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Association between polymorphism near the *MC4R* gene and cancer risk

A meta-analysis

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Abstract

Objective: Genome-wide association studies have identified single nucleotide polymorphisms (SNPs) near the *melanocortin 4 receptor* (*MC4R*), gene which are associated with risk of obesity. Since obesity is an established risk factor of cancer, several studies have examined the association between SNPs near the *MC4R* gene and cancer risk, but the findings are inconsistent. The present study aimed to perform a meta-analysis to clarify the association between SNPs near *MC4R* and cancer risk.

Methods: The PubMed and Embase databases were searched for potentially eligible publications. All studies that evaluated the association between *MC4R* rs17782313 SNP (or its proxy rs12970134) and cancer risk were included. The pooled odds ratios with 95% confidence intervals (CIs) were calculated using the random-effects model. And subgroup analysis by cancer type (colorectal cancer, endometrial cancer and breast cancer) was conducted for further investigate the association.

Results: A total of 6 eligible studies (6517 cases and 16,886 controls) were included in the present meta-analysis. The results indicated that *MC4R* rs17782313 SNP was moderately associated with cancer risk (odds ratio = 1.12, 95% CI = 1.01–1.24). However, the subgroup analysis between different cancer types shows that rs17782313 is only associated with colorectal cancer but not the endometrial cancer and breast cancer. Risk factor in colorectal cancer was both significantly associated with rs17782313 with and without adjustment for body mass index; while the risk factor of the endometrial cancer and breast cancer were both not associated with the rs17782313 with and without adjustment for body mass index. There was no publication bias for the association between *MC4R* rs17782313 and cancer risk.

Conclusion: The present meta-analysis confirmed the moderate association between *MC4R* rs17782313 and cancer risk.

Abbreviations: BMI = body mass index, CI = confidence interval, MC4R = melanocortin 4 receptor, OR = odds ratio, SNPs = single nucleotide polymorphisms.

Keywords: cancer, *MC4R*, meta-analysis, single nucleotide polymorphism

1. Introduction

In 2008, the genome-wide association studies (GWAS) reported that rs17782313 single nucleotide polymorphism (SNP) mapped 188 kb downstream of the *melanocortin 4 receptor* (*MC4R*) gene was strongly associated with body mass index (BMI) and risk of obesity in European populations.[1] Furthermore, subsequent studies have confirmed the positive association between SNPs in/near the *MC4R* gene and risk of obesity in populations with different races/ethnicities.[2–4]

MC4R is a 332-amino acid protein encoded by a single exon on chromosome 18q22. The rare coding mutations in the *MC4R* gene have been found to be the main cause of human monogenic obesity,[5] suggesting that the *MC4R* gene represents a compelling biological candidate. MC4R expression is also associated with risk of early-onset obesity, increased lean mass and bone mineral density, and enhanced linear growth.[6] Two previous meta-analyses confirmed that the rs17782313 SNP near the *MC4R* gene was associated with risk of obesity[4] and type-2 diabetes.[7] It has been well-documented that obesity is the leading risk factor for many cancers. Therefore, it is important to determine whether *MC4R* SNPs are associated with cancer risk, which may help illuminate the potential biological mechanism between obesity and cancer development. To date, several studies have investigated the associations of *MC4R* SNPs with risk of cancer.[8–14] However, the findings have been contradictory.

The present study aimed to perform a systematic meta-analysis to clarify the association between the rs17782313 SNP (or its proxy) near the *MC4R* gene and risk of cancer.

2. Materials and Methods

2.1. Literature and search strategy

The PubMed and Embase databases were searched for potentially eligible studies. The following key words were used to search for

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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eligible publications: (*melanocortin 4 receptor* OR *MC4R*) and (polymorphism OR variant OR variation OR genotype) and (cancer OR tumor OR carcinoma). The publication language was restricted to the English language. The reference lists of retrieved articles were also hand-searched. The literature search was updated as of September 10, 2019. Since this is a meta-analysis, ethical approval was waived.

2.2. Inclusion criteria and data extraction

The included studies met all the following inclusion criteria:

(1) studies that determined the association of *MC4R* rs17782313 (or its proxy SNP rs12970134, $r^2 > 0.90$) with cancer risk;
(2) studies that had case-control design;
(3) studies that provided an odds ratio (OR) with 95% confidence interval (CI) with or without adjustments for BMI.

The following information were extracted from each study:

(1) name of the first author,
(2) year of publication,
(3) country of origin,
(4) race/ethnicity of the study population,
(5) number of cases and controls,
(6) gender ratio,
(7) mean age,
(8) mean BMI,
(9) cancer type,
(10) the studied SNP, and
(11) the determination of whether BMI was adjusted in the statistical model.

Two authors independently reviewed the articles for compliance with the inclusion/exclusion criteria, resolved any disagreement, and reached a consistent decision after discussion with a third author, if necessary.

2.3. Statistical analysis

The association between *MC4R* rs17782313 and cancer risk was determined by calculating the pooled OR and 95% CI under an additive genetic model. *Z*-test was used to determine the significance of the OR ($P < .05$ was considered statistically significant). Cochrane *Q*-test was conducted to assess the between-study heterogeneity.[15,16] I^2 represented the range for the degree of heterogeneity. A random-effects model (DerSimonian–Laird[15]) was used to calculate the pooled OR when there was between-study heterogeneity ($P \leq .10$ or $I^2 \geq 50\%$). Otherwise, a fixed-effects model (Mantel–Haenszel[16]) was used. Publication bias was assessed by Begg test and Egger test[17] ($P < .05$ was considered statistically significant). The data were analyzed using STATA version 11.0 (StataCorp LP, College Station, TX).

3. Results

3.1. Characteristics of the studies

Figure 1 presents a flow chart describing the process of inclusion/exclusion of studies. The literature search identified 35 potentially relevant articles. A total of 6 publications (6517 cancer cases and 16,886 healthy controls) were finally included in the present meta-analysis. The *MC4R* rs17782313 (or its proxy SNP rs12970134) in each included study was in Hardy-Weinberg Equivalent. The characteristics of the included studies are listed in Table 1.

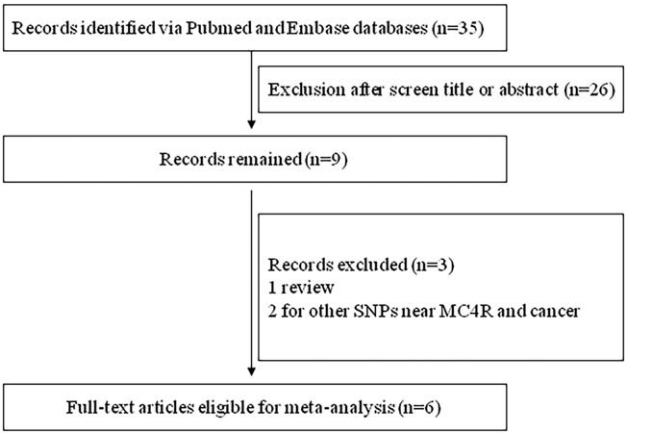

Figure 1. Flowchart for the inclusion/exclusion of studies.

3.2. Meta-analysis results

Before adjusting for BMI, the *MC4R* rs17782313 SNP risk allele was moderately associated with cancer risk (OR = 1.12, 95% CI = 1.01–1.24) in an additive genetic model (Fig. 2). In the subgroup analysis by cancer type, there was a significant association with risk of colorectal cancer (OR = 1.12, 95% CI = 1.04–1.21). In contrast, the *MC4R* rs17782313 SNP was not associated with endometrial cancer (OR = 1.12, 95% CI = 0.87–1.45) or breast cancer (OR = 1.27, 95% CI = 0.77–2.11) (Table 2).

After adjusting for BMI, the *MC4R* rs17782313 SNP risk allele was not associated with cancer risk (OR = 1.08, 95% CI = 0.94–1.23; Fig. 3). In the subgroup analysis by cancer type, the *MC4R* rs17782313 SNP was moderately associated with the risk of colorectal cancer (OR = 1.11, 95% CI = 1.03–1.20; Table 2). While the risk factor of the other 2 cancer type (endometrial cancer and breast cancer) were both not associated with the rs17782313 with and without adjustment for BMI.

3.3. Publication bias

There was no publication bias for the *MC4R* rs17782313 SNP using Begg test ($P = .452$) or Egger test ($P = .275$) before adjusting for BMI, as well as after adjusting for BMI ($P = .308$ and.310, respectively).

4. Discussion

To our knowledge, this is the first meta-analysis that investigated the association between a SNP near the *MC4R* gene and risk of cancer. The present meta-analysis revealed that the *MC4R* rs17782313 SNP is moderately associated with risk of cancer, without adjusting for BMI. However, this association disappeared after adjusting for BMI. It appears that the association between the *MC4R* gene SNP and cancer risk may be mediated through adiposity.

Table 1

Characteristics of studies included in the meta-analysis.

	Cancer type	Country	Race/ ethnicity	Sample size (cases/controls)	Men, %	Age, y	BMI, kg/m^2 (cases/controls)	OR (95% CI)	Adjusted covariates
Tenesa et al, 2009	Colorectal cancer	UK	European	799 vs 782	NA	<55	26.9±5.0/ 27.1±5.2	1.11 (0.96–1.28)	Gender and age
Delahanty et al, 2011	Endometrial cancer	China	East Asian	832 vs 2049	All were women	30–69	Overweight rate (57.7%/33.3%)	1.29 (1.11–1.50)	Age, income, and education
Lurie et al, 2011	Endometrial cancer	Australia, USA, Poland, Canada	European	2619 vs 3900	All were women	61.5±8.9/ 59.7±9.7	NA	0.99 (0.91–1.07)	Age
								0.94 (0.86–1.02)	Age and BMI
Kusinska et al, 2012	Breast cancer	Poland	European	134 vs 367	All were women	57.45	NA	1.01 (0.68–1.51)	None
Lim et al, 2012	Colorectal cancer	USA	Mixed	2033 vs 9640	55%/55%	70.0±8.6/ 68.0±8.6	27.2±4.9/ 26.8±4.8	1.12 (1.02–1.22)	Age, gender, and ethnicity
								1.11 (1.01–1.21)	Age, gender, ethnicity, and BMI
da Cunha et al, 2013	Breast cancer	Brazil	European (80%)	100 vs 148	All were women	24–86/25–80	Overweight rate (63%/57%)	1.70 (1.02–2.98)	None
								1.66 (1.05–2.65)	Age and BMI

NA = not available.

Several previous GWAS have identified a large number of SNPs associated with obesity. The *FTO* gene is one of the first loci identified for obesity risk by GWAS. A most recent meta-analysis conducted by Kang et al revealed that the *FTO* gene rs9939609 SNP was not significantly associated with risk of cancer, regardless of the adjustment for BMI. However, in the subgroup analysis, this variant moderately increased the risk of endometrial cancer and pancreatic cancer, which was mediated by adiposity.[18] Similarly, the authors also found a significant association between the *MC4R* gene rs17782313 SNP and risk of cancer, which mediated through BMI. Notably, a recent large-scale study suggested that *MC4R* gene SNPs are not associated with risk of

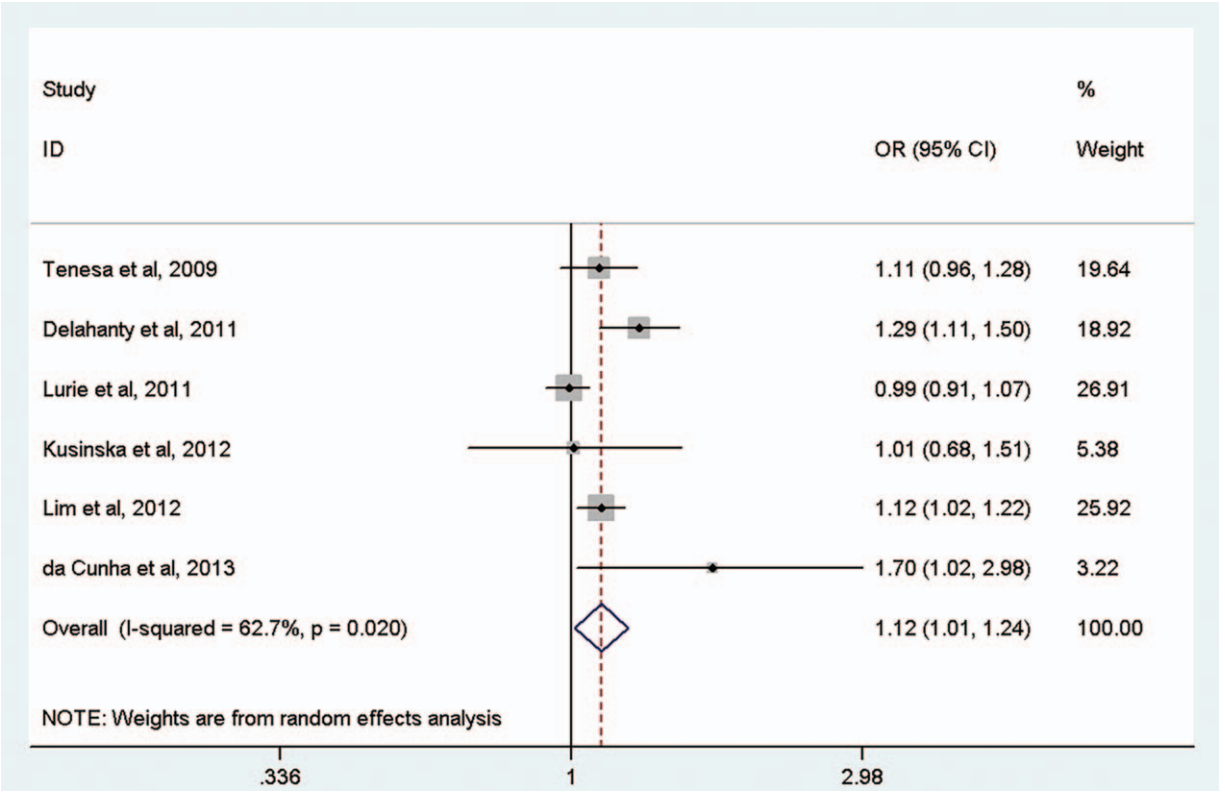

Figure 2. The meta-analysis of the association between *MC4R* rs17782313 and cancer risk without adjusting for body mass index.

Table 2

Meta-analysis of the association between *MC4R* rs17782313 and cancer risk by cancer type.

	No of studies (cases/controls)	OR (95% CI)	*P* z-test	I^2 (%)	$P_{heterogeneity}$	Statistical model
Without adjustment for BMI						
Total	6 (6517/16886)	1.12 (1.01-1.24)	.029	62.7	.020	Random
Colorectal cancer	2 (2832/10422)	1.12 (1.04-1.21)	.004	0.0	.917	Fixed
Endometrial cancer	2 (3451/5949)	1.12 (0.87-1.45)	.387	89.1	.002	Random
Breast cancer	2 (234/515)	1.27 (0.77-2.11)	.356	57.1	.127	Fixed
With adjustment for BMI						
Total	4 (5551/14470)	1.08 (0.94-1.23)	.263	75.2	.007	Random
Colorectal cancer	2 (2832/10422)	1.11 (1.03-1.20)	.008	0	1.000	Fixed
Endometrial cancer	1 (2619/3900)	0.94 (0.86-1.02)	.155	—	—	—
Breast cancer	1 (100/148)	1.66 (1.05-2.65)	.032	—	—	—

colorectal cancer, regardless of adjusting for BMI.[14] However, that study did not focus on the rs17782313 SNP, which is the interest of the present study.

The mechanism underlying the association between the *MC4R* SNP and cancer risk remains unclear. Similar to the *FTO* gene, the *MC4R* gene is also highly expressed in the central nervous system, which regulates the energy metabolism.[19] It was reported that MC4R may regulate food choice and intake, and energy expenditure through a distinct pathway.[20,21] However, further studies are needed to clarify the potential biological pathways through which these *MC4R* SNPs increase the risk of obesity and cancer.

It is important to focus on an organ system, which might encompass two or more different cancer types (eg, genitourinary cancer). However, merely 6 studies met the inclusion criteria. Thus, an analysis that focused on an organ system could not be performed. In addition, it is also important to assess the association between SNPs and different endocrine-driven cancers. However, due to the unavailability of data, subgroup analysis was performed by cancer type (colorectal cancer, endometrial cancer and breast cancer).

The present study had 2 strengths. First, the OR was extracted with 95% CI, with the adjustment of covariates from individual studies, to calculate the summary estimate, which represents an accurate estimate. Second, a total 6517 cancer cases and 16,886 healthy controls were included in the present meta-analysis, which greatly improved the statistical power. However, 2 limitations should be considered. First, although the total sample

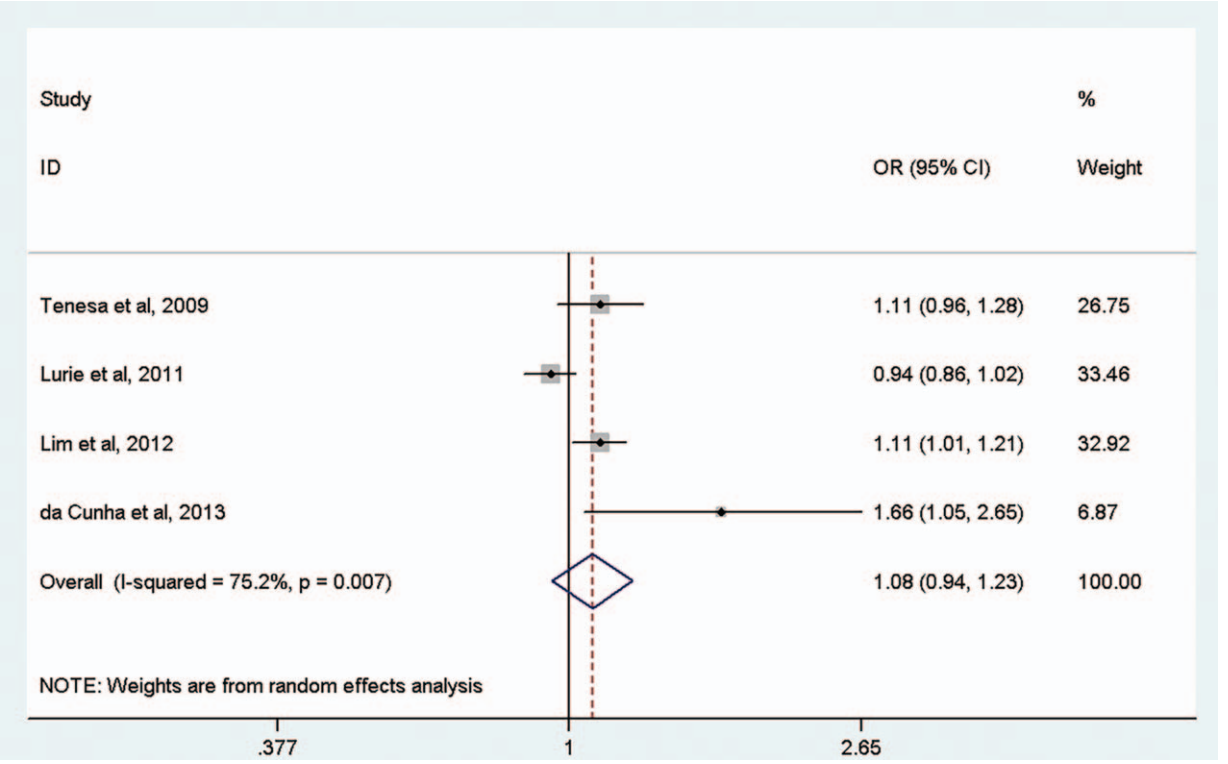

Figure 3. The meta-analysis of the association between *MC4R* rs17782313 and cancer risk with the adjustment for body mass index.

size was sufficiently large, merely 6 studies were included. In addition, the subgroup analysis by cancer type should be interpreted with caution due to the limited studies available for each cancer type. Second, there was a significant between-study heterogeneity in the meta-analysis, even although a random effects model was used to overcome this limitation. In addition, the further meta-regression analysis did not reveal any potential confounders that may explain the between-study heterogeneity.

In summary, there might be an association between the *MC4R* rs17782313 SNP and risk of cancer, which might be mediated by adiposity. Further studies are necessary to identify the causal variant near the *MC4R* gene, as well as the underlying mechanism between the *MC4R* gene SNP and risk of cancer.

Author contributions

Conceptualization: Zeng Tian, Hongjun Xie.
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Supervision: Yu Kang.
Validation: Jing Zhao.
Visualization: Jing Zhao.
Writing – original draft: Zeng Tian, Jing Zhao, Hongjun Xie.
Writing – review & editing: Hongjun Xie.

References

[1] Loos RJF, Lindgren CM, Li S, et al. Common variants near MC4R are associated with fat mass, weight and risk of obesity. Nat Genet 2008;40:768–75.
[2] Speliotes EK, Willer CJ, Berndt SI, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat Genet 2010;42:937–48.
[3] Wen WQ, Cho YS, Zheng W, et al. Meta-analysis identifies common variants associated with body mass index in east Asians. Nat Genet 2012;44:307–11.
[4] Xi B, Chandak GR, Shen Y, et al. Association between common polymorphism near the MC4R gene and obesity risk: a systematic review and meta-analysis. PLoS One 2012;7:e45731.
[5] Farooqi IS, Yeo GSH, Keogh JM, et al. Dominant and recessive inheritance of morbid obesity associated with melanocortin 4 receptor deficiency. J Clin Invest 2000;106:271–9.
[6] Farooqi IS, Keogh JM, Yeo GSH, et al. Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. N Engl J Med 2003;348:1085–95.
[7] Xi B, Takeuchi F, Chandak GR, et al. Common polymorphism near the MC4R gene is associated with type 2 diabetes: data from a meta-analysis of 123,373 individuals. Diabetologia 2012;55: 2660–6.
[8] Tenesa A, Campbell H, Theodoratou E, et al. Common genetic variants at the MC4R locus are associated with obesity, but not with dietary energy intake or colorectal cancer in the Scottish population. Int J Obes 2009;33:284–8.
[9] Delahanty RJ, Beeghly-Fadiel A, Xiang YB, et al. Association of obesity-related genetic variants with endometrial cancer risk: a report from the shanghai endometrial cancer genetics study. Am J Epidemiol 2011;174:1115–26.
[10] Kusinska R, Górniak P, Pastorczak A, et al. Influence of genomic variation in FTO at 16q12.2, MC4R at 18q22 and NRXN3 at 14q31 genes on breast cancer risk. Mol Biol Rep 2012;39:2915–9.
[11] Lurie G, Gaudet MM, Spurdle AB, et al. The obesity-associated polymorphisms FTO rs9939609 and MC4R rs17782313 and endometrial cancer risk in non-Hispanic White women. PLoS One 2011;6: e16756.
[12] Lim U, Wilkens LR, Monroe KR, et al. Susceptibility variants for obesity and colorectal cancer risk: The multiethnic cohort and PAGE studies. Int J Cancer 2012;131:E1038–43.
[13] da Cunha PA, de Carlos Back LK, Sereia AFR, et al. Interaction between obesity-related genes, FTO and MC4R, associated to an increase of breast cancer risk. Mol Biol Rep 2013;40:6657–64.
[14] Yang B, Thrift AP, Figueiredo JC, et al. Common variants in the obesity-associated genes FTO and MC4R are not associated with risk of colorectal cancer. Cancer Epidemiol 2016;44:1–4.
[15] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
[16] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22: 719–48.
[17] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.
[18] Kang Y, Liu F, Liu Y. Is FTO gene variant related to cancer risk independently of adiposity? An updated meta-analysis of 129,467 cases and 290,633 controls. Oncotarget 2017;8:50987–96.
[19] Willer CJ, Speliotes EK, Loos RJF, et al. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. Nat Genet 2009;41:25–34.
[20] Razquin C, Marti A, Martinez JA. Evidences on three relevant obesogenes: MC4R, FTO and PPARc. Approaches for personalized nutrition. Mol Nutr Food Res 2011;55:136–49.
[21] Balthasar N, Dalgaard LT, Lee CE, et al. Divergence of melanocortin pathways in the control of food intake and energy expenditure. Cell 2005;123:493–505.