Association of \textit{LEP} G2548A and \textit{LEPR} Q223R Polymorphisms with Cancer Susceptibility: Evidence from a Meta-Analysis

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Abstract

\textbf{Background:} Numerous epidemiological studies have examined associations of genetic variations in \textit{LEP} (G2548A, -2548 nucleotide upstream of the ATG start site) and \textit{LEPR} (Q223R, nonsynonymous SNP in exon 6) with cancer susceptibility; however, the findings are inconsistent. Therefore, we performed a meta-analysis to comprehensively evaluate such associations.

\textbf{Methods:} We searched published literature from MEDLINE, EMBASE, Web of Science and CBM for eligible publications. We also assessed genotype-based mRNA expression data from HapMap for rs7799039 (G2548A) and rs1137101 (Q223R) in normal cell lines derived from 270 subjects with different ethnicities.

\textbf{Results:} The final analysis included 16 published studies of 6569 cases and 8405 controls for the \textit{LEP} G2548A and 19 studies of 7504 cases and 9581 controls for the \textit{LEPR} Q223R. Overall, \textit{LEP} G2548A was statistically significantly associated with an increased risk of overall cancer (AA vs. GG: OR=1.27, 95% CI=1.05-1.54; recessive model: OR=1.19, 95% CI=1.00-1.41). Further stratifications by cancer type showed an increased risk for prostate cancer (recessive model: OR=1.26, 95% CI=1.05-1.51) but not for other cancers. For \textit{LEPR} Q223R, no statistical evidence for an association with risk of cancer was found for all; however, further stratification by ethnicity showed an increased risk for Africans but not for other ethnicities. No significantly differences in \textit{LEP} and \textit{LEPR} mRNA expression were found among genotypes or by ethnicity.

\textbf{Conclusions:} Despite some limitations, this meta-analysis found some statistical evidence for an association between the \textit{LEP} 2548AA genotype and overall risk of cancer, particularly for prostate cancer, but given this variant did not have an effect on mRNA expression, this association warrants additional validation in large and well-designed studies.

Introduction

Cancer is recognized as one of the leading causes of death in economically developed countries as well as in developing countries. With the estimated 12.7 millions of cancer cases and 7.6 millions of cancer deaths occurred in 2008, cancer has become a major public health challenge [1]. Because of the combination of earlier detection and improved treatment, the overall cancer mortality is decreasing over the last decade. However, the global burden of cancer continues to increase, largely due to the increased longevity and subsequent growth of the world populations that increasingly adopt cancer-causing behaviors [1]. While the mechanism of carcinogenesis is still not fully understood, it has been suggested that environmental
factors, interplaying with low-penetrance susceptibility genes, may be important in the development of cancer [2,3].

Leptin (LEP, also called OB for obese), an adipocyte-derived hormone, produced predominantly by white adipose tissue, regulates appetite and weight, body metabolism and reproductive functions together with the leptin receptor (LEPR) (Figure 1) [4]. The LEP gene, located at chromosome 7q31.3, encodes a 16 kDa protein that has been consistently shown to be associated with endocrinologic metabolism [5]. It has been also suggested that leptin could contribute to serum insulin levels and the development of type 2 diabetes [6] and that leptin is involved in the pathophysiology of obesity [7,8] and carcinogenesis [9-14]. Leptin exerts its physiological action through its receptor (LEPR, also called CD295, and its gene is located at chromosome 1p31), which is a single transmembrane protein distributed in many types of tissues [15].

LEP and LEPR are highly polymorphic, and a number of single nucleotide polymorphisms (SNPs) have been identified in these two genes [6,8,16,17]. For example, there are at least 383 reported SNPs in the LEP gene region and 3117 reported SNPs in the LEPR gene region (http://www.ncbi.nlm.nih.gov/projects/SNP). However, only few of these reported SNPs are potentially functional and ever studied for their associations with cancer susceptibility. For LEP, there are two SNPs that reportedly change amino acid of the protein but only G2548A (rs7799039) was extensively investigated for its association with cancer risk; for LEPR, there are five common (minor allele frequency > 0.05) SNPs that may cause amino acid changes, but only Q223R (rs1137101) was studied for its association with cancer susceptibility. Because the results from these studies are inconsistent [9-14,16,18-40], we performed a meta-analysis of the published reports to further evaluate the association of these two SNPs with the risk of cancer.

**Figure 1.** Gene structural characteristics of leptin and leptin receptor and their roles in regulating adipose tissue mass. The locations of LEP G2548A (A) and LEPR Q223R (B) with possible leptin functions and the pathway of regulating adipose tissue mass (C).

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Materials and Methods

Identification and eligibility of relevant studies

Published studies were included, if they met the following three inclusion criteria: (a) evaluating the association between LEP G2548A (or A19G) and/or LEPR Q223R SNPs and cancer risk, (b) using a case-control design, (c) providing sufficient data for calculation of an odds ratio (OR) with 95% confidence interval (CI).

We searched electronic literature MEDLINE, EMBASE, Web of Science and Chinese Biomedical (CBM) (http://www.imicams.ac.cn) databases for all relevant articles using the search terms: "leptin or LEP", "leptin receptor gene or LEPR", "variant, variation or polymorphism" and "cancer, carcinoma or tumor" (the last search was updated on March 10, 2013). All eligible studies were retrieved, and their bibliographies were manually checked for other relevant publications. Review articles and bibliographies of other relevant studies identified were hand-searched as well to find additional eligible studies. Only published studies with full-text articles in English or Chinese were included. If more than one article was published using the same patient population, only the latest or the largest study was used in this meta-analysis. Two authors independently assessed the articles for compliance with the inclusion criteria, and disagreement was resolved by discussions until the consensus was reached.

Data extraction

The following information was collected from each study: first author's surname, publication date, ethnicity of the study population, cancer type, source used for controls, total number of cases and controls, and numbers of cases and controls with the AA, AG and GG genotypes for LEP G2548A and LEPR Q223R, respectively.

Genotype and gene expression correlation analysis

The data on LEP and LEPR genotype and transcript (mRNA) expression levels were available online (http://app3.titan.uio.no/biotools/help.php?app=snpxp) [41]. The genotyping data were derived from The HapMap phase II release 23 data set consisting of 3.96 million SNP genotypes from 270 individuals from four populations (CEU: 90 Utah residents with ancestry from northern and western Europe; CHB: 45 unrelated Han Chinese in Beijing; JPT: 45 unrelated Japanese in Tokyo; YRI: 90 Yoruba in Ibadan, Nigeria) [42,43]. The transcript (mRNA) expression data by genotypes were from EBV-transformed B lymphoblastoid cell lines from the same 270 individuals [44,45].

Statistical methods

The strength of associations of LEP G2548A and LEPR Q223R SNPs with cancer risk was assessed by calculating ORs with the corresponding 95% CIs. For LEP G2548A, the pooled ORs were performed for homozygous model (AA vs. GG), heterozygous model (AG vs. GG), and dominant model (AA+AG vs. GG). For LEPR Q223R, the pooled ORs were also performed for homozygous model (GG vs. AA), heterozygous model (AG vs. AA), recessive model (GG vs. AG+AA), and dominant model (GG+AG vs. AA). The homogeneity assumption was verified by using a Chi square-based Q-test. If the studies were found to be homogeneous (with P>0.10 for the Q test), the pooled OR estimate of all studies was calculated by the fixed-effects model (the Mantel–Haenszel method) [46]. If homogeneity could not be assumed, a random-effects model (the DerSimonian and Laird method) was used [47]. Subgroup analyses were performed by cancer type, ethnicity, study design and sample size (i.e., no. of cases ≥150 vs. no. of cases <150). To verify the presence of potential publication bias, a standard error of log (OR) for each study was plotted against its log (OR). Funnel plot asymmetry was assessed by Egger’s linear regression test [48]. To assess the effect of individual studies on the overall risk of cancers, sensitivity analyses were performed by excluding each study individually and recalculating the ORs and 95% CI. The mRNA expression levels between the strata were assessed by using a Student’s t test, and the trend tests of transcript expression levels by genotypes were evaluated by using General linear model. This meta-analysis was performed using the software STATA version 10.0 (Stata Corporation, College Station, TX) and SAS software (version 9.1; SAS Institute, Cary, NC). All P values were two-sided, and a P<0.05 was considered statistically significant.

Results

Study characteristics

As shown in Figure 2, a total of 115 published records were retrieved, of which 85 were excluded after the abstracts were found to be irrelevant, and three papers were excluded, for two [49,50] of which were covered by another study [11], and one was written in Russian [26]. Finally, 27 papers met the inclusion criteria and were included in the meta-analysis (Table 1). Overall, 16 studies with 6569 cases and 8405 controls investigated the LEP G2548A (or A19G) SNP, and another 19 studies with 7504 cases and 9581 controls investigated the LEPR Q223R SNP. The study of Teras et al. [29] on the two SNP was included only in the calculation of the dominant model, because the genotype distribution was not presented in enough detail.

Meta-analysis results

The overall results suggested a statistically significant association between LEP G2548A (or A19G) and risk of cancer (AA vs. GG: OR=1.27, 95% CI=1.05-1.54; AA vs. AG+GG: OR=1.19, 95% CI=1.00-1.41) (Table 2, Figure 3). In the subgroup analysis by ethnicity, a statistically significant association was found for Caucasians (AA vs. GG: OR=1.24, 95% CI=1.01-1.53; recessive model: OR=1.23, 95% CI=1.01-1.51) and Africans (AA vs. GG: OR=3.17, 95% CI=1.54-6.51; recessive model: OR=2.62, 95% CI=1.31-5.26) but not for other ethnic groups. In the subgroup analysis by tumor type, the LEP 2548A (or 19G) allele was significantly associated with risk of prostate cancer (AA vs. AG+GG: OR=1.26, 95% CI=1.05-1.51) but not with cancers of the breasts and colorectal or other specified cancers. In the
subgroup analysis by sample size, a statistically significant association was found for studies with sample sizes <150 (AA vs. GG: OR=1.78, 95% CI=1.24-2.54; AA vs. AG+GG: OR=1.33, 95% CI=1.00-1.78) but not for those with sample sizes ≥150.

For the *LEPR* Q223R SNP, no statistically significant association with cancer risk was found (Table 3, Figure 4). In the stratified analysis by ethnicity, however, a statistically significant association was observed for Africans (GG vs. AA: OR=1.85, 95% CI=1.23-2.79; GA vs. AA: OR=1.48, 95% CI=1.08-2.01; GG vs. GA+AA: OR=1.48, 95% CI=1.07-2.05; GG+GA vs. AA: OR=1.58, 95% CI=1.14-2.20), but not for Caucasians and other ethnic populations. No statistically significant association was found in the further stratification by tumor type, source of controls, and sample size.

The mRNA expression by genotypes

The mRNA expression levels of *LEP* and *LEPR* by the genotypes for four ethnicities are shown in Table 4. We did not find any differences in mRNA expression by genotypes among different ethnicities. No trend of transcript expression levels by genotypes was found for *LEP* or *LEPR*. These data suggest that the variants under investigation may not have a significant effect on gene expression, at least at mRNA levels.

Publication bias

For *LEP* G2548A (or A19G), there was evidence for publication bias under a homozygous additive model (the Egger's test: AA vs. GG: \( P=0.034 \)); however, this was not observed under other genetic models (AG vs. GG: \( P=0.174 \); recessive model: \( P=0.138 \); dominant model: \( P=0.071 \)). The publication bias may be ascribed to small sample sizes the included studies had. When studies with cases smaller than 150 in numbers were excluded, the publication bias disappeared, but the significant association also disappeared.

No publication bias was detected for *LEPR* Q223R (the Egger’s test: GG vs. AA: \( P=0.559 \), AG vs. AA: \( P=0.686 \), recessive model: \( P=0.600 \), dominant model: \( P=0.600 \)).

Discussion

It is well recognized that individual susceptibility to cancer varies, even with the same environmental exposure. Therefore, a role for genetic variation, such as SNPs of genes involved in...
carcinogenesis, has been suggested. Epidemiological studies have shown that overweight and obesity might be associated with an increased risk of cardiovascular disease and type II diabetes; moreover, excessive body weight has been directly associated with risk of cancer at several organ sites, including the colon, breasts (in postmenopausal women), endometrium, esophagus, and kidney [51]. Formerly, immune dysfunction has been shown to be associated with obesity [20], whereas leptin concentrations were recently found to be higher in Africans, compared with Caucasians, after adjustment for BMI and other factors [52].

The Q223R SNP (but not the K109R or K656N SNPs) of the LEPR gene has been reported to be associated with obesity and to predict a small percentage of body weight and body composition variability in a genetically homogeneous population [8]. Previous reports demonstrated that genetic variation in LEPR affected cancer susceptibility with significantly higher frequency of the LEPR 223Arg allele in patients than in controls [9,11,22,24,33]; however, this association was not be replicated by later studies [14,16,19,23,31,36]. Likewise, previous reports also demonstrated that LEP 2548AA was associated with an increased risk of cancer [12,13,20,21,33,34]; however, replication of this finding by others also failed as well [25,28,31].

In this meta-analysis, we found statistical evidence for a significant but weak association of cancer risk with the LEP G2548A (or A19G) SNP but not with the LEPR Q223R SNP. There are several biologically plausible explanations for this finding. Firstly, it has been described that genetic variants in the promoter region of LEPR can influence leptin expression, possibly at the transcriptional level, thereby altering adipose secretion levels of the hormone [17]. Additionally, it is also likely that the observed association may be due to improved study power from pooling studies with small sample sizes that separately may have had insufficient statistical power to detect a weak effect. Thus, in the genotype-based mRNA expression analysis using data from HapMap for the LEP G2548A, we did not find statistical difference may be ascribed to small sample size for each ethnicity or the G2548A may have a weak effect.
In conclusion, this meta-analysis found that the LEPR Q223R was associated with a weakly increased risk of cancer, mainly for prostate cancer, while LEPR G2548A was not. However, given the relatively limited sample sizes and the lack of detailed information, this analysis with mixed ethnicities did not provide sufficient statistical power to investigate the real association. Third, most of the studies used hospital-based controls that may result in some selection biases. Finally, the lack of original data such as age, sex, smoking and drinking status, BMI, environmental factors and other lifestyle, limited our ability to further evaluate of gene-environment interactions.

In conclusion, this meta-analysis found that the LEPR 2548AA genotype was associated with a weakly increased risk of cancer, mainly for prostate cancer, while LEPR Q223R was not. However, given the relatively limited sample sizes and the lack of detailed information, this analysis with mixed ethnicities was not able to address cancer outcomes and biological evidence for genotype-phenotype (mRNA expression) correlations. It is clear that further studies are warranted to validate the association between the LEPR G2548A polymorphism and cancer risk.

### Table 2. Meta-analysis of the association between LEPR G2548A polymorphism and cancer risk.

| Variables | No. of studies\(^a\) | Homozygous co-dominant \(P_{het}^b\) | Heterozygous co-dominant \(P_{het}^b\) | Recessive \(P_{het}^b\) | Dominant \(P_{het}^b\) |
|-----------|----------------------|-----------------------------|---------------------------------|----------------------|----------------------|
| All       | 15                   | 1.27 (1.05-1.54)             | 1.04 (0.96-1.13)                | 1.19 (1.00-1.41)     | 0.000                |
| Cancer type |                      |                             |                                 |                      |                      |
| Breast    | 2                    | 1.91 (0.82-4.45)             | 0.025                           | 1.02 (0.86-1.21)     | 0.033                |
| Colorectal| 5                    | 0.97 (0.76-1.20)             | 1.03 (0.92-1.17)                | 0.92 (0.81-1.05)     | 0.188                |
| Prostate  | 3                    | 1.42 (0.94-2.12)             | 1.13 (0.94-1.36)                | 1.26 (1.05-1.51)     | 0.068                |
| Others    | 5                    | 1.32 (0.91-1.92)             | 0.96 (0.74-1.24)                | 0.736                | 0.004                |
| Ethnicity |                      |                             |                                 |                      |                      |
| Caucasian | 10                   | 1.24 (1.01-1.53)             | 0.036                           | 0.99 (0.89-1.10)     | 0.333                |
| Latin American | 1                | 2.53 (0.89-7.18)             | /                               | 2.97 (1.17-7.50)     | 1.08 (0.53-2.21)     |
| African   | 1                    | 3.17 (1.54-6.51)             | 1.45 (1.01-2.07)                | 2.62 (1.31-5.26)     | 1.62 (1.14-2.29)     |
| Asian     | 1                    | 0.88 (0.05-14.69)            | 1.29 (0.07-22.42)               | 0.69 (0.30-1.61)     | 1.00 (0.06-16.46)    |
| Mixed     | 2                    | 0.94 (0.79-1.13)             | 0.455                           | 1.05 (0.91-1.22)     | 0.796                |
| Source of controls |                  |                             |                                 |                      |                      |
| Hospital  | 9                    | 1.70 (1.10-2.61)             | 0.002                           | 1.10 (0.94-1.29)     | 0.028                |
| Population | 5                    | 1.22 (1.05-1.41)             | 0.604                           | 0.99 (0.88-1.13)     | 0.894                |
| Mixed     | 1                    | 0.92 (0.76-1.11)             | 1.06 (0.91-1.23)                | 0.89 (0.75-1.05)     | 1.02 (0.88-1.17)     |
| Sample size in cases |                  |                             |                                 |                      |                      |
| < 150     | 6                    | 1.78 (1.24-2.54)             | 0.677                           | 1.29 (0.98-1.71)     | 0.060                |
| >=150     | 9                    | 1.16 (0.95-1.43)             | 0.003                           | 1.02 (0.94-1.11)     | 0.588                |

\(^a\) Only presented the study with enough detail, one study was included only in the calculation of the dominant model.

\(^b\) P value of the Q-test for heterogeneity test.

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cancer risk for the G2548A polymorphism may be ascribed to some selection bias. In contrast to another meta-analysis, however, we were not able to find a statistically significant association between LEPR Q223R and risk of breast cancer [53]. This could be explained by the fact that we included a latest study on breast cancer that included 1972 cases and 1775 controls, a null study that was not included in the previous meta-analysis.

In exploring possible functional relevance of the SNPs under investigation, we did not find any differences in or trends of the mRNA expression levels of LEPR and LEPR by their genotypes in four ethnic groups. Cancer is a complex and multifactorial disease, and gene-gene and gene-environment interactions may contribute greatly to its occurrence, but a single nucleotide alteration may be insufficient to alter the mRNA expression, even for those SNPs in the coding regions that may lead to amino acid change or the polymorphisms in a promoter may have a subtle, potential effect on the gene expression.

Though we performed this meta-analysis using the pooled data that can yield more reliable or statistically more powerful results, several limitations should be addressed. First, significant heterogeneity were found for both of these two polymorphisms that may influence the interpretation of the results. Second, the individual sample sizes for cases of most studies included in the analysis were relatively small (<500) except for seven studies [25,27-29,34,36,39], and there were only one study based on the population of Latin Americans, Africans and Asians for the G2548A polymorphism, respectively, which did not provide insufficient statistical power.
Figure 3. Forest plot for AA vs. GG of LEP G2548A polymorphism.

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## Table 3. Meta-analysis of the association between LEPR Q223R polymorphism and cancer risk.

| Variables                | No. of studies | Homozygous co-dominant | Heterozygous co-dominant | Recessive | Dominant |
|--------------------------|----------------|-------------------------|--------------------------|-----------|----------|
|                          |                | GG vs. AA | AG vs. AA | (GG vs. AG+AA) | (GG+AG vs. AA) | P<sub>het</sub> | P<sub>het</sub> | P<sub>het</sub> |
| All                      | 18             | 1.02 (0.76-1.39) | 1.08 (0.88-1.34) | 0.98 (0.82-1.18) | 1.03 (0.83-1.29) | 0.000 |
| Cancer type              |                |             |            |              |            |         |         |         |
| Breast                   | 9              | 0.94 (0.62-1.42) | 0.97 (0.72-1.31) | 0.95 (0.76-1.20) | 0.93 (0.70-1.24) | 0.000 |
| Colorectal               | 2              | 1.15 (0.86-1.53) | 1.25 (0.70-2.23) | 1.09 (0.85-1.39) | 0.789 | 1.23 (0.76-1.98) | 0.130 |
| Prostate                 | 1              | 0.82 (0.52-1.29) | 0.85 (0.58-1.26) | 0.89 (0.59-1.34) | 0.84 (0.59-1.19) | / |
| Others                   | 6              | 1.09 (0.49-2.39) | 1.27 (0.83-1.94) | 0.029 | 1.04 (0.62-1.75) | 0.000 |
| Ethnicity                |                |             |            |              |            |         |         |         |
| Caucasian                | 9              | 1.06 (0.84-1.40) | 1.10 (0.96-1.26) | 0.363 | 0.98 (0.78-1.24) | 0.006 1.06 (0.91-1.23) | 0.075 |
| East Asian               | 6              | 0.44 (0.08-2.48) | 0.49 (0.11-2.13) | 0.000 | 0.79 (0.46-1.36) | 0.000 0.44 (0.09-2.33) | 0.000 |
| African                  | 2              | 1.85 (1.23-2.79) | 0.275 | 1.48 (1.08-2.01) | 0.302 | 1.48 (1.07-2.05) | 0.403 1.58 (1.14-2.20) | 0.245 |
| Mixed                    | 1              | 0.91 (0.76-1.09) | 0.92 (0.78-1.08) | 0.97 (0.84-1.12) | / | 0.92 (0.79-1.06) | / |
| Source of controls       |                |             |            |              |            |         |         |         |
| Hospital                 | 12             | 0.86 (0.49-1.51) | 0.99 (0.69-1.43) | 0.000 | 0.89 (0.66-1.19) | 0.000 0.90 (0.60-1.38) | 0.000 |
| Population               | 6              | 1.22 (0.84-1.76) | 1.14 (0.86-1.51) | 0.000 | 1.12 (0.90-1.39) | 0.001 1.11 (0.84-1.46) | 0.000 |
| Sample size in cases     |                |             |            |              |            |         |         |         |
| < 150                    | 6              | 0.89 (0.37-2.12) | 0.014 | 1.06 (0.55-2.13) | 0.046 | 0.84 (0.51-1.38) | 0.040 1.02 (0.53-2.01) | 0.034 |
| >=150                    | 12             | 1.04 (0.75-1.46) | 0.000 | 1.07 (0.85-1.35) | 0.000 | 1.02 (0.84-1.24) | 0.000 1.02 (0.80-1.31) | 0.000 |

- Only presented the study with enough detail, one study was included only in the calculation of the dominant model.
- *P* value of the Q-test for heterogeneity test.

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Figure 4. Forest plot for the LEPR Q223R polymorphism (recessive model).

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Table 4. *LEP* and *LEPR* mRNA expression by the genotypes of SNPs, using data from the HapMap 

| Populations | LEP rs7799039 (G2548A) |  | LEPR rs1137101 (Q223R) |  |
|-------------|-------------------------|---|------------------------|---|
| Genotypes   | No.         | Mean ± SD | P<sub>b</sub> | Genotypes   | No.         | Mean ± SD | P<sub>b</sub> |
| CHB         |  |             |  |  |  |             |  |
| GG          | 4        | 8.82±0.22  | 0.913 | GG          | 36       | 8.70±0.23  | 0.819 |
| AG          | 15       | 8.66±0.23  | 0.229 | AG          | 8        | 8.78±0.22  | 0.402 |
| AA          | 26       | 8.73±0.23  | 0.422 | AA          | 1        | 8.53       | 0.468 |
| AG/AA       | 41       | 8.70±0.23  | 0.311 | AG/AA       | 9        | 8.75±0.22  | 0.575 |
| JPT<sup>d</sup> |  |             |  |  |  |             |  |
| GG          | 1        | 8.41       | 0.653 | GG          | 32       | 8.52±0.22  | 0.774 |
| AG          | 18       | 8.51±0.24  | 0.688 | AG          | 12       | 8.50±0.15  | 0.774 |
| AA          | 26       | 8.53±0.20  | 0.562 | AA          | 0        | -          | -     |
| AG/AA       | 44       | 8.52±0.21  | 0.609 | AG/AA       | 12       | 8.50±0.15  | 0.774 |
| CEU<sup>d</sup> |  |             |  |  |  |             |  |
| GG          | 20       | 8.53±0.30  | 0.473 | GG          | 26       | 8.49±0.27  | 0.427 |
| AG          | 44       | 8.45±0.24  | 0.228 | AG          | 44       | 8.48±0.23  | 0.902 |
| AA          | 21       | 8.47±0.25  | 0.492 | AA          | 19       | 8.43±0.22  | 0.421 |
| AG/AA       | 65       | 8.45±0.24  | 0.242 | AG/AA       | 63       | 8.46±0.23  | 0.674 |
| YRI<sup>d</sup> |  |             |  |  |  |             |  |
| GG          | 87       | 8.57±0.24  | 0.749 | GG          | 31       | 8.57±0.27  | 0.698 |
| AG          | 2        | 8.62±0.05  | 0.749 | AG          | 46       | 8.59±0.22  | 0.728 |
| AA          | 0        | -          | -    | AA          | 12       | 8.51±0.26  | 0.561 |
| AG/AA       | 2        | 8.62±0.05  | 0.749 | AG/AA       | 58       | 8.57±0.22  | 0.936 |

<sup>a</sup> Genotyping data and mRNA expression levels for *LEP* or *LEPR* by genotypes were obtained from the HapMap phase II release 23 data from EBV-transformed lymphoblastoid cell lines from 270 individuals, including 45 unrelated Han Chinese in Beijing (CHB).

<sup>b</sup> Two-side Student’s t test within the stratum.

<sup>c</sup> P values for the trend test of mRNA expression among three genotypes for each SNP from a general linear model.

<sup>d</sup> There were missing data because genotyping data for six individuals were not available for *LEP* and three individuals were not available for *LEPR*.

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Supporting Information

Checklist S1. (DOC)

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Conceived and designed the experiments: LXQ QYW. Performed the experiments: JH RR BX. Analyzed the data: JH. Contributed reagents/materials/analysis tools: XYZ LQX. Wrote the manuscript: JH LXQ QYW.

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