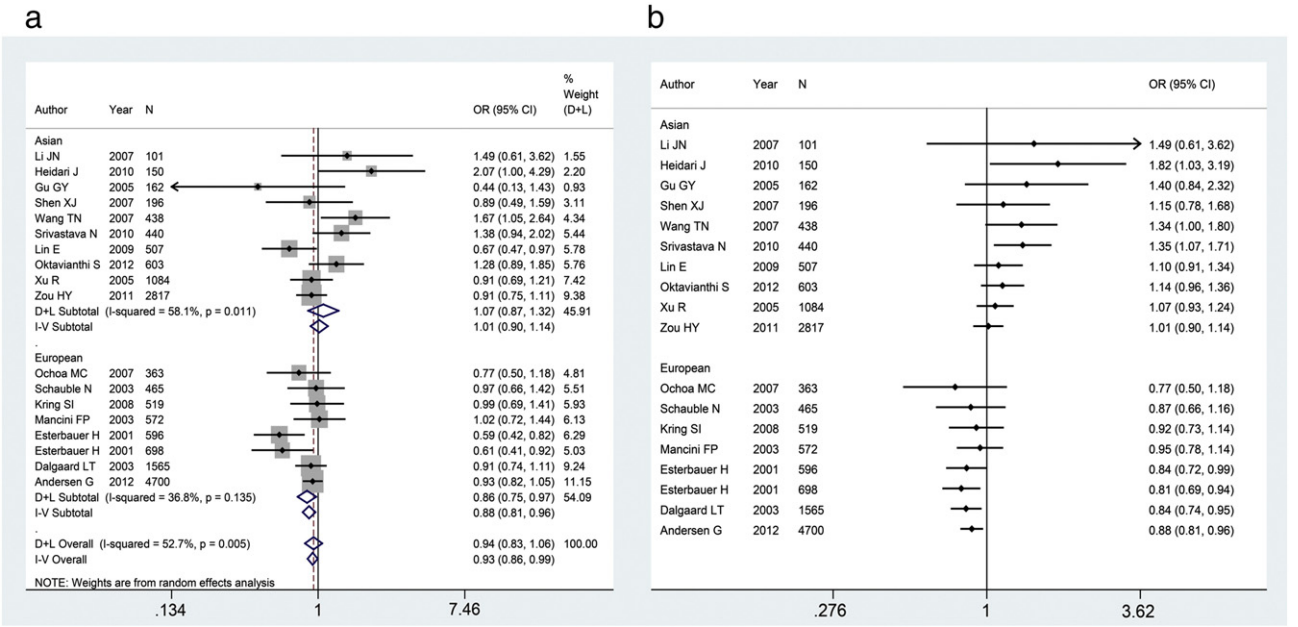

Fig. 3. Stratified analysis of the association of -866G/A polymorphism with overweight and obesity by ethnicity. (a) Meta-analysis for the association of the -866G/A polymorphism with overweight and obesity under dominant model (GA+AA vs. GG). (b) Cumulative meta-analysis for the association of -866G/A polymorphism with overweight and obesity under dominant model.

Between-study heterogeneity is a usual concern in meta-analyses (Munafo and Flint, 2004), which was also observed in our analysis under most of the inherited models regarding the association of *UCP2* polymorphisms with overweight and obesity. After stratification analysis by ethnicity, the heterogeneity in some comparison groups remained significant. To further explore the source of heterogeneity, we performed a meta-regression analysis involving covariates such as publication year, sex, age, and sample size. However, none of the covariates was found to contribute to the between-study heterogeneity regarding the associations of aforementioned polymorphisms with overweight and obesity. It suggested that some other confounding factors, such as design quality, representativeness and general characteristics of the participants, environmental exposures, and non-uniform genotyping methods may be responsible for the heterogeneity. However, we failed to evaluate the role of these factors in the source of heterogeneity in our analysis due to inadequate information in the original articles.

No significant between-study heterogeneity ($I^2 < 50$) was found in the recessive model regarding the association of Ala55Val polymorphism with overweight and obesity. Available data suggested a stable association of T allele of Ala55Val polymorphism with an increased risk of overweight and obesity in the recessive model for the Asian population. Studies indicated that the Ala55Val polymorphism had effects on metabolic rate and nocturnal physical activity (Astrup et al., 1999; Klannemark et al., 1998; Walder et al., 1998). T allele of the polymorphism was reported to be associated with lower energy expenditure and lower fat oxidation (Astrup et al., 1999), which may be implicated in the pathogenesis of overweight and obesity. In this meta-analysis, we failed to fully explore the source of between-study heterogeneity observed in most of the inherited models. Although significant associations were revealed in the co-dominant 2, additive and allelic models in the meta-analysis, the conclusions were limited because of the unsolved heterogeneity.

Significant between-study heterogeneity was found in the additive and allelic models regarding the association of 45-bp insertion/deletion polymorphism with overweight and obesity in the overall population. One study (Evans et al., 2000) that was a key contributor to the heterogeneity was identified using sensitive analysis. The between-study heterogeneity largely decreased after the key contributor was excluded, and the conclusions were consistent with those before sensitive analysis. In our meta-analysis, no evidence was observed on the association of *UCP2* 45-bp insertion/deletion polymorphism with overweight and obesity both in European and Asian populations.

Associations of -866G/A polymorphism with the risk of obesity were evaluated using meta-analysis by Andersen et al. (2013) and Liu et al. (2013) before. In this study, we performed a meta-analysis based on 15,976 individuals from 18 studies with strict eligible criteria to provide robust evidence. Available data in our meta-analysis suggested a stable association of -866G/A polymorphism with overweight and obesity in the population of European descent. The pooled ORs for GA+AA vs. GG, GA vs. GG, AA vs. GG and A vs. G for Europeans were 0.88, 0.89, 0.85 and 0.91, respectively, which were consistent with previous researches (Andersen et al., 2013; Liu et al., 2013). Besides, we identified a significant association of -866G/A polymorphism with overweight and obesity under additive model (2AA+GA vs GG) for the population of European descent. However, no evidence was observed in all the aforementioned models for the population of Asian descent. Oberkofler et al. indicated a reduced *UCP2* mRNA level in intraperitoneal adipose tissue in obese individuals (Oberkofler et al., 1998). A allele of -866G/A polymorphism was reported to be associated with enhanced *UCP2* mRNA expression in adipose tissue in European population (Esterbauer et al., 2001), which may explain its protective effect against overweight and obesity.

Obesity is a heterogeneous disorder caused by complex gene × gene and gene × environment interactions. The effects of Ala55Val and -866G/A polymorphisms on overweight and obesity differed in Europeans and Asians, which may be attributed to different genetic backgrounds. Significant linkage disequilibrium has been observed among Ala55Val, 45-bp insertion/deletion, and -866G/A polymorphisms in overweight and obese populations (Esterbauer et al., 2001; Ochoa et al., 2007; Oktavianthi et al., 2012; Wang et al., 2007). Lack of consideration of the effects of adjacent loci may partially explain the discrepancies among individual studies. Since limited information was provided in the included studies, effects of haplotypes on overweight and obesity could not be evaluated in our meta-analysis, which require further investigation.

The conclusions of our meta-analysis should be considered under the following limitations. First, the outcome of interest was not uniform in all the included studies. Cases were defined as morbidly obese population, obese population, or combined population of overweight and obesity in different studies. The cutoff used for overweight or obesity differed in studies with the same target population. Second, subgroup

analysis was performed to decrease potential between-study heterogeneity; however, limited studies and small sample size in some subgroups may lead to an underpowered result. Third, since insufficient information was provided in the original studies, we failed to fully explore the source of between-study heterogeneity under some circumstances. Last, language was restricted to English and Chinese in the search strategy, which may limit the result.

Conclusions

In conclusion, meta-analyses of currently available studies supported that T allele of Ala55Val polymorphism was associated with an increased risk of overweight and obesity under recessive model, especially for populations of Asian descent; and A allele of -866G/A polymorphism had a protective effect on overweight and obesity, especially for European populations. However, 45-bp insertion/deletion polymorphism is not a susceptibility locus to overweight and obesity. Additional association studies with large sample size and sufficient information allowing powerful stratification analyses are needed to provide more robust evidence to the conclusions. The roles of haplotypes of *UCP2* gene in the pathogenesis of overweight and obesity require to be clarified in future researches.

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