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ORIGINAL ARTICLE

Gene polymorphisms of adiponectin and leptin receptor are associated with early onset of type 2 diabetes mellitus in the Taiwanese population

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Objective: Adipocytokine genes encoding adiponectin *(ADIPOQ)* and the leptin receptor (*LEPR*) affect glucose and fatty acid metabolism. The purpose of this study was to examine the association between early-onset type 2 diabetes mellitus (T2DM) and variability within these two genes in the Han Chinese population of Taiwan.
Subjects: A cross-sectional study of 999 patients from the Han Chinese population of Taiwan with early-onset T2DM ($n=264$; age at diagnosis, 20 to <45 years) and late-onset T2DM ($n=735$; age at diagnosis, $\geqslant 45$ years) was performed. Blood samples from T2DM patients were taken for DNA extraction, and levels of serological markers were measured at enrollment. Seven single-nucleotide polymorphisms (SNPs) were selected for genotyping (three SNPs in *AIDPOQ* and four SNPs in *LEPR*) by polymerase chain reaction in each patient.
Results: Polymorphisms at the position rs10937273 in *ADIPOQ* and at the positions rs1892534 and rs2211651 in *LEPR* were statistically associated with early-onset T2DM ($P=0.0246$, 0.0014 and 0.0012, respectively). C-reactive protein levels were significantly different among the early-onset T2DM patients with different genotypes at the SNPs rs1892534 and rs2211651 in *LEPR* ($P=0.003$ and $P=0.004$, respectively). In addition, fasting glucose levels were also significantly different among different genotypes at the SNP rs1892534 in *LEPR* ($P=0.038$).
Conclusion: We conclude that the polymorphisms in the adipocytokine genes *ADIPOQ* and *LEPR* are significantly associated with the age at diagnosis of T2DM in the Han Chinese population of Taiwan.
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Keywords: adiponectin; leptin receptor; polymorphism; early-onset; type 2 diabetes; Taiwan

Introduction

Type 2 diabetes mellitus (T2DM) is a major public health concern facing the world today.[1] It is a complex disease involving both environmental and genetic contributing factors. Recent evidence suggests that the incidence of T2DM in young adults is increasing worldwide.[2–6] T2DM patients with an early onset have a longer disease duration and exposure to adverse risk factors, leading to diabetes-related complications with significant morbidity and mortality. Candidate gene and genome-wide association studies across multiple populations[7–11] have identified heterogeneity in the genetic determinants involved in the development of diabetes and its associated risk factors. However, only a few studies have examined the influence of this genetic heterogeneity on the age at diagnosis of T2DM, and no high-impact genes have been directly linked to T2DM onset.[12–16]

One risk factor that has shown a strong association with the early onset of T2DM is obesity in children, adolescents and young adults. Researchers have found that adipose tissue

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has a role not only in energy storage but also in the regulation of many pathological processes, such as coronary artery disease, cancer and T2DM.[17,18] Adipose tissue can produce adipocytokines, including adiponectin, leptin, resistin and visfatin, that can mediate the differentiation of adipose tissue and affect glucose and fatty acid metabolism. Among these adipocytokines, adiponectin and leptin are the most abundant and are thought to provide an important link between obesity, insulin resistance and related inflammatory disorders.

Adiponectin is encoded by *ADIPOQ* located in the chromosomal region 3q27, a region identified as a susceptibility locus for the metabolic syndrome and T2DM.[19,20] Adiponectin is an important contributor to peroxisome proliferator-activated receptor-γ-mediated improvements in insulin sensitivity.[21] Moreover, adiponectin stimulates β-oxidation in rat hepatocytes and downregulates the expression of sterol-regulatory-element-binding protein-1C, a major regulator of gene expression for mediators of lipid synthesis. A recent comprehensive review[6] showed that a few *ADIPOQ* single-nucleotide polymorphisms (SNPs) were associated with adiponectin levels and insulin resistance, but none were consistently associated with diabetes or obesity as measured by body mass index (BMI).

Like adiponectin, leptin also has a critical role in the regulation of fat metabolism. Leptin prevents obesity by acting on leptin receptors to stimulate glucose uptake and fatty acid oxidation in skeletal muscles and liver. Additionally, leptin and its receptor inhibit insulin secretion by pancreatic β-cells.[22] Homozygous autosomal mutations in the leptin receptor gene (*LEPR*) in mice lead to obesity and insulin resistance, which can be reversed by the introduction of a neuron-specific *LEPR*-B transgene.[23] In agreement with these findings, common genetic variants at *LEPR*, located in chromosomal region 1p31, have been associated with obesity,[24] insulin resistance, T2DM[25] and variations in leptin levels[26,27] in different populations.

On the basis of these observations, we investigated the association between the variability in *ADIPOQ* and *LEPR*, and the early onset of T2DM in the Han Chinese population of Taiwan.

Materials and methods

Patient and data collection

We enrolled 999 T2DM patients (aged >20 years) from the China Medical University Hospital in Taiwan. Informed consent was obtained from all patients. Diabetes was diagnosed based on the medical records and fasting plasma-glucose levels by using the American Diabetes Association Criteria.[28] Subjects with type 1 diabetes, gestational diabetes and maturity-onset diabetes of the young were excluded from this study. All the participants were of Han Chinese origin, who account for 98% of Taiwan's population. According to the age recommended by the American Diabetes Association for T2DM screening in adults, patients with type 2 diabetes were segregated into two subgroups: (1) early-onset diabetes ($n=264$; age at diagnosis, at least 20 years but <45 years) and (2) late-onset diabetes ($n=735$; age at diagnosis, $\geqslant 45$ years). Data regarding age, sex, duration of disease, weight, height, and circumference of waist and hip (waist to hip ratio) of the patient were obtained from questionnaires. Blood samples for genomic DNA isolation were collected using venipuncture, and serological tests, including fasting glucose, hemoglobin A1c, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, C-reactive protein, and C-peptide, were performed at the time of enrollment. The study was reviewed by the ethics committee of China Medical University Hospital, and performed according to the tenets of the Declaration of Helsinki for research involving human subjects.

SNP selection and genotyping

We selected three SNPs, rs822387 (5′ promoter), rs6444175 (3′ UTR) and rs1093273 (intronic region), in *AIDPOQ* and four SNPs, rs1137100 (Lys109Arg), rs1137101 (Gln223Arg), rs1892534 and rs2211651, in *LEPR* for genotyping. Deviation from the Hardy–Weinberg equilibrium was not observed for any of the SNPs. All the selected SNPs showed a significant association with protein levels in a previous study,[29] or were identified as susceptibility genes from a genome-wide association study.[27] For genotyping, all blood samples were de-identified before analysis, and only the project investigator had access to the link of individual identities. Laboratory personnel involved in genotyping were blinded to the diabetes age-at-onset status of patients. Genomic DNA was extracted from peripheral blood leukocytes by using the Genomic DNA kit (Qiagen, Valencia, CA, USA), and genotyping was performed using an allele-specific extension and ligation assay (Illumina, Inc., San Diego, CA, USA) according to the manufacturer's instructions.

Statistical analyses

The distributions of genotype and allelic frequency in the polymorphisms in early-onset (age, <45 years) or late-onset (age, $\geqslant 45$ years) T2DM patients were analyzed using the χ^2-test or the Fisher exact test for differences in proportions. Odds ratios were calculated from the genotype and allelic frequency with a 95% confidence interval by using an unconditional logistical regression. Moreover, we assessed the effects of BMI on the association between all SNPs and diagnosis age by testing for the presence of interactions between BMI and each SNP in samples from early- vs late-onset T2DM patients. All statistical analyses were conducted using SAS statistical software, version 9.1 (SAS Institute Inc., Cary, NC, USA), and *P*-values of <0.05 (two-sided) were considered significant.

Results

In our database, 26.4% ($n=264$) of the subjects had early-onset T2DM (mean age at diagnosis, 38.2 (5.6) years), and 73.6% ($n=735$) of the subjects had late-onset T2DM (mean age at diagnosis, 55.9 (7.9) years). Table 1 compares clinical and biomedical parameters in early-onset and late-onset T2DM subjects. We observed a higher number of men, younger subjects, lower waist to hip ratio, longer disease duration and lower C-peptide values in the early-onset T2DM subjects.

In genotype association tests, the polymorphisms at position rs10937273 in *ADIPOQ* and at positions rs1892534 and rs2211651 in *LEPR* were statistically associated with early-onset T2DM ($P=0.0246$, 0.0014 and 0.0012, respectively). Furthermore, in allelic frequency analysis, the frequency of the A allele at position rs1892534 and the frequency of the T allele at position rs2211651 were significantly lower in patients with early-onset T2DM than in those with late-onset T2DM, with an odds ratio of 0.62 (95% confidence interval: 0.46, 0.82) and 0.64 (95% confidence interval: 0.48, 0.85), respectively, in a univariate model (Table 2). However, neither the distribution of the genotype nor the allelic frequency of the SNPs rs822387 and rs6444175 within *ADIPOQ,* and the SNPs rs1137100 and rs1137101within *LEPR* were statistically different between the two groups (Table 3). Moreover, there was no change in the effect of genes on early-onset T2DM when the BMI was adjusted in the logistical regression model. Furthermore, a BMI × genotype interaction was not found in the association between the SNPs studied here and early-onset T2DM.

The effect of genotypes on clinical serology tests among the early-onset T2DM patients was also investigated. C-reactive protein levels were significantly different among the early-onset T2DM patients with different genotypes at the SNPs rs1892534 and rs2211651 in *LEPR* ($P=0.003$ and 0.004, respectively; Table 4). In addition, the fasting-glucose levels were found to be significantly different among different genotypes at the SNP rs1892534 in *LEPR* ($P=0.038$). None of the other serological tests, including those for insulin, C-peptide, hemoglobin A1c, high-density lipoprotein, low-density lipoprotein, cholesterol and triglycerides, were significantly different among the genotypes at the SNP rs10937273 in *ADIPOQ,* and the SNPs rs1892534 and rs2211651 in *LEPR*.

Table 1 Characteristics of type 2 diabetes mellitus patients at entry, grouped as patients with an onset age of less than 45 years and those with an onset age of 45 years or more

	Onset age of T2DM (years)		P-*value*
	<45 (n = *264, 26.4%*)	*45+* (n = *735, 73.6%*)	
Education N *(%)*			
Under high school	62 (23.5)	411 (55.9)	<0.0001
High school	137 (51.9)	223 (30.3)	
College or above	65 (24.6)	101 (13.7)	
Sex (% of males)	145 (54.9)	344 (46.8)	0.0236
Age (years)	50.3 (10.0)	63.8 (9.1)	<0.0001
Age at diagnosis (years)	38.2 (5.6)	55.9 (7.9)	<0.0001
DM duration (years)	12.1 (8.9)	7.9 (6.1)	<0.0001
Body mass index (kg m^{-2})	25.4 (4.4)	25.1 (3.6)	0.32
Height (cm)	162.9 (8.9)	159.7 (8.2)	<0.0001
Weight (kg)	68.7 (13.5)	65.3 (11.2)	0.0001
Waist to hip ratio	0.91 (0.06)	0.92 (0.07)	0.0185
Abnormal[a]	174 (65.9)	520 (40.8)	0.1431
Hip (cm)	97.2 (8.7)	96.9 (7.4)	0.72
Waist (cm)	88.5 (11.0)	89.3 (9.8)	0.30
Glu-AC (mg dl^{-1})	144.1 (41.3)	144.3 (44.0)	0.93
Insulin (mU l^{-1})	14.9 (13.1)	15.1 (16.7)	0.82
CRP (mg l^{-1})	0.27 (0.45)	0.34 (0.95)	0.12
C-peptide (ng ml^{-1})	2.39 (1.6)	2.92 (2.0)	<0.0001
HbA1c (%)	7.98 (1.50)	7.91 (1.48)	0.54
High-density lipoprotein (mg dl^{-1})	49.5 (14.1)	48.5 (13.8)	0.30
Triglycerides (mg dl^{-1})	168.2 (153.4)	160.9 (110.3)	0.48

Abbreviations: CRP, C-reactive protein; DM, diabetes mellitus; Glu-AC, fasting glucose; HbA1c, hemoglobin A1c. [a]Abnormal waist to hip ratio was >0.9 and >0.85 for men and women, respectively.

Discussion

In this study, we investigated the influence of polymorphisms in the adipocytokine genes *ADIPOQ* and *LEPR* on T2DM patients with an early onset in a Taiwanese population. A significant association was identified between the polymorphisms within *ADIPOQ* SNP rs10937273, *LEPR* SNPs rs1892534 and rs2211651, and the age at onset of T2DM.

Promoter polymorphisms within *ADIPOQ* have been shown to affect the plasma levels of adiponectin,[30] which are inversely associated with obesity and hyperinsulinemia.[31] The susceptibility SNP rs1093273 (intronic region) analyzed in the present study is grouped by linkage disequilibrium with rs1648707, which has been associated with adiponectin levels, but not consistently with T2DM.[6] Although the *ADIPOQ* SNPs rs822387 (promoter region) and rs6444175 (3′-UTR) were also reportedly associated with plasma adiponectin levels within the Caucasian population;[29,30] these SNPs were not significantly associated with the age at diagnosis of T2DM within the Chinese population residing in Taiwan.

Other proteins involved in the regulation of fat metabolism are leptin (an adipocyte-specific hormone that regulates body weight) and its receptor protein encoded by *LEPR*. Leptin receptor protein belongs to the gp130 family of cytokine receptors, which are known to stimulate gene transcription via activation of cytosolic STAT proteins. A genome-wide association study by Sun *et al*.[27] reported that the *LEPR* SNPs rs1137100, rs1137101 and rs4655555 were significantly associated with the plasma-soluble leptin

Table 2 Genotype and allele frequency of *ADIPOQ* markers between type 2 diabetes mellitus patients with an onset age of <45 years and those with an onset age of ⩾45 years

Type 2 diabetes patients			*Normal*	P-*value*[d]	P-*value*[e]	*OR (95% CI)*[f]
SNP ID	*Early onset*[a] N *(%)*	*Late onset*[b] N *(%)*	*HCB*[c] N *(%)*			
rs10937273						
G/G	79 (29.92)	268 (36.46)	34 (40.48)	0.0246	0.5227	1
A/G	145 (54.92)	332 (45.17)	38 (45.24)			1.48 (1.08, 2.04)*
A/A	40 (15.15)	135 (18.37)	12 (14.29)			1.01 (0.65, 1.55)
G allele	303 (57.4)	868 (59.05)	106 (63.10)	0.5062	0.2562	1
A allele	225 (42.6)	602 (40.95)	62 (36.90)			1.07 (0.88, 1.31)
rs822387						
T/T	252 (95.82)	699 (95.10)	80 (95.24)	0.6383		1.18 (0.59, 2.35)
C/T	11 (4.18)	36 (4.9)	4 (4.76)			1
C/C	0 (0)	0 (0)	0 (0)			—
T allele	515 (97.91)	1434 (97.55)	164 (97.62)	0.6424	0.9828	1.18 (0.59, 2.33)
C allele	11 (2.09)	36 (2.45)	4 (2.38)			1
rs6444175						
G/G	144 (54.55)	426 (57.96)	44 (52.38)	0.0688	0.6802	1
A/G	108 (40.91)	253 (34.42)	33 (39.29)			1.26 (0.94, 1.69)
A/A	12 (4.55)	56 (7.62)	7 (8.33)			0.63 (0.33, 1.22)
G allele	396 (75.0)	1105 (75.0)	121 (72.02)	0.9382	0.3733	1
A allele	132 (25.0)	365 (25.0)	47 (27.98)			1.01 (0.80, 1.27)

Abbreviations: HCB, Han Chinese population in Beijing; CI, confidence interval; OR, odds ratio; SNP, single-nucleotide polymorphism. [a]Subjects whose age at diagnosis was ⩾20 years but <45 years. [b]Subjects whose age at diagnosis was ⩾45 years. [c]Normal population from HCB (data from HapMap database). [d]*P*-value from χ^2-test; compared early-onset type 2 diabetic patients with late-onset type 2 diabetic patients. [e]*P*-value from χ^2-test; compared type 2 diabetic patients with a normal population from HCB. [f]Logistic regression model, univariate analyses. **P*-value <0.05.

receptor (sOB-R) levels in 1504 women of European ancestry. In the present study, we observed a significant association between the T2DM age of diagnosis and the *LEPR* SNPs rs1892534 and rs2211651, which are in strong linkage disequilibrium with the SNP rs4655555, but not with SNPs rs1137100 and rs1137101. Although leptin receptor levels were not measured in the present study, a significant difference in the mean value of C-peptide, a marker of insulin secretion, was observed among the three different genotypes of SNPs rs1892534 and rs2211651.

The relationship between the age of onset of T2DM and non-genetic factors was also explored in the 999 patients with T2DM. Our data showed that the early onset of T2DM might be associated with age, gender, disease duration, waist to hip ratio and serum C-peptide level. Higher BMI values and hypertriglyceridemia in T2DM patients diagnosed before 40 years of age, compared with those diagnosed after 40 years of age, were also observed in the present study, although the results did not reach statistical significance. These findings are in agreement with those previously reported in a study of Mexican patients with T2DM.[12] Other non-genetic factors that may affect our results are treatments for diabetes, such as insulin, sulfonylureas or biguanides drugs, which may result in weight loss (increased BMI), lower cholesterol levels or hypoglycemia. Unfortunately, detailed drug information for each patient was not available, and thus the data could not be adjusted for treatment types in this model. Removal of subjects without any treatment (2.6%) from the analyses did not affect the outcomes. Overall, the results reported here are consistent with previous studies and provide additional evidence to support the contribution of non-genetic risk factors in the development of early-onset T2DM.[32] Further studies are necessary to confirm the effect of these non-genetic factors on the early onset of T2DM.

Although this study shows a correlation between some of the SNPs analyzed and early-onset T2DM, it has a few limitations. The statistical power of this study may have been insufficient to detect weak associations given the small sample size of our control population, a normal Han Chinese population in Beijing (HCB; data from HapMap database). Distribution of the genotypes of the identified SNPs was not significantly different between the normal HCB and the T2DM patients enrolled in the present study (Tables 2 and 3), suggesting an inadequate statistical power in the small HCB control population. Alternatively, the SNPs examined in this study may not have important roles in developing T2DM or might not capture all possible genetic variations in *ADIPOQ* and *LEPR*. Further work exploring other variants in these two genes within this population, as well as experiments addressing genetic changes and their relationship to adipocytokine levels (that is, adiponectin and leptin) and/or protein function will help to identify the true causal variants. Finally, findings from our sample population

Table 3 Genotype and allele frequency of *LEPR* markers between type 2 diabetes mellitus patients with an onset age of <45 years and those with an onset age of ⩾45 years

	Type 2 diabetes patients		*Normal*	P-*value*[d]	P-*value*[e]	*OR (95% CI)*[f]
SNP ID	*Early onset*[a] N *(%)*	*Late onset*[b] N *(%)*	*HCB*[c] N *(%)*			
rs1137100						
G/G	180 (68.44)	525 (71.92)	50 (62.5)	0.5575	0.1582	1
A/G	76 (28.90)	189 (25.89)	29 (36.25)			1.17 (0.86, 1.61)
A/A	7 (2.66)	16 (2.19)	1 (1.25)			1.28 (0.52, 3.15)
G allele	436 (82.89)	1239 (84.86)	129 (80.63)	0.2856	0.2083	1
A allele	90 (17.11)	221 (15.14)	31 (19.37)			1.16 (0.88, 1.51)
rs1137101						
G/G	205 (77.65)	591 (80.52)	36 (80.0)	0.8575	0.5860	1
A/G	57 (21.59)	137 (18.66)	8 (17.78)			1.20 (0.85, 1.70)
A/A	2 (0.76)	6 (0.82)	1 (2.22)			0.96 (0.19, 4.80)
G allele	467 (88.44)	1319 (89.85)	80 (88.89)	0.3675	0.8585	1
A allele	61 (11.56)	149 (10.15)	10 (11.11)			1.16 (0.84, 1.59)
rs1892534						
A/A	181 (68.56)	582 (79.51)	65 (77.38)	0.0014	0.6533	1
A/G	80 (30.30)	143 (19.54)	19 (22.62)			1.78 (1.31, 2.48)*
G/G	3 (1.14)	7 (0.96)	0 (0)			1.38 (0.35, 5.38)
A allele	442 (83.71)	1307 (89.28)	149 (88.69)	0.0008	0.7346	1
G allele	86 (16.29)	157 (10.72)	19 (11.31)			1.62 (1.22, 2.15)*
rs2211651						
T/T	179 (67.80)	578 (78.64)	63 (75)	0.0012	0.5368	1
G/T	82 (31.06)	147 (20.00)	21 (25)			1.80 (1.31, 2.48)*
G/G	3 (1.14)	10 (1.36)	0			0.97 (0.26, 3.56)
T allele	440 (83.33)	1303 (88.64)	147 (87.5)	0.0017	0.9219	1
G allele	88 (16.67)	167 (11.36)	21 (12.5)			1.56 (1.18, 2.06)*

Abbreviations: BMI, body mass index; HCB, Han Chinese population in Beijing; CI, confidence interval; OR, odds ratio; SNP, single-nucleotide polymorphism. [a]Subjects whose age at diagnosis was ⩾20 years but <45 years. [b]Subjects whose age at diagnosis was ⩾45 years. [c]Normal population from HCB (data from HapMap database). [d]*P*-value from χ^2-test; compared early-onset type 2 diabetic patients with late-onset type 2 diabetic patients. [e]*P*-value from χ^2-test; compared type 2 diabetic patients with a normal population from Han Chinese in Beijing. [f]Logistic regression model, univariate analyses. **P*-value <0.05.

Table 4 Association between the polymorphism of *ADIPOQ* and *LEPR* and the serological markers in early-onset type 2 diabetes mellitus patients

	rs10937273				*rs1892534*				*rs2211651*			
	G/G	*A/G*	*A/A*	P-*value*[a]	*A/A*	*G/A*	*G/G*	P-*value*[a]	*T/T*	*G/T*	*G/G*	P-*value*[a]
Glu-AC	141.6 (37.9)	145.4 (42.5)	144.2 (44.1)	0.814	140.1 (37.3)	153.7 (48.3)	128.3 (38.0)	0.038*	140.3 (37.6)	152.8 (47.8)	128.3 (38.0)	0.061
Insulin	15.4 (14.0)	14.4 (11.8)	15.4 (15.5)	0.831	15.1 (13.1)	14.3 (13.2)	15.8 (10.9)	0.884	15.1 (13.1)	14.1 (13.1)	15.8 (10.9)	0.841
HbA1c	8.1 (1.4)	8.0 (1.5)	7.7 (1.6)	0.512	7.90 (1.41)	8.14 (1.68)	8.47 (1.47)	0.425	7.90 (1.41)	8.13 (1.66)	8.47 (1.47)	0.427
CRP	0.31 (0.38)	0.27 (0.52)	0.16 (0.16)	0.248	0.23 (0.34)	0.31 (0.55)	1.08 (1.47)	0.003*	0.24 (0.35)	0.30 (0.55)	1.08 (1.47)	0.004*
C-peptide	2.63 (1.9)	2.30 (1.4)	2.22 (1.4)	0.250	2.28 (1.54)	2.60 (1.74)	2.70 (0.87)	0.312	2.30 (1.55)	2.56 (1.72)	2.70 (0.87)	0.434
Cholesterol	188.9 (36.4)	187.0 (38.6)	195.1 (39.8)	0.497	188.9 (38.0)	188.9 (38.7)	174.0 (32.0)	0.797	188.5 (38.5)	190.1 (37.7)	174.0 (32.0)	0.757
HDL	48.6 (13.6)	48.6 (14.2)	54.5 (13.9)	0.053	50.3 (14.8)	47.8 (12.5)	47.7 (3.2)	0.430	49.9 (14.5)	48.8 (13.5)	47.7 (3.2)	0.819
LDL	117.8 (37.2)	116.2 (36.5)	124.9 (37.7)	0.425	115.8 (35.1)	123.3 (40.8)	112.0 (27.5)	0.302	115.7 (35.4)	123.4 (40.0)	112.0 (27.5)	0.282
Triglycerides	178.2 (155.7)	169.4 (164.9)	143.9 (94.9)	0.511	178.2 (176.7)	147.7 (80.8)	122.6 (26.6)	0.275	178.2 (177.7)	148.4 (80.1)	112.7 (26.6)	0.286

Abbreviations: ANOVA, analysis of variance; CRP, C-reactive protein; Glu-AC, fasting glucose; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein. [a]*P*-value for analysis of variance (ANOVA) test. All values are presented as mean (s.d.). **P*-value <0.05.

(Chinese population in Taiwan) may not be applicable to other populations. Further confirmation of these results in a larger number of subjects from a more diverse population would strengthen our findings.

In conclusion, our study shows that polymorphisms within the adipocytokine genes *ADIPOQ* and *LEPR* were significantly associated with the age at diagnosis of T2DM in a Chinese population in Taiwan. Our observations suggest

that genetic variations of *ADIPOQ* and *LEPR* might be useful to detect the genetic susceptibility of a patient to early-onset T2DM.

Conflict of interest

The authors declare no conflict of interest.

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