Original Article

CDH13 Genetic Polymorphisms, Adiponectin and Ischemic Stroke: a Chinese Family-based Sib-pair Study*

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Abstract

Objective To understand the relationships between *CDH13* (T-cadherin) genetic polymorphisms, adiponectin levels and ischemic stroke, and possible interactions between *CDH13* polymorphisms and other risk factors.

Methods We recruited 342 Chinese ischemic stroke sib pairs. We genotyped rs4783244 and rs7193788 on *CDH13* using time-of-flight mass spectrometry genotyping technology and measured total and high-molecular weight (HMW) adiponectin levels. We investigated associations between SNPs and ischemic stroke, and interactions between SNPs and other risk factors using multi-level mixed-effects regression model.

Results In individuals without ischemic stroke, *CDH13* rs4783244 was associated with total adiponectin levels (per T: Coef = -0.257, P = 0.001). *CDH13* rs7193788 was associated with total adiponectin levels (per A: Coef = -0.221, P = 0.001) and HMW adiponectin levels (per A: Coef = -0.163, P = 0.003). rs7193788 was significantly associated with ischemic stroke (GA/AA *vs.* GG: *OR* = 1.55, 95% *CI*: 1.07 to 2.24, P = 0.020) after Bonferroni correction (α = 0.025). There was an interaction between rs7193788 and diabetes (P = 0.036). Compared to diabetes-free individuals with rs7193788 GG genotype, diabetes patients with rs7193788 GA/AA genotypes had higher risks for ischemic stroke (*OR* = 2.64, 95% *CI*: 1.58-4.40, P < 0.001).

Conclusion *CDH13* genetic polymorphisms are associated with adiponectin levels and ischemic stroke. An interaction is found between *CDH13* SNP and diabetes for ischemic stroke.

Key words: *CDH13*; Genetic polymorphisms; Adiponectin; Ischemic stroke; Sib pair

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INTRODUCTION

Stroke is the leading cause of disability and mortality worldwide[1]. Stroke burden continues to increase, especially in developing countries[2]. Incidence rate of ischemic stroke (IS) is high in China[3]. It is valuable to evaluate genetic and environmental risk factors for IS in Chinese population.

Low serum adiponectin level is a predisposing factor for type 2 diabetes, hypertension and cardiovascular diseases[4-6]. Laboratory evidences suggest that the anti-inflammatory and anti-atherogenic properties of adiponectin can protect vascular system[7-9]. These favorable effects attributed to adiponectin intrigue people to investigate whether it can also lower the risk of ischemic stroke. However, the direct association between adiponectin and development of IS remains to be inconsistent[10]. This might due to possible confounding effect of environmental factors on adiponectin levels. Discussing associations between adiponectin related genetic polymorphisms and IS can avoid this problem.

Genome-wide association studies (GWAS) concerning adiponectin levels identified some risk genetic polymorphisms. SNPs on *ADIPOQ*, *ARL15* and *FER* genes were associated with plasma adiponectin levels in European population[11-13]. GWAS for Asian populations discovered novel risk loci on other genes, including rs3865188 on *CDH13* (T-cadherin) gene in Filipino women[14] and Korean individuals[15], and rs4783244 on *CDH13* gene in Japanese[16] and Chinese[17] populations. rs4783244 was further proved to be associated with high-molecular weight (HMW) adiponectin levels in East Asian populations[18]. *CDH13* is the encoding gene of T-cadherin, which is a major adiponectin receptor in vasculature[19-20]. GWAS results suggest that *CDH13* may play an important role on adiponectin levels in Asian populations.

Previous studies revealed some associations between adiponectin related SNPs and IS. Cheong et al. found that 6 polymorphisms on *ADIPOQ* were strongly associated with ischemic stroke[21]. Chung et al. reported associations between *CDH13* rs4783244, rs8047711, rs7193788 and ischemic stroke[17]. However, most genetic epidemiological studies focusing on the association between *CDH13* and stroke adopted population-based case-control study design. Its vulnerability to the problem of population stratification often undermined the accuracy of statistical analysis, and thus led to false negative findings[22]. Sib pair study design compares genetic polymorphisms between full siblings with same genetic backgrounds, which counteracts confounding due to population stratification[23]. What's more, the aggregation of risk genetic material in sib pairs prone to IS might be in favor of discovering de novo risk loci.

To understand the relationships between *CDH13* polymorphisms, adiponectin levels and IS, this study discussed: 1) the associations between *CDH13* genetic polymorphisms and adiponectin levels; 2) the associations between *CDH13* genetic polymorphisms and IS; 3) the interactions between *CDH13* genetic polymorphisms and other risk factors for IS.

MATERIALS AND METHODS

Subjects

The current study is a part of Fangshan Family-based Ischemic Stroke Study In China (FISSIC) program, which is an ongoing family-based genetic epidemiological study. The protocol was described in details elsewhere[24]. In brief, we recruited Northern Chinese Han pedigrees from Fangshan District, which is located in the southwest of Beijing, China. The inclusion criteria for IS patients were: 1) diagnosis of at least one ischemic stroke confirmed by the study neurologist on the basis of history, medical records, and head imaging by CT or MRI; 2) at least 18 years old by the time of enrolment in the study; 3) at least one full sibling or parent alive in areas nearby; 4) written informed consent by the patient or surrogate. The exclusion criteria for IS patients were: 1) diagnosis of TIA only; 2) diagnosis of vasospasm after subarachnoid hemorrhage; 3) diagnosis of Mendelian disorders: CADASIL, Fabry disease, MELAS, or sickle cell anaemia; 4) diagnosis of iatrogenic ischemic stroke associated with a surgical/ interventional procedure such as coronary artery bypass grafting, carotid endarterectomy, or heart valve surgery; 5) diagnosis of ischemic stroke associated with autoimmune condition or endocarditis. The inclusion criteria for IS-free siblings were: 1) over 18 years old; 2) had no medical history of IS. The exclusion criteria for IS-free siblings were: 1) uncapable of coorperating during physical examinations; 2) refused to provide blood samples.

Since June 2005 to June 2013, we recruited 342 discordant IS sib pairs (684 individuals in total) using proband-initiated contact method[25]. Each discordant IS sib pair contained one confirmed IS

patient and one IS-free full sibling.

Ischemic Stroke Confirmation

Medical records including patient history, physical examination, laboratory testing and brain imaging data of every IS patient were collected from local hospitals and sent to study neurologists for stroke confirmation. The IS-free status was identified using the Questionnaire for Verifying Stroke-Free Status (QVSFS)[26-27]. Siblings with negative responses to all 8 questions and with no IS medical history were defined as IS-free siblings.

Assessment of Total and HMW Adiponectin Levels

Fasting venous blood samples were collected from every participant. Blood samples were transferred into labeled vacuum tubes containing EDTA, and then they were centrifuged at 4000 rpm for 15 min to obtain serum.

Total adiponectin and HMW adiponectin concentrations (ng/mL) in serum were estimated by commercially available ELISA kits (EK0595, Boster, Wuhan, China; CSB-E13400h, Cusabio, Wuhan, China) using TECAN GENios Plus enzyme-linked immunosorbent assay reader (TECAN, Grödig, Austria).

Anthropometric and Biochemical Indices Determinations

Surveys were carried out by trained and qualified staffs. Demographic information was collected by a standard questionnaire. A current smoker was a person who had at least 1 cigarette per day. An ex-smoker was a person who had regularly smoked but had quitted smoking for at least 1 month. A non-smoker was a person who had never smoked. The current and ex-smokers were both treated as smokers during the analysis. A drinker was a person who had ever had at least 50 milliliter white spirit per week and lasted for at least 6 months. Sitting blood pressure was examined for 3 times using brachial blood pressure meters (HEM-7200, Omron Healthcare, Kyoto, Japan). The mean of the second and the third observed values was taken as one's final blood pressure. BMI was calculated as weight/height^2 (kg/m^2). BMI ≥ 25 was defined as overweight/obesity, while BMI < 25 was defined as normal. Hypertension was defined as a diagnosis of hypertension, antihypertensive therapy, SBP ≥ 140 mmHg or DBP ≥ 90 mmHg during examination. Diabetes was defined as a diagnosis of diabetes, antidiabetic therapy, or fast blood glucose (FBG) ≥ 7.0 mmol/L.

Fasting venous blood samples were tested in Peking University Health Science Center Key Laboratory of Epidemiology for fast blood glucose (FBG, mmol/L), total cholesterol (TC, mmol/L), total triglycerides (TG, mmol/L), high density lipoprotein cholesterol (HDL-C, mmol/L), and low density lipoprotein cholesterol (LDL-C, mmol/L).

Genotyping of SNPs

A GWAS performed in Chinese Han population identified three quantitative trait loci (QTL) regulating the adiponectin levels, i.e. rs4783244, rs8047711, and rs7193788 on *CDH13* gene[17]. Another GWAS in Singaporean Chinese showed strong associations between *CDH13* rs4783244 and adiponectin levels[18]. The minor allele frequency (MAF) of rs8047711 is relatively low. Considering the sample size of the present study, we selected *CDH13* rs4783244 and rs7193788 as candidate SNPs.

DNA was isolated from peripheral venous blood leucocytes. DNA genotyping was performed using time-of-flight mass spectrometry genotyping technology with MassARRAY iPLEX platform (Sequenom Inc, San Diego, California, USA) following the manufacturer's protocol. Genotypes were assessed by MassARRAY® Typer Analyzer version 4.0. The call rates for 2 SNPs were all above 99.0%. A randomly chosen subgroup of 5% of DNA samples went through repeat analysis to verify reproducibility. The results of duplicated samples were 100% consistent.

Ethics Statement

The study design was explained to every subject during recruitment. Every participant gave written informed consent. This project was approved by the Ethics Committee of Peking University Health Science Center, Beijing, China.

Statistical Analysis

Adiponectin levels, HMW adiponectin levels and total triglycerides (TG) were analyzed on natural logarithmic scales because of their skewed distribution. Continuous variables were described as mean ± standard deviation and Student *t*-test was adopted to compare means across groups. Categorical variables were described as frequency and proportion, and Pearson's χ^2 test was used for comparisons between groups.

Hardy-Weinberg equilibrium (HWE) for each SNP

was estimated, and no violation was found for any SNP. HWE *P*-values for all SNPs were shown in Table 3. To avoid reverse causality, we investigated the associations between 2 SNPs and total and HMW adiponectin levels in IS-free individuals and IS patients respectively. Because individuals in each group were unrelated individuals from different pedigrees, these associations were analyzed using linear regression model. Considering the shared genetic backgrounds of full siblings and the compromised individual independence, we applied multi-level mixed-effects regression models to investigate the associations between *CDH13* SNPs and IS[28]. We employed Bonferroni correction due to multiple testing. SNPs with $P < 0.05/2 = 0.025$ were considered significant. We estimated interactions between two SNPs in *CDH13* and smoking, drinking, BMI, history of hypertension, history of diabetes for IS by adding multiplicative terms in multi-level mixed-effects regression models. Statistical analyses were performed by STATA (version 13, Stata Corporation, Texas, USA).

RESULTS

Anthropometric, Lifestyle Characteristics and Biochemical Indices of ischemic Stroke Sib-pairs

A total of 342 Chinese Han discordant IS sib pairs consisting of 342 confirmed IS patients and 342 IS-free siblings were enrolled in the present study. The mean age at enrollment for IS patients was 61.09 ± 9.22. The mean age at enrollment for IS-free siblings was 57.52 ± 9.05. The mean age at onset for IS patients was 55.4 ± 9.09. Compared with IS-free siblings, IS patients were older, had a higher proportion of male, and had higher rates of diabetes mellitus and hypertension. IS patients also had higher smoking rate, as well as higher FBG levels, higher TG levels and lower HDL-C levels. The total adiponectin levels of IS patients were lower than IS-free siblings.

There were no significant differences with respect to alcohol consumption, BMI, TC, LDL-C, and HMW adiponectin levels between IS patients and IS-free siblings (Table 1).

Associations between CDH13 SNPs and Adiponectin Levels In IS-free individuals, rs4783244 T allele was associated with total adiponectin levels (per T allele: Coef = -0.257, $P = 0.001$) but not HMW adiponectin levels (per T allele: Coef = -0.079 $P = 0.204$). Compared with rs4783244 GG genotype, GT/TT genotypes were associated with lower total adiponectin levels (GT/TT *vs.* GG: Coef = -0.265, $P = 0.008$).

In IS-free siblings, rs7193788 A allele was associated with total adiponectin levels (per A allele: Coef = -0.221, $P = 0.001$) and HMW adiponectin levels

Table 1. Anthropometric, Lifestyle Characteristics and Biochemical Indices of Ischemic Stroke Sib-pairs

Items	IS	IS-free Siblings	*P*
N	342	342	-
Age	61.09 ± 9.22	57.52 ± 9.05	< 0.001^
Male	223 (65.20)	170 (49.71)	< 0.001^
Diabetes mellitus	143 (41.81)	84 (24.56)	< 0.001^
Hypertension	297 (86.84)	213 (62.28)	< 0.001^
Smoker	203 (59.36)	150 (43.86)	< 0.001^
Drinker	127 (37.13)	105 (30.70)	0.063
BMI	26.37 ± 3.57	26.18 ± 3.55	0.456
FBG	6.51 ± 2.78	5.98 ± 2.48	0.005^
TC	4.25 ± 1.23	4.27 ± 1.17	0.810
ln TG	0.49 ± 0.58	0.36 ± 0.62	0.002^
HDL-C	1.27 ± 0.44	1.40 ± 0.53	< 0.001^
LDL-C	2.87 ± 0.86	2.87 ± 0.81	0.969
ln total adiponectin	8.75 ± 0.89	8.92 ± 0.86	0.035^
ln HMW adiponectin	7.46 ± 0.74	7.54 ± 0.70	0.180

Note. Continuous variables were described as mean ± standard deviation. Categorical variables were described as frequency (proportion). IS: ischemic stroke; BMI: body mass index, kg/m^2; FBG: fast blood glucose, mmol/L; TC: total cholesterol, mmol/L; ln TG: natural logarithmically transformed total triglycerides, mmol/L; HDL-C: high-density lipoprotein cholesterol, mmol/L; LDL-C: low-density lipoprotein cholesterol, mmol/L; ln total adiponectin: natural logarithmically transformed total adiponectin, ng/mL; ln HMW adiponectin: natural logarithmically transformed high-molecular weight adiponectin, ng/mL. ^$P < 0.05$.

(per A allele: Coef = -0.163, *P* = 0.003). Compared with rs7193788 GG genotype, GA/AA genotypes were associated with lower total adiponectin levels (GA/AA *vs.* GG: Coef = -0.303, *P* = 0.006) and lower HMW adiponectin levels (GA/AA *vs.* GG: Coef = -0.222, *P* = 0.013). However, these associations were not found in IS patients (Table 2).

Associations between CDH13 SNPs and Ischemic Stroke *CDH13* rs7193788 was significantly associated with IS after Bonferroni correction (α = 0.025). Compared with individuals of rs7193788 GG genotype, those of GA/AA genotypes had higher risks of IS (GA/AA *vs.* GG: unadjusted: *OR* = 1.48, 95% *CI*: 1.05-2.09, *P* = 0.025; adjusted: *OR* = 1.55, 95% *CI*: 1.07-2.24, *P* = 0.020). No association was found between rs4783244 and IS (Table 3).

Interactions between CDH13 SNPs and Other Risk Factors for IS We investigated interactions between 2 *CDH13* SNPs and smoking, drinking, BMI, history of hypertension, history of diabetes for IS. We observed a statistically significant interaction between *CDH13* rs7193788 and diabetes (*P* = 0.036). Compared to diabetes-free individuals with rs7193788 GG genotype, diabetes patients with rs7193788 GA/AA genotypes had higher risks for IS (unadjusted: *OR* = 3.17, 95% *CI*: 1.96-5.12, *P* < 0.001; adjusted: *OR* = 2.64, 95% *CI*: 1.58-4.40, *P* < 0.001)

No interaction was found between *CDH13* rs4783244 and diabetes for IS (*P* = 0.268). However, compared to diabetes-free individuals with rs4783244 GG genotype, diabetes patients with rs4783244 GT/TT genotypes had higher risks for IS (Unadjusted: *OR* = 2.50, 95% *CI*: 1.62-3.86, *P* < 0.001; adjusted: *OR* = 2.03, 95% *CI*: 1.27-3.24, *P* = 0.003) (Table 4).

Table 2. Associations between *CDH13* SNPs and Adiponectin Levels in IS patients and IS-free Siblings

SNP	Genotype	IS Patients			IS-free Siblings		
		Mean ± SD	Coef	*P**	Mean ± SD	Coef	*P**
Total adiponectin							
rs4783244	per T	-	-0.062	0.473	-	-0.257	0.001^
	GG	8.83 ± 0.97	Ref	-	9.05 ± 0.91	Ref	-
	GT/TT	8.69 ± 0.83	-0.137	0.241	8.83 ±0.82	-0.265	0.008^
rs7193788	per A	-	-0.086	0.302	-	-0.221	0.001^
	GG	8.98 ± 0.76	Ref	-	9.00 ± 0.86	Ref	-
	GA/AA	8.70 ± 0.93	-0.274	0.051	8.71 ± 0.85	-0.303	0.006^
HMW adiponectin							
rs4783244	per T	-	-0.034	0.649	-	-0.079	0.204
	GG	7.49 ± 0.74	Ref	-	7.56 ± 0.76	Ref	-
	GT/TT	7.43 ± 0.74	-0.063	0.529	7.53 ± 0.64	-0.073	0.366
rs7193788	per A	-	-0.017	0.816	-	-0.163	0.003^
	GG	7.46 ± 0.73	Ref	-	7.61 ± 0.70	Ref	-
	GA/AA	7.43 ± 0.81	-0.037	0.759	7.36 ± 0.66	-0.222	0.013^

Note. *Adjusting for age, sex, diabetes mellitus, hypertension, smoking status, drinking status, BMI, ln TG, HDL-C. HMW adiponectin: high-molecular weight adiponectin. ^*P* < 0.05.

Table 3. Associations between *CDH13* SNPs and Ischemic Stroke

SNP	Location	MAF	HWE *P*-Value	Genotype	Unadjusted			Adjusted*		
					OR	95% *CI*	*P*	*OR*	95% *CI*	*P*
rs4783244	16:82628663	T (0.348)	0.818	GG	Ref	-	-	Ref	-	-
				GT/TT	1.05	0.79, 1.40	0.736	1.09	0.80, 1.49	0.582
rs7193788	16:82622555	G (0.478)	0.666	GG	Ref	-	-	Ref	-	-
				GA/AA	1.48	1.05, 2.09	0.025^	1.55	1.07, 2.24	0.020^

Note. *Adjusting for age, sex, diabetes mellitus, hypertension, smoking status, drinking status, BMI, lnTG, HDL-C. MAF: minor allele frequency. ^*P* < 0.05.

DISCUSSION

The present study explored the relationships between 2 *CDH13* genetic polymorphisms (rs4783244 and rs7193788), adiponectin levels and ischemic stroke. We also discussed the interactions between SNPs and other risk factors for IS. The results suggested significant associations between 2 SNPs and adiponectin levels, an association between rs7193788 and IS, and an interaction between rs7193788 and history of diabetes for IS.

Adiponectin is a secretory adipocyte-derived endocrine with antiatherogenic and anti-inflamatory properties[29-30]. Adiponectin exists in two forms in serum, as lower molecular weight (LMW) species or as high molecular weight (HMW) complex consisting of 12-18 subunits[31]. HMW adiponectin is biologically active. HMW-to-total adiponectin ratio is a good determinant of glucose intolerance or insulin sensitivity[32-33]. Adiponectin levels were associated with genetic polymorphisms. Genome-wide association studies (GWAS) identified several SNPs located on *CDH13* gene as possible causal factors in Asian populations. *CDH13* is the coding gene for T-cadherin, which is a receptor for hexameric and HMW adiponectin and is mainly expressed in endothelial and smooth muscle cells[20]. We observed the associations between *CDH13* polymorphisms and total and HMW adiponectin levels in IS-free siblings but not IS patients, indicating that the onset of IS may have a significant influence on adiponectin levels.

rs4783244 located in intron 1 of the *CDH13* gene. rs7193788 located in promoter region of *CDH13* gene. A GWAS in Chinese Han population suggested that G allele of rs4783244 and G allele of rs7193788 were associated with higher adiponectin levels[17]. In another GWAS concerning Singaporean Chinese, rs4783244 showed strong associations both with total adiponectin levels and HMW adiponectin levels[18]. We replicated these findings in the present sib pair study. Otsuka et al. found an association between schizophrenia and a GACAG haplotype consisted of rs7193788 and four other SNPs in promoter region of *CDH13*. The nucleotide substitutions in this region might influence the transcriptional activity of *CDH13* promoter[34]. This potential biological function of rs7193788 might be an explanation for its associations with total and HMW adiponectin levels found in our study.

Although adiponectin was associated with traditional cardiovascular risk factors, the association between adiponectin and ischemic stroke remained controversial[35-40]. Adiponectin levels can be influenced by many changeable factors, which made it hard to eliminate the effect of environmental confounders in cross-sectional studies. To verify the causal relationship between adiponectin and IS, it was reasonable to discuss the associations between adiponectin related genetic polymorphisms and IS. *ADIPOQ* rs266729 was a well-studied SNP which showed an association with decreased risk of ischemic stroke[41-42]. 6 SNPs in *ADIPOQ* gene were associatied with IS risk in Korean population[21]. Chung et al. reported that rs4783244 was associated with ischemic stroke in Chinese population[17]. However, we didn't draw the same conclusion in the present study. Instead, we found that rs7193788 was associated with IS. Individuals with rs7193788 GA/AA genotypes endured lower adiponectin levels, and had

Table 4. Interactions between *CDH13* SNPs and Diabetes for Ischemic Stroke

Diabetes	Genotype	Unadjusted			Adjusted*			*P* for Interaction
		OR	95% *CI*	*P**	*OR*	95% *CI*	*P**	
rs4783244								
No	GG	Ref	-	-	Ref	-	-	
	GT/TT	0.96	0.67, 1.37	0.825	0.99	0.67, 1.45	0.941	0.268
Yes	GG	1.78	1.12, 2.83	0.015^	1.53	0.93, 2.52	0.092	
	GT/TT	2.50	1.62, 3.86	< 0.001^	2.03	1.27, 3.24	0.003^	
rs7193788								
No	GG	Ref	-	-	Ref	-	-	
	GA/AA	1.19	0.78, 1.83	0.421	1.20	0.76, 1.89	0.425	0.036^
Yes	GG	1.30	0.68, 2.46	0.424	1.12	0.57, 2.21	0.735	
	GA/AA	3.17	1.96, 5.12	< 0.001^	2.64	1.58, 4.40	< 0.001^	

Note. *Adjusting for age, sex, hypertension, smoking status, drinking status, BMI, lnTG, HDL-C. ^$P < 0.05$.

higher risks of IS compared with individuals with GG genotypes, which was compatible with the hypothesis that *CDH13* genetic polymorphisms can impact the risk of ischemic stroke through its influence on adiponectin levels.

Interactions between *CDH13* polymorphisms and environmental factors were studied before. Jo et al. observed that the association between *CDH13* and adiponectin can be modified by smoking and obesity. Obese smokers with risk *CDH13* rs3865188 polymorphisms were at 6.2-fold higher risk for hypoadiponectinemia[43]. Chung et al. reported an interaction between *CDH13* rs4783244 and sex for HOMA-IR/T2DM. However, no interactions were found between rs4783244 and smoking for T2DM or stroke[17]. Diabetes impairs endothelium function and augments the formation of atherosclerotic lesions[44]. The presence of diabetes can significantly increase the risk of stroke[45-46]. Adiponectin played a vascular protective role by preserving endothelial cell function[47]. It is of value to discuss the joint effect of *CDH13* SNPs and diabetes for IS. An interaction between rs7193788 and diabetes for IS was found in this study. Individuals with rs7193788 risk genotypes, as well as diabetes, had higher risks of IS.

The present study applied a sib pair design. This design provided resistance to problems associated with population stratification that can occur in case-control studies, while the unique family-based design lowered the possibility of false positive discoveries[48]. We applied multi-level mixed-effects regression model to analyze sib pair data, for it can gain more power than traditional family based algorithms. Considering the limited sample size, using multi-level mixed-effects regression model may increase the possibility of true positive discoveries.

However, there were still some limitations. The main limitation of this study was its sample size. The small sample size could decrease statistical power. However, because of the strict recruitment requirement of eligible patients and full siblings, sib pair studies are far more difficult and expensive to undertake than case control studies[23]. Second, considering the small sample size, we didn't analyze the relationships between SNPs and IS subtypes. The associations between adiponectin and different etiologic subtypes of IS may be different, for low adiponectin levels were found to be significantly associated with increased risk of large artery atherosclerosis (LAA) stroke but not non-LAA stroke[49]. Third, given the cross-sectional nature of our data, the relationships between adiponectin levels and IS were not analyzed. Thus, further studies will be needed to confirm the results.

CONCLUSIONS

CDH13 genetic polymorphisms are associated with adiponectin levels in IS free individuals. *CDH13* rs7193788 is associated with IS. An interaction is found between *CDH13* SNP and diabetes for IS.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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