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# The association of six single nucleotide polymorphisms and their haplotypes in CDH13 with T2DM in a Han Chinese population

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**Abstract**

T-cadherin (CDH13) is an adiponectin receptor. Genome-wide association studies have identified the *CDH13* gene as one of the most important candidate genes in influencing plasma adiponectin levels. Several studies recently reported single-nucleotide polymorphisms (SNPs) in *CDH13* gene were associated with T2DM. The purpose of this study was to investigate the association between T2DM and 6 SNPs (rs11646213, rs12596316, rs3865188, rs12444338, rs12051272, and rs7195409) in the *CDH13* gene in a Han Chinese population. A total of 674 subjects with T2DM and 588 subjects without T2DM were genotyped using the TaqMan method. Our data showed that there was an association between the SNP-rs12596316 genotype and T2DM ($P < .05$). Moreover, an overdominant model of inheritance showed that being an rs12596316AG heterozygote increased the risk of T2DM ($P = .0041$, odds ratio = 1.39; 95% confidence interval 1.11–1.73) in comparison with rs12596316AA-GG. The other 5 SNPs did not show associations with T2DM, either in the allele levels or in different inheritance models. The haplotype analysis showed that there were no associations between any haplotypes and T2DM. Our results revealed that genetic variations in the *CDH13* gene were associated with T2DM susceptibility in a Han Chinese population. These results highlight the need to study the functional effects of these *CDH13* gene variants in relation to the risk of developing T2DM.

**Abbreviations:** CDH13 = T-cadherin, FPG = fasting plasma glucose, HbA1c = glycosylated hemoglobin, HDL-C = high-density lipoprotein cholesterol, HWE = Hardy-Weinberg equilibrium, LD = linkage disequilibrium analysis, LDL-C = low-density lipoprotein cholesterol, NDM = non-diabetes mellitus, SNPs = single-nucleotide polymorphisms, T2DM = type 2 diabetes mellitus, TC = total cholesterol, TG = triglycerides.

**Keywords:** adiponectin, *CDH13* gene, Chinese population, polymorphisms, T2DM

## 1. Introduction

Diabetes is a significant threat to public health in China. The latest survey showed that the overall prevalence of diabetes in the adult Chinese population has reached 11.6%.[1] More and more studies have proved the genetic factors played a key role in the development of type 2 diabetes mellitus (T2DM), which is characterized by insulin resistance and islet beta cell dysfunction.

Adiponectin, as one of the most abundant plasma protein, plays a crucial role in the development of T2DM by increasing insulin sensitivity and by improving islet beta cell dysfunction and the beta-oxidation of fatty acids.[2–5] There are 3 predominant forms of adiponectin in plasma: a trimmer, a hexamer, and a high molecular weight multimer. Accumulated evidence has shown that the high-molecular-weight adiponectin is a more active form, which is considered to be more strongly related to T2DM, hypertension, and cardiovascular disease.[6–8]

T-cadherin (CDH13), which is expressed in endothelium and smooth muscle, has been reported to be a high-molecular-weight adiponectin receptor.[9] CDH13 is not only involved in the pathophysiology of T2DM by being a third receptor of adiponectin but also regulates insulin secretion directly, independent of adiponectin.[10] In recent years, genome-wide association studies have shown that single-nucleotide polymorphism (SNP) loci located in the promoter and intron regions of the *CDH13* gene, such as rs11646213, rs12596316, rs3865188, rs12051272, and rs7195409, have been associated with plasma adiponectin levels in different ethnic populations.[11–15] Moreover, variations in CDH13, such as rs11646213, have been reported to be associated with metabolic syndrome and hypertension.[12,16]

To investigate the association between the CDH13 gene and T2DM in a Han Chinese population, in the present study, we evaluated the association of T2DM with *CDH13* gene SNPs and their haplotypes in a Han Chinese population; 4 of the included SNPs (rs11646213, rs12596316, rs3865188, and rs12444338)

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are located in the promoter region of CDH13, 1 SNP (rs12051272) is located in intron 1, and 1 SNP (rs7195409) is located in intron 7. Our results revealed the role of genetic variations of the *CDH13* gene in the development of T2DM in a Han Chinese population.

## 2. Materials and Methods

### 2.1. Ethics statement

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (the Institutional Review Board of the Second People's Hospital of Yunnan Province) and with the Helsinki Declaration of 1975, which was revised in 2008. Informed consent was obtained from all subjects to be included in the study.

### 2.2. Subjects

From December 2011 to January 2015, a total of 674 patients (422 males and 252 females) with T2DM at the Second People's Hospital of Yunnan Province were renrolled. During the same period, 588 controls (353 males and 235 females) were determined as non diabetes mellitus subjects (NDM) who took routine examinations at the same hospital. The diagnosis criteria of T2DM were the World Health Organization criteria in 1999. The exclusion criteria of NDM group included subjects with diabetic family history, impaired glucose tolerance, and hypertension or coronary heart disease. All the subjects (T2DM and NDM) were unrelated Chinese Han population.

### 2.3. Anthropometric measurements

Anthropometric measurements included body weight (kg), height (cm), waist circumference (cm) that were done in duplicate. Body weight and height were measured with enrolled subjects not wearing shoes and in light clothing. In standing position, waist circumference (WC) was assessed at the midpoint between the iliac crest and the lower costal margin. Body mass index (BMI) was calculated as body weight (kg)/height (m) squared.

### 2.4. Biochemical parameters

Blood samples were collected after an overnight fast. Fasting plasma glucose (FPG) was tested via the glucose oxidase method. Total cholesterol (TC) was detected using the oxidase method. High-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were detected using the direct method. Triglycerides (TGs) were determined via glycerol-3-phosphate oxidase methods. Glycosylated hemoglobin (HbA1c) were determined by immunoturbidimetry. All the biochemical parameters were performed on a HITACHI 7600–020 Automatic Analyzer.

### 2.5. Genotyping of the CDH13 gene SNPs

A hydroxybenzene-chloroform method was used to isolate genomic DNA from each blood sample. Genotyping of the 6 SNPs (rs11646213, rs12596316, rs3865188, rs12444338, rs12051272, and rs7195409) in the *CDH13* gene was detected using a TaqMan SNP genotyping assay (Applied Biosystems, Foster City, CA). To identify the accuracy of SNP genotyping by TaqMan assay, we have randomly selected some products for sequencing to identity the TaqMan results.

### 2.6. Statistical analysis

The anthropometric measurements, glucose and lipid features of the subjects enrolled in the present study were expressed as the mean ± standard deviation. The analyses of the differences between the T2DM and NDM groups were performed using SPSS 13 (Chicago, IL). The genotype, allele and haplotype frequencies for the SNPs, and the Hardy-Weinberg equilibrium (HWE), linkage disequilibrium analysis (LD), and haplotype-specific risks analysis were calculated using the SHEsis software (http://analysis2.bio-x.cn/myAnalysis.php). SNPstats program was applied to analyze the genotype association for the inheritance mode in a case-control pattern.[17] The model with the smallest Akaike information criterion and Bayes information criterion was identified as the best fitting genetic model for each SNP.[17] Sex and age were included in the mode of inheritance analysis as a covariate. A $P$ value of less than .05 was considered to be statistically significant.

## 3. Results

### 3.1. Subject characteristics

For age and sex, the T2DM and NDM groups showed no significant statistic differences. But the metabolic parameters, including BMI, WC, TC, TG, HDL-C, LDL-C, FPG, and HbA1c, were significantly different between T2DM and NDM subjects (Table 1).

### 3.2. Association of the 6 SNPs in the CDH13 gene with T2DM

The allele and genotype frequencies of the 6 SNPs (rs11646213, rs12596316, rs3865188, rs12444338, rs12051272, and rs7195409) in the *CDH13* gene are presented in Table 2. The genotype frequencies for the SNPs were in HWE for the T2DM and NDM groups ($P > .05$), except for rs12596316 in the case group ($P = .037$). The allele and genotype distributions of the rs11646213, rs3865188, rs12444338, rs12051272, and rs7195409 SNPs in the *CDH13* gene had no association with T2DM ($P > .05$) (Table 2). The allele frequencies for rs12596316 were not different between the T2DM and NDM groups ($P > .05$); however, the genotype distribution for rs12596316

**Table 1**

**Clinical characteristics of the subjects enrolled in the present study.**

| | T2DM | NDM | P |
|---|---|---|---|
| N | 674 | 588 | |
| Age, y | 50.645 ± 11.724 | 50.102 ± 11.171 | .354 |
| Sex (M/F) | 422/252 | 353/235 | .400 |
| Age/M, y | 49.222 ± 11.781 | 49.167 ± 10.321 | .944 |
| Age/F, y | 53.028 ± 11.254 | 51.506 ± 12.228 | .153 |
| Body mass index, kg/m$^2$ | 24.630 ± 3.813 | 21.959 ± 4.171 | <.001 |
| Waist circumference, cm | 89.102 ± 9.438 | 79.429 ± 13.069 | <.001 |
| Total cholesterol, mmol/L | 4.870 ± 1.103 | 4.401 ± 0.837 | <.001 |
| Triglycerides, mmol/L | 2.578 ± 2.063 | 1.674 ± 1.171 | <.001 |
| High-density lipoprotein-cholesterol, mmol/L | 1.085 ± 0.283 | 1.283 ± 0.284 | <.001 |
| Low-density lipoprotein-cholesterol, mmol/L | 2.679 ± 1.006 | 2.063 ± 0.599 | <.001 |
| Fasting plasma glucose, mmol/L | 7.832 ± 2.377 | 4.932 ± 0.593 | <.001 |
| HbA1C (%) | 8.929 ± 2.742 | 5.178 ± 0.477 | <.001 |

Data are represented as mean ± standard deviation. HbA1c = glycosylated hemoglobin NDM = non-diabetes mellitus, T2DM = type 2 diabetes mellitus.

**Table 2**

**Comparison of genotypic and allelic distribution of 6 SNPs (rs11646213, rs12596316, rs3865188, rs12444338, rs12051272, and rs7195409) between T2DM and NDM.**

| SNPs | Allele | | $\chi^2$ | *P* | Odds ratio (95% CI) | | | | $\chi^2$ | *P* | Hardy-Weinberg equilibrium |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs11646213 | A (freq) | T (freq) | | | | A/A (freq) | A/T (freq) | T/T (freq) | | | |
| T2DM | 1125 (0.835) | 223 (0.165) | 0.130 | .718 | 0.962 (0.778~1.189) | 471 (0.699) | 183 (0.272) | 20 (0.030) | 1.091 | .580 | 0.665 |
| NDM | 981 (0.840) | 187 (0.160) | | | | 409 (0.700) | 163 (0.279) | 12 (0.021) | | | 0.361 |
| rs12596316 | A (freq) | G (freq) | | | | A/A (freq) | A/G (freq) | G/G (freq) | | | |
| T2DM | 851 (0.631) | 497 (0.369) | 1.006 | .316 | 0.920 (0.781~1.083) | 256 (0.380) | 339 (0.503) | 79 (0.117) | 7.984 | .018 | 0.037 |
| NDM | 765 (0.651) | 411 (0.349) | | | | 258 (0.439) | 249 (0.423) | 81 (0.138) | | | 0.096 |
| rs3865188 | A (freq) | T (freq) | | | | A/A (freq) | A/T (freq) | T/T (freq) | | | |
| T2DM | 847 (0.628) | 50 1 (0.372) | 0.872 | 0.350 | 0.925 (0.786~1.089) | 261 (0.387) | 325 (0.482) | 88 (0.131) | 3.276 | .194 | 0.400 |
| NDM | 760 (0.646) | 416 (0.354) | | | | 253 (0.430) | 254 (0.432) | 81 (0.138) | | | 0.181 |
| rs12444338 | G (freq) | T (freq) | | | | G/G (freq) | G/T (freq) | T/T (freq) | | | |
| T2DM | 875 (0.649) | 473 (0.351) | 0.187 | .666 | 0.964 (0.818~1.137) | 283 (0.420) | 309 (0.458) | 82 (0.122) | 1.270 | .530 | 0.868 |
| NDM | 773 (0.657) | 403 (0.343) | | | | 261 (0.444) | 251 (0.427) | 76 (0.129) | | | 0.203 |
| rs12051272 | G (freq) | T (freq) | | | | G/G (freq) | G/T (freq) | T/T (freq) | | | |
| T2DM | 886 (0.657) | 462 (0.343) | 0.346 | .556 | 0.952 (0.806~1.123) | 289 (0.429) | 308 (0.457) | 77 (0.114) | 1.900 | .387 | 0.711 |
| NDM | 786 (0.668) | 390 (0.332) | | | | 270 (0.459) | 246 (0.418) | 72 (0.122) | | | 0.173 |
| rs7195409 | A (freq) | G (freq) | | | | A/A (freq) | A/G (freq) | G/G (freq) | | | |
| T2DM | 1174 (0.871) | 174 (0.129) | 2.409 | .121 | 1.195 (0.954~1.500) | 509 (0.755) | 156 (0.231) | 9 (0.013) | 2.705 | .259 | 0.444 |
| NDM | 999 (0.849) | 177 (0.151) | | | | 424 (0.721) | 151 (0.257) | 13 (0.022) | | | 0.918 |

CI = confidence interval, NDM = non-diabetes mellitus, SNP = single-nucleotide polymorphism, T2DM = type 2 diabetes mellitus.

was significantly different between the T2DM and NDM groups ($P = .018$) (Table 2).

### 3.3. Mode of inheritance analysis of the 6 SNPs in the CDH13 gene with relation to T2DM

Table 3 and Supplementary Tables 1–5, http://links.lww.com/MD/B714, present the results of analyses to determine the mode of inheritance for each of the 6 SNPs. The inheritance model with the best fit for rs12596316 was an overdominant model. The AG genotype of rs12596316 was a risk genotype for the development of T2DM ($P = .004$, odds ratio [OR] = 1.39; 95% confidence interval [CI]: 1.11–1.73) in the overdominant inheritance model after adjustments were made to account for age and sex. The other 5 SNPs (rs11646213, rs3865188, rs12444338, rs12051272, and rs7195409) had no observed associations with T2DM in any of the inheritance models.

### 3.4. Association of the haplotypes of the CDH13 gene SNPs with T2DM

The results of LD analysis are shown in Supplementary Table 6, http://links.lww.com/MD/B714. When D' ≥0.700 in the LD analysis, the SNPs were considered to construct the haplotypes. After the haplotypes were constructed, we observed that the rs11646213-rs12596316-rs3865188-rs12444338-rs12051272 haplotype was not different between the T2DM and NDM groups in the present study (supplementary Table 7, http://links.lww.com/MD/B714).

## 4. Discussion

In the present study, we investigated the associations between 6 SNPs in the *CDH13* gene with T2DM in a Han Chinese population. Our results showed that the rs12596316 AG genotype was a risk genotype for the development of T2DM in the overdominant inheritance model. The other 5 SNPs (rs11646213, rs3865188, rs12444338, rs12051272, and rs7195409) had no observed associations with T2DM in terms of alleles, genotypes or in various inheritance models. In addition, the haplotype analysis also showed no association with T2DM.

Many studies have reported that adiponectin levels were associated with T2DM, hypertension, and cardiovascular disease.[6–8] In addition, the *CDH13* gene has been considered to be one of the most important candidate genes in influencing

**Table 3**

**Different inheritance models analysis of the SNP rs12596316 between the T2DM and NDM group.**

| Model | Genotype | NDM (freq) | T2DM (freq) | Odds ratio (95%CI) | *P* | Akaike information criterion | Bayes information criterion |
|---|---|---|---|---|---|---|---|
| Co dominant | A/A | 258 (0.439) | 256 (0.380) | 1.00 | .016 | 1743.60 | 1769.30 |
| | A/G | 249 (0.424) | 339 (0.503) | 1.38 (1.09–1.75) | | | |
| | G/G | 81 (0.138) | 79 (0.117) | 0.99 (0.69–1.41) | | | |
| Dominant | A/A | 258 (0.439) | 256 (0.380) | 1.00 | .029 | 1745.00 | 1765.60 |
| | A/G-G/G | 330 (0.561) | 418 (0.620) | 1.29 (1.03–1.61) | | | |
| Recessive | A/A-A/G | 507 (0.862) | 595 (0.883) | 1.00 | .280 | 1748.70 | 1769.20 |
| | G/G | 81 (0.138) | 79 (0.117) | 0.83 (0.60–1.16) | | | |
| Overdominant | A/A-G/G | 339 (0.576) | 335 (0.497) | 1.00 | .004 | 1741.60 | 1762.10 |
| | A/G | 249 (0.424) | 339 (0.503) | 1.39 (1.11–1.73) | | | |
| Log-additive | — | — | — | 1.09 (0.93–1.29) | .290 | 1748.70 | 1769.20 |

rs12596316 association with response status (n = 1262, adjusted by sex + age). NDM = non-diabetes mellitus, SNP = single-nucleotide polymorphism, T2DM = type 2 diabetes mellitus.

**Table 4**

**Reported associations of *CDH13* gene 6 SNPs (rs11646213, rs12596316, rs3865188, rs12444338, rs12051272, and rs7195409) with adiponectin level and adiponectin-related metabolic diseases in different populations.**

| Populations | SNP | Allele (freq) | | Characteristics | Genome-wide association studies | Ref. |
|---|---|---|---|---|---|---|
| | rs11646213 | A | T | | | |
| Swedes | | 0.39–0.40 | | AA genotype is associated with metabolic syndrome in women | No | [16] |
| Germany | | 0.39–0.41 | | A allele had a decreased risk of hypertension | Yes | [12] |
| Estonians | | 0.35 | | A allele had a decreased risk of hypertension | Yes | [12] |
| British | | — | | A allele had a decreased risk of hypertension | Yes | [12] |
| Filipino | | — | | adiponectin level ($P = 1.27 \times 10^{-6}$) | Yes | [14] |
| Chinese (Taiwan) | | | 0.17 | T allele is associated with higher adiponectin | No | [18] |
| European | | 0.41 | | adiponectin level ($P = .10$) | Yes | [19] |
| | rs12596316 | A | G | | | |
| Korean | | | 0.30–0.31 | G allele is a associated with lower adiponectin and high-molecular-weight adiponectin | Yes | [13] |
| | rs3865188 | A | T | | | |
| Korean | | | 0.30–0.31 | T allele is associated with lower adiponectin and high-molecular-weight adiponectin | Yes | [13] |
| Filipino | | | 0.47 | T allele is associated with lower adiponectin level | Yes | [14] |
| Japanese | | | 0.31 | A allele is associated with higher adiponectin | No | [20] |
| | rs12444338 | G | T | | | |
| Chinese (Taiwan) | | | 0.34 | T allele is associated with lower adiponectin | No | [18] |
| | rs12051272 | G | T | | | |
| Japanese | | | 0.30–0.31 | T allele is a associated with lower adiponectin | Yes | [15] |
| Chinese (Taiwan) | | | 0.33 | T allele is associated with lower adiponectin | No | [18] |
| Japanese | | — | 0.31 | G allele is a associated with higher adiponectin | No | [20] |
| | rs7195409 | A | G | | | |
| Europeans | | — | — | Adiponectin level ($P = 2.00 \times 10^{-5}$) | Yes | [11] |
| Filipino | | 0.90 | 0.10 | Adiponectin level ($P = .16$) | Yes | [14] |

SNP = single-nucleotide polymorphism.

plasma adiponectin levels. However, in the present study, the rs11646213, rs3865188, rs12444338, rs12051272, and rs7195409 SNPs in the *CDH13* gene, which have been shown to be associated with adiponectin levels, metabolic syndrome, and hypertension in various populations (Table 4), failed to show any associations with T2DM in a Chinese population. One possible explanation for this inconsistency is that the various populations that have been studied have different genetic backgrounds, including differences in SNP frequencies. For example, rs11646213 has been shown to have a stronger association with adiponectin levels in Filipino women[14] and in a Chinese Taiwan population,[18] but rs11646213 did not show a similar association in Europeans ($P = .10$).[19] In a European population, the rs11646213 A allele accounted for approximately 42% as the minor allele. The rs11646213 A allele frequency was shown to account for approximately 82% in an East Asian population (http://asia.ensembl.org/Homo_sapiens/Variation/Population?db=core;r=16:82608546–82609546;v=rs11646213;vdb=variation;vf=107813875). Moreover, in 2009, Ling et al [11] reported that rs7195409 was associated with adiponectin levels in Europeans ($P = 2.0 \times 10^{-5}$). However, Wu et al [14] did not find an association between rs7195409 and adiponectin levels in Filipino women. The frequencies of the G allele have also been shown to be different between European and Asian populations (http://asia.ensembl.org/Homo_sapiens/Variation/Population?db=core;r=16:83493487–83494487;v=rs7195409;vdb=variation;vf=105240787#population_freq_EUR).

Associations between the *CDH13* gene rs3865188, rs12444338, and rs12051272 SNPs and adiponectin levels have been reported in several Asian populations. In 20102 genome-wide association studies, 1 in a Korean population[13] and 1 involving Filipino women,[14] found that the *CDH13* gene rs3865188T allele was associated with lower adiponectin levels. Furthermore, in 2015, Kitamoto et al reported that the rs3865188 A allele was associated with higher adiponectin levels in a Japanese population.v The rs12444338 and rs12051272 have also been shown to be associated with adiponectin levels in a Chinese Han population in Taiwan and in a Japanese population.[15,18,20] However, in this study, we did not observe any association between rs3865188, rs12444338, and rs12051272 and T2DM, even though these SNPs have similar minor allele frequencies in Asian populations. The reasons behind these differences could be that the SNPs located in the *CDH13* gene do not influence adiponectin levels in Han Chinese populations. In addition, the unfavorable effects of the SNPs on adiponectin levels could have been compensated for through upregulation of adiponectin receptor sensitivity,[21] and therefore, this compensatory mechanism could have led to the lack of associations between the 5 SNPs in the *CDH13* gene and T2DM. The other potential reason is that the *CDH13* gene could have multiple roles in the development of T2DM in a Han Chinese population or that the effects of the *CDH13* gene SNPs on T2DM could have been obscured by other genetic factors. At last, the genetic heterogeneity of Han population could be another reasons that the Han population could be categorized into “Southern Han" and “Northern Han" according to their distinct genetic background.[22–24] Moreover, Yunnan Han Chinese in present study was clustered between “Southern Han" and “Northern Han."[25] As we did not measure adiponectin levels in the T2DM and NDM groups, which is also a limitation of our study, we could not investigate any associations between the genetic data, adiponectin levels, and T2DM risk.

In 2010, Jee et al[13] found an association between rs12596316 in the *CDH13* gene and adiponectin levels in a Korean population, especially in high-molecular-weight adiponectin levels. They also reported that the rs12596316 G allele was associated not only with adiponectin levels but also specifically

with high-molecular-weight adiponectin levels. Their results suggested that rs12596316 might be involved in the pathogenesis of adiponectin-related diseases, such as T2DM. In the present study, our results did not show an association between the rs12596316 allele and T2DM in a Chinese Han population. However, in the genotype and inheritance models analyses, we observed that the rs12596316 AG genotype was a risk genotype for the development of T2DM. It is interesting that the heterozygote was associated with the disease. However, several studies have reported that heterozygotes had a genetic risk factor associated with phenotypes related to cancer.[26–28] In 2008, Jazdzewski et al reported that being an rs2910164 GC heterozygote reduced the mature miR-146a. Thus, being an rs2910164 GC heterozygote was associated with papillary thyroid carcinoma ($P=.000007$, OR = 1.62; 95% CI: 1.3–2.0).[28] Then, in 2014, Gu et al[27] found that the ataxia telangiectasia mutated gene rs373759 AG increased the risk of papillary thyroid carcinoma ($P=.03$, OR = 1.38; 95% CI: 1.03–1.87). In 2015, Wang et al[26] reported having the rs10877887 TC heterozygote located in the let-7 promoter region was associated with papillary thyroid carcinoma ($P=.007$, OR = 0.73; 95% CI: 0.57–0.92). These findings suggested that being a heterozygote for certain SNPs could be a risk factor for the development of disease. Thus, our data indicated that the rs12596316 AG heterozygous might change *CDH13* gene promoter activity and that this heterozygous was associated with T2DM.

## 5. Conclusions

In this study, we evaluated the associations between 6 SNPs in CDH13 and T2DM in a Han Chinese population. Our results showed that the rs12596316 AG genotype was a risk genotype for the development of T2DM in the overdominant inheritance model. The other five SNPs (rs11646213, rs3865188, rs12444338, rs12051272, and rs7195409) had no observed associations with T2DM in terms of alleles, genotypes, and the various inheritance models. The SNPs haplotypes did not show any associations with T2DM. In the future, larger-scale studies are needed to better clarify and examine the association between CDH13 variants and T2DM susceptibility. Moreover, the function of rs12596316 AG in CDH13 promoter activity and expression should be investigated.

## References


[1] Xu Y, Wang L, He J, et al. Prevalence and control of diabetes in Chinese adults. JAMA 2013;310:948–59.

[2] Weyer C, Funahashi T, Tanaka S, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 2001;86:1930–5.

[3] Tschritter O, Fritsche A, Thamer C, et al. Plasma adiponectin concentrations predict insulin sensitivity of both glucose and lipid metabolism. Diabetes 2003;52:239–43.

[4] Abbasi F, Chu JW, Lamendola C, et al. Discrimination between obesity and insulin resistance in the relationship with adiponectin. Diabetes 2004;53:585–90.

[5] Retnakaran R, Hanley AJ, Raif N, et al. Adiponectin and beta cell dysfunction in gestational diabetes: pathophysiological implications. Diabetologia 2005;48:993–1001.

[6] Zhu N, Pankow JS, Ballantyne CM, et al. High-molecular-weight adiponectin and the risk of type 2 diabetes in the ARIC study. J Clin Endocrinol Metab 2010;95:5097–104.

[7] Saito I, Yamagishi K, Chei CL, et al. Total and high molecular weight adiponectin levels and risk of cardiovascular disease in individuals with high blood glucose levels. Atherosclerosis 2013;229:222–7.

[8] Baumann M, von Eynatten M, Dan L, et al. Altered molecular weight forms of adiponectin in hypertension. J Clin Hypertens 2009;11:11–6.

[9] Hug C, Wang J, Ahmad NS, et al. T-cadherin is a receptor for hexameric and high-molecular-weight forms of Acrp30/adiponectin. Proc Natl Acad Sci U S A 2004;101:10308–13.

[10] Tyrberg B, Miles P, Azizian KT, et al. T-cadherin (Cdh13) in association with pancreatic beta-cell granules contributes to second phase insulin secretion. Islets 2011;3:327–37.

[11] Ling H, Waterworth DM, Stirnadel HA, et al. Genome-wide linkage and association analyses to identify genes influencing adiponectin levels: the GEMS Study. Obesity (Silver Spring) 2009;17:737–44.

[12] Org E, Eyheramendy S, Juhanson P, et al. Genome-wide scan identifies CDH13 as a novel susceptibility locus contributing to blood pressure determination in two European populations. Hum Mol Genet 2009; 18:2288–96.

[13] Jee SH, Sull JW, Lee JE, et al. Adiponectin concentrations: a genome-wide association study. Am J Hum Genet 2010;87:545–52.

[14] Wu Y, Li Y, Lange EM, et al. Genome-wide association study for adiponectin levels in Filipino women identifies CDH13 and a novel uncommon haplotype at KNG1-ADIPOQ. Hum Mol Genet 2010;19: 4955–64.

[15] Morisaki H, Yamanaka I, Iwai N, et al. CDH13 gene coding T-cadherin influences variations in plasma adiponectin levels in the Japanese population. Hum Mut 2012;33:402–10.

[16] Fava C, Danese E, Montagnana M, et al. A variant upstream of the CDH13 adiponectin receptor gene and metabolic syndrome in Swedes. Am J Cardiol 2011;108:1432–7.

[17] Sole X, Guino E, Valls J, et al. SNPStats: a web tool for the analysis of association studies. Bioinformatics 2006;22:1928–9.

[18] Teng MS, Hsu LA, Wu S, et al. Association of CDH13 genotypes/haplotypes with circulating adiponectin levels, metabolic syndrome, and related metabolic phenotypes: the role of the suppression effect. PLoS One 2015;10:e0122664.

[19] Heid IM, Henneman P, Hicks A, et al. Clear detection of ADIPOQ locus as the major gene for plasma adiponectin: results of genome-wide association analyses including 4659 European individuals. Atherosclerosis 2010;208:412–20.

[20] Kitamoto A, Kitamoto T, Nakamura T, et al. CDH13 polymorphisms are associated with adiponectin levels and metabolic syndrome traits independently of visceral fat mass. J Atheroscler Thromb 2016;23: 309–19.

[21] Gao H, Kim YM, Chen P, et al. Genetic variation in CDH13 is associated with lower plasma adiponectin levels, but greater adiponectin sensitivity in East Asian populations. Diabetes 2013;62:4277–83.

[22] Zhao TM, Lee TD. Gm and Km allotypes in 74 Chinese populations: a hypothesis of the origin of the Chinese nation. Hum Genet 1989; 83:101–10.

[23] Chu JY, Huang W, Kuang SQ, et al. Genetic relationship of populations in China. Proc Natl Acad Sci U S A 1998;95:11763–8.

[24] Chen R, Ye G, Geng Z, et al. Revelations of the origin of Chinese nation from clustering analysis and frequency distribution of HLA polymorphism in major minority nationalities in mainland China.[in Chinese]. Yi Chuan Xue Bao 1993;20:389–98.

[25] Yao Y, Shi L, Matsushita M, et al. Distribution of HLA-A, -B, -Cw, and -DRB1 alleles and haplotypes in an isolated Han population in Southwest China. Tissue Antigens 2009;73:561–8.

[26] Wang Y, Wei T, Xiong J, et al. Association between genetic polymorphisms in the promoter regions of Let-7 and risk of papillary thyroid carcinoma: a case-control study. Medicine 2015;94:e1879.

[27] Gu Y, Yu Y, Ai L, et al. Association of the ATM gene polymorphisms with papillary thyroid cancer. Endocrine 2014;45:454–61.

[28] Jazdzewski K, Murray EL, Franssila K, et al. Common SNP in pre-miR-146a decreases mature miR expression and predisposes to papillary thyroid carcinoma. Proc Natl Acad Sci U S A 2008;105:7269–74.