Association of four insulin resistance genes with type 2 diabetes mellitus and hypertension in the Chinese Han population

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Abstract Insulin resistance plays an important role in the development of type 2 diabetes mellitus (T2DM) and hypertension. The purpose of the present study was to evaluate the association between four insulin resistance genes (ADIPOQ, LEPR, RETN, and TRIB3) and both T2DM and hypertension. A total of 768 Han Chinese subjects were recruited into this study, including 188 cases who had T2DM alone, 223 cases who had hypertension alone, 181 cases with both T2DM and hypertension, and 176 control subjects with neither T2DM nor hypertension. Twenty-three tag SNPs in four insulin resistance genes were genotyped and analyzed for association with T2DM and hypertension. One intron SNP (rs13306519) in LEPR and one 3’UTR SNP (rs1063537) in ADIPOQ demonstrated a significant association with T2DM (P = 0.024 and 0.014 respectively). Another intron SNP (rs12037879) in LEPR and a promoter region SNP (rs266729) in ADIPOQ were significantly associated with hypertension (P = 0.041 and 0.042, respectively). These associations survived the permutation test (P = 0.023, 0.018, 0.026, and 0.035, respectively). These associations were still found to be significant in the additive model after adjusting for potential confounding factors including age, sex, BMI, HDL, LDL, total cholesterol, and triglyceride levels (P = 0.024, 0.016, 0.04, and 0.043, respectively). No other gene variants were found to be significantly associated with T2DM or hypertension (P > 0.05). None of the studied gene variants were found to be significantly associated with T2DM+ hypertension (P > 0.05). A significant interaction was observed between two SNPs rs13306519 in LEPR and rs266729 in ADIPOQ for T2DM (P_int = 0.012, OR_int = 2.67) and hypertension (P_int = 0.0041, OR_int = 2.23). These findings suggest that variants in ADIPOQ and LEPR are risk factors for T2DM and hypertension in the Chinese population and that variants in RETN and TRIB3 are not major risk factors for these diseases.

Keywords Type 2 diabetes mellitus · Hypertension · Polymorphisms · ADIPOQ · LEPR

Introduction

Both diabetes and hypertension are important public health issues throughout the world. To date, at least 285 million individuals are affected by diabetes (with type II diabetes, type 2 diabetes mellitus (T2DM), accounting for 80–90 % of all cases), and that number is expected to reach 438 million by the year 2030 [1]. From 1994 to 2007, the prevalence of diabetes increased from 2.5 to 9.7 % in China. This has been attributed the aging of the population, urbanization, and lifestyle changes [2]. Hypertension affects nearly 27 % of the population globally and is predicted to increase by about 60 % to a total of 1.56 billion people in 2025 [3]. Hypertension affects 18 % of Chinese adults [4]. High blood pressure is reported in over two-thirds of patients with T2DM, and its development coincides with the development of hyperglycemia [5].
Genetic and environmental factors and their interactions play an important role in the pathogenesis of T2DM and hypertension [6]. It is assumed that glucose tolerance and blood pressure are under the control of a large number of genes, each of which has a relatively mild effect alone. To date, ~40 genetic loci for T2DM and 50 genetic loci for hypertension have been identified in genome-wide association studies [7-9]. Because all these known loci account for only 10% of the susceptibility to T2DM and hypertension, candidate gene studies remain a valid and efficient approach to the identification of new genes and confirmation of the associations between known genes and both T2DM and hypertension in different populations. The use of association studies with SNP tags throughout candidate genes based on their physiological functions is expected to be a useful strategy for the identification of genes that contribute to this complex condition.

Reduced glucose tolerance and high blood pressure are closely associated. Both contribute to cardiovascular morbidity and mortality. Many pathophysiological mechanisms have been proposed for this association. Of these, insulin resistance is considered the most plausible and has drawn a great deal of attention. Genes encoding proteins that can modulate insulin signaling or action are, by definition, excellent candidates for the risk modulation of T2DM and hypertension.

Adipose tissue is considered an endocrine organ. It can regulate whole-body metabolism and both inflammatory and immune responses [10]. These actions are mediated by numerous adipose-tissue-derived hormones, collectively known as adipokines. These include adiponectin, leptin, and resistin. The discovery of these endocrine functions of adipose tissue has prompted the hypothesis that a genetically influenced dysregulation of the adipokine network may contribute to the pathogenesis of insulin resistance and related disorders such as T2DM and hypertension. Adiponectin is a 30 kDa adipocyte-secreted hormone. It is involved in regulation of blood glucose levels, insulin sensitivity, and lipid metabolism [11, 12]. The ADIPOQ gene, which is located on chromosome 3q27, encodes adiponectin. It has been identified as a susceptibility locus for T2DM in genome-wide linkage studies and genomewide association studies [13-16]. The ADIPOQ gene has also been implicated in the etiology of hypertension [17]. The leptin receptor (LEPR) is a single-transmembrane-domain receptor of the cytokine-receptor family. It is distributed widely in the tissue and it has several alternatively spliced isoforms [18]. There is growing evidence indicating that LEPR may play a wide role in human metabolism of insulin, glucose, and triglycerides. The participation of leptin in the hypothalamus has been reported to increase blood pressure through the LEPR [19]. Recent studies have identified associations between variants in the LEPR gene and both T2DM and blood pressure [20-24]. Resistin is a macrophage-derived signaling polypeptide hormone. In humans it has a molecular weight of 12.5 kDa and a length of 108 amino acids. Previous animal studies, have suggested that resistin may play an important role in the pathogenesis of insulin resistance [25, 26]. The resistin (RETN) gene, located on 19p12.2, has been associated with T2DM in several prospective epidemiological studies across a wide variety of population groups, but results have been conflicting [27] Studies on biological function, epidemiology, and genetics, indicate that ADIPOQ, LEPR, and RETN may be associated with T2DM and hypertension.

Tribbles homolog 3 (TRIB3) is a 45 kDa pseudokinase, involved in the impairment of insulin signaling by affecting insulin-induced Akt activation in several insulin target tissues [28]. The TRIB3 gene, located on chromosome 20p13, is associated with T2DM [29, 30]. This makes TRIB3 an excellent candidate for T2DM. In addition, because insulin resistance is the physiopathologic foundation of more than one metabolic syndrome, TRIB3 gene may also be associated with high blood pressure.

In the present study, we evaluated the association between 4 insulin resistance genes (ADIPOQ, LEPR, RETN, and TRIB3) and both T2DM and hypertension. We found several SNPs in LEPR and ADIPOQ to be significantly associated with T2DM and hypertension.

Methods

Cases and control subjects

The study protocol was approved by the Ethics Committee for Human Research of Jilin University. Informed consent was obtained from all participants after explanation of the nature and possible consequences of the study. In the survey, verbal consents were recorded but no written consent. Because the persons are old and most illiterate, well-trained clerks presented at the discussion with the patient and made independent record of his or her observations with impartial witness. Jilin University Ethics Committee approved this procedure.

A total of 768 Chinese subjects were recruited into this study, including 188 cases with T2DM alone, 223 cases with hypertension alone, 181 cases with both T2DM and hypertension, and 176 control subjects with neither T2DM nor hypertension (Table 1). The diagnosis of T2DM was based on clinical and laboratory criteria as defined by the World Health Organization in 1999. We excluded patients with MODY and type I diabetes using fasting blood glucose, clinical information, and personal patient histories. None of the patients with T2DM had ever had ketoacidosis.
The T2DM treatment included oral anti-diabetic drugs and insulin. Blood pressure was measured after a 10 min rest at a sitting position. Hypertension was defined as a mean systolic blood pressure $>$140 mmHg and/or a mean diastolic blood pressure $>$90 mmHg. Patients taking any antihypertensive medication were defined as hypertensive. Exclusion criteria included the presence of any of secondary cause of hypertension, such as chronic renal disease, renal arterial stenosis, primary aldosteronism, contraction of the aorta, thyroid disorders, Cushing syndrome, and pheochromocytoma. The presence of these criteria were confirmed through extensive clinical examinations and investigations (including blood chemistry, renal function tests, endocrine examination, and abdominal sonogram). Control subjects were collected from the same geographic regions as the patients with T2DM and hypertension and had similar ethnic backgrounds. They had no known personal or family history of diabetes or hypertension. Demographic data including age, sex, weight, height, duration of diabetes, and hypertension or current use of anti-hypertensive medications were recorded via interviewer-administered questionnaires. All subjects were Han Chinese from northeastern China.

Polymorphisms and genotyping

Venous blood samples were collected in EDTA-containing tubes from all participants after an overnight fast of at least 10 h. Genomic DNA was extracted from peripheral blood leukocytes. Tag SNPs were selected to cover the whole gene regions of ADIPOQ, LEPR, RETN, and TRIB3 according to the HapMap Han Chinese population (Phase II + III, release 27; Table 2). The tag SNPs located in exons and promoter regions were selected in higher priority. The selected tag SNPs captured all SNPs from 5 kb upstream to 5 kb downstream of the respective genes with $r^2 > 0.8$ and minor allele frequency (MAF) $>$0.1. SNP genotyping was performed by Bio Miao Biological Technology Co. Ltd. (Beijing, China) using a MassARRAY system (Sequenom, San Diego, CA, USA) with the iPLEX assay.

Statistical analysis

Demographic and clinical characteristics were compared between cases and control subjects by using either the chi square test for categorical data or unpaired $t$ test for numerical data as appropriate. Data analyses for SNPs were performed using PLINK (v1.07) [31]. Hardy–Weinberg equilibrium was assessed by using the chi square test. Minor allele frequencies of each SNP between cases and control subjects were compared using Fisher’s exact test. The odds ratio (OR) and 95 % confidence interval (CI) were calculated using logistic regression. A permutation test was performed using the label-swapping and max(T) procedures for 10,000 permutations. The associations between the SNPs and the diseases were further evaluated using logistic regression after adjusting for potential confounding factors including age, sex, BMI, HDL, LDL, total cholesterol, and triglyceride levels. An additive effects model was applied to analysis of allele dosage in which the genotypes AA, AB, BB were coded as 0, 1, and 2, respectively. A represents the rare allele and B represents the common allele. Pairwise SNP–SNP interactions were analyzed using logistic regression. Multiple comparisons were corrected using the Bonferroni method.

Results

Demographic and clinical characteristics of the study subjects are summarized in Table 1. There was a significant difference in gender ($P = 0.01$) and age ($P = 0.02$) between cases with hypertension and control subjects.

All SNPs were found to be in Hardy–Weinberg equilibrium in the control group ($P > 0.01$). One intron SNP
One SNP in LEPR, rs13306519, and one 3' UTR SNP (rs1063537) in ADIPOQ demonstrated a significant association with T2DM ($P = 0.024$ and 0.014 respectively; Table 3). The allele G frequency of rs13306519 was higher in cases with T2DM than in the control subjects (20.6 vs. 13.8%; OR = 1.62; 95% CI, 1.07–2.45). The allele T frequency of rs1063537 was lower in cases with T2DM than in the control subjects (26.8 vs. 36.3%; OR = 0.64; 95% CI, 0.45–0.91). Another intron SNP (rs12037879) in LEPR and a promoter region SNP (rs266729) in ADIPOQ were significantly associated with hypertension ($P = 0.041$ and 0.042 respectively; Table 3). The allele A frequency of rs12037879 was higher in cases with hypertension than in the control subjects (22.8 vs. 16.2%; OR = 1.53; 95% CI, 1.03–2.26). The allele G frequency of rs266729 was higher in cases with hypertension than in the control subjects (25.0% vs. 19.6%; OR = 1.62; 95% CI, 1.07–2.45). These associations survived the permutation test ($P = 0.023, 0.018, 0.026, 0.035, 0.041, 0.042, 0.043$, respectively). These associations remained significant in the additive model after adjusting for potential confounding factors including age, sex, BMI, HDL, LDL, total cholesterol, and triglyceride levels ($P = 0.024, 0.016, 0.04, 0.043, 0.041, 0.042, 0.043$, respectively). No other gene variants were found to be significantly associated with T2DM and hypertension ($P > 0.05$). None of the gene variants studied here was found to be significantly associated with T2DM or hypertension ($P > 0.05$).

SNP–SNP interaction analysis identified a significant interaction between two SNPs rs13306519 in LEPR and rs266729 in ADIPOQ for T2DM ($P_{\text{int}} = 0.012$, OR$_{\text{int}} = 2.67$) and hypertension ($P_{\text{int}} = 0.0041$, OR$_{\text{int}} = 2.23$).

**Discussion**

In present study, we evaluated 23 tag SNPs in 4 critical insulin resistance genes for association with T2DM and hypertension in the Chinese Han population. We found one SNP in ADIPOQ, rs1063537, and one SNP in LEPR, rs13306519, to be significantly associated with T2DM. An SNP in ADIPOQ, rs266729, and another SNP in LEPR, rs12037879, were significantly associated with hypertension. The associations were not significant when adjusted for potential confounders including age, sex, BMI, HDL, LDL, total cholesterol, and triglyceride levels. The interactions between these SNPs provide further evidence for the role of these genes in the development of T2DM and hypertension.
rs12037879, were significantly associated with hypertension. These findings suggest that ADIPOQ and LEPR, which encode proteins associated with insulin resistance, may play an important role in the development of T2DM and hypertension.

ADIPOQ is considered a gene for T2DM and metabolic syndrome. The concentration of adiponectin in the plasma has been suggested to play an important role in the modulation of insulin sensitivity and glucose homeostasis. It has also been found to be decreased in patients with T2DM, hypertension, dyslipidemia, coronary artery disease, and obesity [32–37]. All of these conditions are closely related to insulin resistance. In line with plasma levels of adiponectin, the ADIPOQ gene has been identified as a susceptibility locus for the metabolic syndrome, T2DM, and cardiovascular disease. However, studies of the associations between the ADIPOQ gene with adiponectin level and the metabolic syndrome often show conflicting results [38, 39]. Studies on the associations between ADIPOQ SNPs with T2DM and hypertension in Chinese populations have also produced conflicting results [17, 40–42].

| Gene    | SNP       | Minor allele | MAF   | DM  | HT  | DM + HT | Control subjects | P*   | DM  | HT  | DM + HT |
|---------|-----------|--------------|-------|-----|-----|---------|------------------|------|-----|-----|---------|
| LEPR    | rs12037879| A            | 0.210 | 0.228 | 0.216 | 0.162 | 0.13 | 0.041 | 0.10 |
| LEPR    | rs7554485 | C            | 0.082 | 0.110 | 0.090 | 0.108 | 0.36 | 1.00 | 0.54 |
| LEPR    | rs1137100 | A            | 0.153 | 0.144 | 0.172 | 0.186 | 0.34 | 0.22 | 0.72 |
| LEPR    | rs13306519| G            | 0.206 | 0.191 | 0.192 | 0.138 | 0.024 | 0.07 | 0.07 |
| LEPR    | rs1137101 | A            | 0.133 | 0.135 | 0.100 | 0.128 | 0.63 | 0.82 | 0.32 |
| LEPR    | rs8179183 | C            | 0.057 | 0.062 | 0.074 | 0.043 | 0.53 | 0.41 | 0.17 |
| ADIPOQ  | rs16861194| G            | 0.170 | 0.164 | 0.163 | 0.185 | 0.62 | 0.49 | 0.47 |
| ADIPOQ  | rs266729  | G            | 0.259 | 0.343 | 0.266 | 0.27  | 0.73 | 0.042 | 0.93 |
| ADIPOQ  | rs12495941| T            | 0.421 | 0.374 | 0.408 | 0.382 | 0.34 | 0.88 | 0.52 |
| ADIPOQ  | rs2241766 | G            | 0.286 | 0.282 | 0.269 | 0.256 | 0.39 | 0.45 | 0.73 |
| ADIPOQ  | rs1501299 | A            | 0.279 | 0.254 | 0.276 | 0.275 | 0.93 | 0.54 | 1.00 |
| ADIPOQ  | rs1063537 | T            | 0.268 | 0.436 | 0.310 | 0.363 | 0.014 | 0.06 | 0.19 |
| ADIPOQ  | rs12629945| A            | 0.215 | 0.226 | 0.179 | 0.218 | 1.00 | 0.84 | 0.29 |
| ADIPOQ  | rs6444175 | A            | 0.280 | 0.261 | 0.277 | 0.278 | 1.00 | 0.67 | 1.00 |
| RETN    | rs2161490 | T            | 0.390 | 0.431 | 0.439 | 0.424 | 0.35 | 0.88 | 0.76 |
| RETN    | rs3745368 | A            | 0.153 | 0.150 | 0.145 | 0.134 | 0.51 | 0.59 | 0.74 |
| TRIB3   | rs12626158| A            | 0.222 | 0.248 | 0.247 | 0.213 | 0.85 | 0.29 | 0.35 |
| TRIB3   | rs6051637 | T            | 0.227 | 0.175 | 0.185 | 0.19  | 0.25 | 0.62 | 0.92 |
| TRIB3   | rs6115830 | T            | 0.303 | 0.324 | 0.292 | 0.346 | 0.25 | 0.58 | 0.16 |
| TRIB3   | rs2295491 | A            | 0.108 | 0.151 | 0.130 | 0.15  | 0.13 | 1.00 | 0.49 |
| TRIB3   | rs2295492 | C            | 0.169 | 0.178 | 0.149 | 0.186 | 0.61 | 0.84 | 0.20 |
| TRIB3   | rs6037542 | T            | 0.286 | 0.347 | 0.320 | 0.331 | 0.24 | 0.69 | 0.80 |

Significant SNPs and P values are shown in bold type

DM represents type 2 diabetes, HT represents hypertension

* Obtained from Fisher’s exact test versus control subjects

rs2241766 in exon 2 and SNP rs1501299 in intron 2 are the most widely investigated variants in ADIPOQ. At least 19 studies have shown SNP rs2241766 to be associated with T2DM in the Chinese population, but no association was found in any of 8 other studies [40]. A recent large-scale meta-analysis of 39 studies showed that SNPs rs2241766 and rs1501299 are not associated with T2DM in either Asian or European populations [42]. A meta-analysis of 24 studies suggested no significant association between SNPs rs2241766 and rs1501299 and hypertension in Chinese individuals [41]. A large cardiovascular risk factor prevalence study also failed to find any association between SNPs rs2241766 and rs1501299 and hypertension in Chinese individuals [41]. In the present study, we did not find any significant association between these 2 SNPs and either T2DM or hypertension, which is consistent with previous studies [41, 42]. Intriguingly, three polymorphisms (rs16861194, rs17300539, rs266729) in ADIPOQ were associated with risk of T2DM in European populations but none of these polymorphisms were associated with risk of T2DM in Asian populations [42]. In the present study, no significant association was
observed between SNPs rs16861194 and rs266729 with T2DM in a Chinese Han population. Taken together, these findings suggest that ethnically specific polymorphisms might contribute to the development of T2DM and hypertension in different populations.

In the present study, we found the G allele of a promoter SNP rs266729 in ADIPOQ to be significantly associated with the increased risk of hypertension (OR = 1.41). A previous study in a Hong Kong Chinese population also suggested that genetic variants in the promoter region of ADIPOQ are associated with increased risk of hypertension [17]. The G allele of rs266729 has been linked to decreased serum levels of adiponectin [43]. Because adiponectin has been reported to exert an antiatherosclerotic effect, we might speculate that G allele of rs266729 can influence the abundance of adiponectin in adipose tissue. Low levels of this peptide in serum can directly influence endothelial function. This hypothesis is supported by the observation that both the expression and activity of eNOS are increased in cultured vascular endothelial cells that have been treated with globular adiponectin [44]. This promoter polymorphism is also associated with T2DM in Chinese, French, German, and Swedish populations [22, 40, 45, 46]. One meta-analysis confirmed the association between rs266729 and T2DM, but another meta-analysis did not [39, 47]. The discrepancy between these results may be partially due to ethnic differences in the populations, selection criteria of the study subjects, and sample size.

It has been proposed that SNPs in the 3′UTR of ADIPOQ, like promoter SNPs, may remodel adiponectin conformation, causing T2DM [48]. In the present study, one 3′UTR SNP, rs1063537, found in ADIPOQ, was found to be significantly associated with T2DM. To the best of our knowledge, this is the first time that this SNP has been shown to be associated with T2DM. One previous study reported the T allele of rs1063537 to be associated with higher adiponectin levels in Caucasian women [49]. Other research groups found another 2 SNPs (rs1063539 and rs6773957) in 3′UTR of ADIPOQ to be associated with T2DM in the Chinese population [50, 51]. SNP rs6773957 was found to be associated with adiponectin level in a genome-wide association study [52]. The HapMap data in Asian samples show that rs1063537 is in linkage disequilibrium with rs1063539 and rs6773957.

Genetic variants in the LEPR gene have been reported to have a profound impact on body weight, insulin resistance, blood pressure, and other metabolic disease parameters [23, 38]. In the present study, we found one intron SNP, rs13306519, in LEPR to be significantly associated with T2DM and another intron SNP rs12037879 was found to be significantly associated with hypertension. To our knowledge, this is the first time that these two LEPR SNPs have been associated with T2DM and hypertension. Further studies in different populations are needed to confirm our findings.

The nonsynonymous SNP rs1137101 (Gln223Arg), which is in the LEPR gene, has been extensively investigated in a wide range of populations. The G allele of rs1137101 has been associated with lower blood pressure [23]. However, the A allele has been associated with increased insulin and leptin levels and the risk of developing T2DM [53]. Another two nonsynonymous SNPs, rs8179183 (Lys656Asn) and rs1137100 (Arg109Lys), have been reported to be associated with hypertension and T2DM [54, 55]. However, the results of published studies have been inconsistent [23, 53]. One study performed in the Chinese population showed rs1137101 to be associated with hypertension but not with T2DM [56]. In the present study, we did not find any association between these 3 SNPs with T2DM or hypertension. This could be partly explained by a lack of statistical power sufficient to detect variants that are likely to confer only a modest effect on T2DM and hypertension. Further studies with larger sample size and greater statistical power are required to confirm these associations.

Intriguingly, a significant interaction was identified between two SNPs rs13306519 in LEPR and rs266729 in ADIPOQ for both T2DM (P_inter = 0.012, OR_inter = 2.67) and hypertension (P_inter = 0.0041, OR_inter = 2.23), suggesting that individuals carrying variants of both genes might have a higher risk of developing T2DM and hypertension than those carrying variants in single genes.

The RETN and TRIB3 genes have been found to be associated with T2DM in previous studies, but the results are often conflicting [27, 29, 30]. In the present study, no significant association was found between the RETN and TRIB3 genes and any medical condition, suggesting that genetic variants in these genes may not be major risk factors for the development of T2DM or hypertension in the Chinese population.

It is crucial to avoid population stratification in genetic association studies. One of the strengths of the present study is the ethnically matched cases and control subjects. The observed association in our study is unlikely to have been affected by population stratification. Another major strength of our study is the relatively large sample size in both the disease and control groups. Although the sample size examined in the present work is smaller than those of other large-scale studies, the power calculations suggest that these samples have sufficient power to detect common variants with moderate genetic effects. Specifically, these samples for T2DM had 86.7% power to detect variants with minor allele frequencies of 0.15 and OR of 1.6 at significance level of 0.05. The samples for hypertension had 91.7% power to detect variants with minor allele frequencies of 0.15 and ORs of 1.6 at a significance level of...
0.05. All four genes investigated in this study have been found to be associated with T2DM and hypertension in previous studies, but the results are often conflicting. The purpose of the present study was to evaluate these associations in a different population. Because this study was not a discovery study, we did not attempt to replicate our results in independent samples. One limitation of the present study was that we did not investigate rare variants but only SNP tags with a MAF >0.1. We therefore could not rule out the possibility of the existence of rare variants in these genes that might be associated with T2DM and hypertension. Our sample size would not provide sufficient power for a detection of the associations of these rare variants with T2DM and hypertension. A larger sample and resequencing of the whole gene coding regions would be required to elucidate the role of these rare variants in the development of T2DM and hypertension. Although the selected tag SNPs evaluated in this study are not sufficient to define fine structure of the haplotype block in this population, the purpose of the present study was to investigate the association of these genes with T2DM and hypertension. It was anticipated that these selected tag SNPs would be capable of capturing the majority of polymorphisms in these genes. As the associations we observed in the present study were nominally significant, it is possible that these associations are false positives. However, it is statistically impossible for a candidate gene study like this one to yield a very small $P$ values like those reported in a genome-wide association studies with thousands of samples. Permutation tests suggest that these nominal associations are likely to be true associations.

Serum levels of adipokines, including adiponectin, leptin, and resistin, have been reported to be involved in the development and progression of both T2DM and hypertension. Genetic variants in genes encoding these adipokines have been found to be associated with serum levels of these adipokines. It would be interesting to investigate the association between the gene variants and the serum levels of these adipokines. However, because serum levels of these adipokines were not measured in the present study, it is impossible to perform such an analysis as part of this project. Further studies are warranted.

In summary, the present findings suggest that variants in ADIPOQ and LEPR are significant risk factors for T2DM and hypertension. However, variants in RETN and TRIB3 are not major risk factors for the development of these complex disorders, at least in the Chinese population.

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References

1. IDFID Epidemiology and Mobidity (2011) In: International Diabetes Federation. http://www.idf.org/. Accessed 1 March 2011
2. Yang W, Lu J, Weng J, Jia W, Ji L, Xiao J, Shan Z, Liu J, Tian H, Ji Q, Zhu D, Ge J, Lin L, Chen L, Guo X, Zhao Z, Li Q, Zhou Z, Shan G, He J (2010) Prevalence of diabetes among men and women in China. N Engl J Med 362:1090–1101
3. Kearney PM, Whelton M, Reynolds R, Muntner P, Whelton PK et al (2005) Global burden of hypertension: analysis of worldwide data. Lancet 365:217–223
4. Wu Y, Huxley R, Li L, Anna V, Xie G et al (2008) Prevalence, awareness, treatment, and control of hypertension in China: data from the China National Nutrition and Health Survey 2002. Circulation 118:2679–2686
5. Ferrannini E, Cushman WC (2012) Diabetes and hypertension: the bad companions. Lancet 380:601–610
6. Harrison M, Maresso K, Broeckel U (2008) Genetic determinants of hypertension: an update. Curr Hypertens Rep 10:488–495
7. Hindorff LA, Sethupathy P, Junkins HA, Ramos EM, Mehta JP et al (2009) Potential etiologic and functional implications of genome-wide association loci for human diseases and traits. Proc Natl Acad Sci USA 106:9362–9367
8. Simino J, Rao DC, Freedman BI (2012) Novel findings and future directions on the genetics of hypertension. Curr Opin Nephrol Hypertens 21:500–507
9. Travers ME, McCarthy MI (2011) Type 2 diabetes and obesity: genomics and the clinic. Hum Genet 130:41–58
10. Scherer PE (2006) Adipose tissue: from lipid storage compartment to endocrine organ. Diabetes 55:1537–1545
11. Heid IM, Wagner SA, Gohlke H, Iglseder B, Mueller JC et al (2006) Genetic architecture of the APM1 gene and its influence on adiponectin plasma levels and parameters of the metabolic syndrome in 1,727 healthy Caucasians. Diabetes 55:375–384
12. Ziemke F, Mantzoros CS (2010) Adiponectin in insulin resistance: lessons from translational research. Am J Clin Nutr 91:2585S–261S
13. Kisselbah AH, Sonnenberg GE, Myklebust J, Goldstein M, Bromer K et al (2000) Quantitative trait loci on chromosomes 3 and 17 influence phenotypes of the metabolic syndrome. Proc Natl Acad Sci USA 97:14478–14483
14. Lillioja S, Wilton A (2009) Agreement among type 2 diabetes linkage studies but a poor correlation with results from genome-wide association studies. Diabetologia 52:1061–1074
15. Mori Y, Otabe S, Dina C, Yasuda K, Populaire C et al (2002) Genome-wide search for type 2 diabetes in Japanese affected sib-pairs confirms susceptibility genes on 3q, 15q, and 20q and identifies two new candidate loci on 7p and 11p. Diabetes 51:1247–1255
16. Vionnet N, Hani EH, Dupont S, Gallina S, Francke S et al (2000) Genomewide search for type 2 diabetes-susceptibility genes in French whites: evidence for a novel susceptibility locus for early-onset diabetes on chromosome 3q27-qter and independent
17. Ong KL, Li M, Tso AW, Xu A, Chenry SS et al (2010) Association of genetic variants in the adiponectin gene with adiponectin level and hypertension in Hong Kong Chinese. Eur J Endocrinol 163:251–257

18. Stefan N, Vozarova B, Del Parigi A, Ossowski V, Thompson DB et al (2002) The Glu223Arg polymorphism of the leptin receptor in Pima Indians: influence on energy expenditure, physical activity and lipid metabolism. Int J Obes Relat Metab Disord 26:1629–1632

19. Beltowski J (2006) Role of leptin in blood pressure regulation and arterial hypertension. J Hypertens 24:789–801

20. Gan RT, Yang SS (2012) The 223A–G polymorphism of the leptin receptor gene is associated with macroangiopathy in type 2 diabetes mellitus. Mol Biol Rep 39:4759–4764. doi:10.1007/s1033-011-1268-2

21. Gottlieb MG, Bodanese LC, Leite LE, Schwanke CH, da Piccoli C et al (2009) Association between the Glu223Arg polymorphism of the leptin receptor and metabolic syndrome in free-living community elderly. Metab Syndr Relat Disord 7:341–348

22. Gu HF, Abulaiti A, Ostenson CG, Humphreys K, Wahlestedt C, Brooks AE, Elendic S (2004) Single nucleotide polymorphisms in the proximal promoter region of the adiponectin (APM1) gene are associated with type 2 diabetes in Swedish Caucasians. Diabetes 53(Suppl 1):S31–S35

23. Rosmond R, Chagnon YC, Holm G, Chagnon M, Perusse L et al (2000) Hypertension in obesity and the leptin receptor gene locus. J Clin Endocrinol Metab 85:3126–3131

24. Sober S, Org E, Kepp K, Juhanson P, Eyheramendy S et al (2009) Targeting 160 candidate genes for blood pressure regulation with a genome-wide genotyping array. PLoS One 4:e6034

25. Meier U, Gressner AM (2004) Endocrine regulation of energy metabolism: review of pathobiological and clinical chemical aspects of leptin, ghrelin, adiponectin, and resistin. Clin Chim Acta 350:1511–1525

26. Miner JL (2004) The adipocyte as an endocrine cell. J Anim Sci 82:935–941

27. Menzaghi C, Trischitta V, Doria A (2007) Genetic influences of adiponectin on insulin resistance, type 2 diabetes, and cardiovascular disease. Diabetes 56:1198–1209

28. Prudente S, Sesti G, Pandolfi A, Andreozzi F, Consoli A et al (2012) The Mammalian Tribbles Homolog TRIB3, Glucose Homeostasis, and Cardiovascular Diseases. Endocr Rev 33:526–546

29. Permut MA, Wasson JC, Suarez BK, Lin J, Thomas J et al (2001) A genome scan for type 2 diabetes susceptibility loci in a genetically isolated population. Diabetes 50:681–685

30. Watanabe RM, Ghosh S, Langefeld CD, Valle TT, Hauser ER et al (2000) The Finland-United States investigation of non-insulin-dependent diabetes mellitus genetics (FUSION) study. II. An autosomal genome scan for diabetes-related quantitative-trait loci. Am J Hum Genet 67:1186–1200

31. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA et al (2007) PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet 81:559–575

32. Pollin TI, Tanner K, O’Connell JR, Ott SH, Damcott CM et al (2005) Linkage of plasma adiponectin levels to 3q27 explained by association with variation in the APM1 gene. Diabetes 54:268–274

33. Chow WS, Cheung BM, Tso AW, Xu A, Wat NM et al (2007) Adiponectin gene expression in a predictor for the development of hypertension: a 5-year prospective study. Hypertension 49:1453–1461

34. Imatoh T, Miyazaki M, Momose Y, Tanihara S, Une H (2008) Adiponectin levels associated with the development of hypertension: a prospective study. Hypertens Res 31:229–233

35. Yamamoto Y, Hirose H, Saito I, Tomita M, Taniyama M et al (2002) Correlation of the adipocyte-derived protein adiponectin with insulin resistance index and serum high-density lipoprotein-cholesterol, independent of body mass index, in the Japanese population. Clin Sci 103:137–142

36. Kumada M, Kihara S, Sumitsuji S, Kawakami T, Matsumoto T et al (2003) Association of hypoadiponectinemia with coronary artery disease in men. Arterioscler Thromb Vasc Biol 23:85–89

37. Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K et al (1999) Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 257:79–83

38. Enns JE, Taylor CG, Zahradka P (2011) Variations in adipokine genes ADIPOQ, Lep, and LepR are associated with risk for obesity-related metabolic disease: the modulatory role of gene-nutrient interactions. J Obes 2011:168659

39. Menzaghi C, Trischitta V (2010) Genetics of serum resistin: a paradigm of population-specific regulation? Diabetologia 53:226–228

40. Li Y, Yang Y, Shi L, Li X, Zhang Y, Yao Y (2012) The association studies of ADIPOQ with type 2 diabetes mellitus in Chinese populations. Diabetes Metab Res Rev 28(7):551–559. doi:10.1002/dmrr.2309

41. Xi B, He D, Wang Q, Xue J, Liu M, Li J (2012) Common polymorphisms (rs2241766 and rs1501299) in the ADIPOQ gene are not associated with hypertension susceptibility among the Chinese. Mol Biol Rep 39:877–8775

42. Chu H, Wang M, Zhong D, Shi D, Ma L, Tong N, Zhang Z (2013) AdipoQ polymorphisms are associated with type 2 diabetes mellitus: a meta-analysis study. Diabetes Metab Res Rev 29(7):532–545. doi:10.1002/dmrr.2424

43. Vasseur F, Helbecque N, Lobbens S, Vasseur-Delannoy V, Dina C et al (2005) Hypoadiponectinemia and high risk of type 2 diabetes are associated with adiponectin-encoding (ACDC) gene promoter variants in morbid obesity: evidence for a role of ACDC in diabetes. Diabetologia 48:892–899

44. Hattori Y, Suzuki M, Hattori S, Kasai K (2003) Globular adiponectin upregulates nitric oxide production in vascular endothelial cells. Diabetologia 46:1543–1549

45. Vasseur F, Helbecque N, Dina C, Lobbens S, Delannoy V et al (2002) Single-nucleotide polymorphism haplotypes in the both proximal promoter and exon 3 of the APM1 gene modulate adipocyte-secreted adiponectin hormone levels and contribute to the genetic risk for type 2 diabetes in French Caucasians. Hum Mol Genet 11:2607–2614.
4545G/C are associated respectively with obesity and with non-obesity in Chinese type 2 diabetes. Diabetes Res Clin Pract 84:205–210

52. Ling H, Waterworth DM, Stirnadel HA, Pollin TI, Barter PJ et al (2009) Genome-wide linkage and association analyses to identify genes influencing adiponectin levels: the GEMS Study. Obesity (Silver Spring) 17:737–744

53. Guizar-Mendoza JM, Amador-Licona N, Flores-Martinez SE, Lopez-Cardona MG, Ahuatzin-Tremary R et al (2005) Association analysis of the Gln223Arg polymorphism in the human leptin receptor gene, and traits related to obesity in Mexican adolescents. J Hum Hypertens 19:341–346

54. Salopuro T, Pulkkinen L, Lindstrom J, Eriksson JG, Valle TT et al (2005) Genetic variation in leptin receptor gene is associated with type 2 diabetes and body weight: the finish diabetes prevention study. Int J Obes (Lond) 29:1245–1251

55. Wauters M, Mertens I, Rankinen T, Chagnon M, Bouchard C et al (2001) Leptin receptor gene polymorphisms are associated with insulin in obese women with impaired glucose tolerance. J Clin Endocrinol Metab 86:3227–3232

56. Gu P, Jiang W, Chen M, Lu B, Shao J et al (2012) Association of leptin receptor gene polymorphisms and essential hypertension in a Chinese population. J Endocrinol Invest 35(9):859–865. doi:10.3275/8238